

**First Principles of Gastroenterology and Hepatology
in Adults and Children**

Volume I
Gastroenterology

A. B. R. Thomson, E. A. Shaffer, T. Gonska, Editors

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Volume I Gastroenterology



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The Editors



Editor Biographies

Dr. Alan Thomson has been President of the Canadian Association of Gastroenterology, a member of the Bockus Society, two-term Governor for Western Canada for the American College of Gastroenterology, winner of the prestigious University Cup in 2001, a recipient of the Gold Medal in Medicine of the Royal College of Physicians and Surgeons (Canada), Chief Royal College examiner in Gastroenterology, Director of the Division of Gastroenterology, three-time Teacher of the Year at the University of Alberta, Award for Excellence in Mentoring Graduate Students and Postdoctoral Fellows, and awarded Distinguished University Professor. He helped found the Gastroenterology Training Fellows annual course, The Canadian Digestive Disease Foundation, The Canadian Helicobacter Study Group, The Canadian Journal of Gastroenterology, and First Principles of Gastroenterology. He joined the Faculty of Medicine at the University of Alberta in 1975, where he began his career as a clinician, teacher, and investigator. He cherishes the privilege of having helped train more than 60 GI training fellows and graduate students. Dr. Thomson's basic research interest is in the mechanisms of intestinal adaptation, the absorption of nutrients, and the modification of this adaptive response in health and in disease models. His clinical research interests involve the study of human gastric secretion and the coordination and conduct of clinical trials for patients with peptic disorders, as well as inflammatory and irritable bowel diseases. Dr. Thomson has authored over 700 scientific papers and review articles, and has written or edited ten books. Dr. Thomson is a Distinguished Emeritus University Professor, University of Alberta, and is currently an Adjunct Professor at Western University.

Eldon Shaffer is a Gastroenterologist who has held leadership positions in academic Medicine. At a university level, Dr. Shaffer was founding Division Head (Gastroenterology); founding chair, Gastrointestinal Research Group; Associate Dean (Clinical Affairs); Department Head (Internal Medicine), and Regional Clinical Department Head (Internal Medicine), all in the Faculty of Medicine, University of Calgary. At a national level, he was the first and founding President of Canadian Association for Study of the Liver; President, Canadian Association of Gastroenterology; President, Canadian Society for Clinical Investigation; Chair of the Medical Advisory Board, Crohn's and Colitis Foundation; President, Canadian Professors of Medicine; and Chair, Finance Committee of the Alberta Society of Gastroenterology. At an international level, he served on committees for the American College of Gastroenterology, the American Association for the Study of the Liver Disease and the American Gastroenterological Association, chairing the Liver Biliary section for the American Gastroenterological Association and sitting on the AGA Council and the Organizing Committee (Chair, Public Relations Committee) for the World Congress of



Gastroenterology (Montreal 2005). His personal research activity has yielded over 500 papers, abstracts and edited texts. A recognized educator, Dr. Shaffer has received awards nationally from the Canadian Association of Gastroenterology and regionally in Alberta and from his Faculty of Medicine. He currently is a Professor of Medicine in the Division of Gastroenterology and Hepatology, University of Calgary, where he enjoys an active consulting practice in Gastroenterology and continues to maintain his education and research interests that span from hepatobiliary diseases through functional gut disease and eosinophilic gastrointestinal disease.

Tanja Gonska is an Assistant Professor at the Division of Paediatric Gastroenterology, Hepatology and Nutrition, University of Toronto, with a subspecialty focus on paediatric pancreas diseases and Cystic Fibrosis. She holds an appointment at the Research Institute of the Hospital for Sick Children and the Institute of Medical Science, Toronto. Following Medical school in Muenster, Paediatric Residency training at the Children's Hospital in Freiburg, Germany, and Fellowship training at the Hospital for Sick Children, Dr. Gonska has decided to continue her academic career in Paediatric Pancreatology and Cystic Fibrosis as staff physician at the Hospital for Sick Children. She has enjoyed mentorship by Profs. Peter Durie, Christine Bear and Paul Quinton. Next to her involvement in an international consortium to advance the knowledge in paediatric pancreatitis, her research interest is focused on forwarding our understanding in transepithelial ion and fluid transport in airway and intestine. Further, her innovative approach to develop new measures of functional outcome supports current strategies to cure Cystic Fibrosis disease.



Contributors

ADAMS, P.C., London Health Sciences Centre-University Campus,
339 Windermere Rd., London, ON N6A 5A5.
Tel: (519) 858-5125 Fax: (519) 858-5114 E-mail: padams@uwo.ca

ALLARD, J.P., University Health Network-Toronto General Hospital,
EW 217A-200 Elizabeth St., Toronto, ON M5G 2C4.
Tel: (416) 340-5159 Fax: (416) 348-0065 E-mail: johane.allard@utoronto.ca

ASPINALL, A. I., Department of Medicine, Teaching Research Wellness Building,
1403 - 29 Street NW, Calgary, AB T2N 2T9.
Tel: (403) 592-5049 Fax: (403) 592-5090 Email: aaspinal@ucalgary.ca

BAIN, V.G., University of Alberta, 205 College Plaza, 8215- 112th St.,
Edmonton, AB T6G 2C8.
Tel: (780) 492-8128 Fax: (780) 492-8130 E-mail: vince.bain@ualberta.ca

BURAK, K., Department of Medicine, Teaching Research Wellness Building,
University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 2T9.
Tel: (403) 592-5049 Fax: (403) 592-5090 E-mail: kwburak@ucalgary.ca

BURNSTEIN, M., Interim Division, General Surgery, University of Toronto,
St. Michael's Hospital, 38 Shuter St., Suite 504, Toronto, ON M5B 1A6.
Tel: (416) 864-6050 Fax: (416) 864-5668 E-mail: burnsteinm@smh.toronto.on.ca

BURSEY, R.F., Associate Professor of Medicine, Memorial University,
Health Sciences Centre, 300 Prince Philip Dr., St. John's, NL A1B 3V6.
Tel: (709) 777-6960 Fax: (709) 777-8044 E-mail: fbursey@mun.ca

CARPENTIER, S., Division of Gastroenterology, Department of Medicine, McGill
University, Royal Victoria Hospital, 687 Pine Ave West, R.2.28, Montreal, QC H3A1A1
Tel: (514)843-1616; Fax: (514)843-1421 E-mail: scarpentier@dal.ca

CHAMPION, M.C., Internal Medicine/Gastroenterology, The Ottawa
Hospital-Civic Campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4674 Fax: (613) 761-5269 E-mail: mchampion@ottawahospital.on.ca

CLANDININ, M. T., Department of Agricultural, Food & Nutritional Science,
University of Alberta, 4-002C Li Ka Shing Ctr for Hlth Rsch Innovation, Edmonton,
AB T6G 2E1 Tel: 780.492.5188 Fax: 780.492.8855 E-mail: tclandinin@professorpufa.co

COFFIN, C.S., Department of Medicine, Teaching Research Wellness Building,
University of Calgary, 3280 Hospital DR NW, Calgary T2N4Z6.
Tel: (403) 592-5049 Fax: (403) 592-5038 E-mail: cscoffin@ucalgary.ca



CONGLY, S. E., Department of Medicine, Teaching Research Wellness Building,
1403 - 29 Street NW, Calgary, AB T2N 2T9.
Tel: (403) 592-5049 Fax: (403) 592-5090 E-mail: stephencongly@gmail.com

DUBÉ, C., Division of Gastroenterology, The Ottawa Hospital,
1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4603 Fax: (613) 761-5068 E-mail: cdube@ottawahospital.on.ca

ELKADRI, A., Paediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children, 555 University Avenue
Toronto, ON M5G 1X8
Email: abdul.elkadri@sickkids.ca.

FARDY, J.M., Gastroenterology/Internal Medicine, Memorial University,
Faculty of Medicine, Health Sciences Centre, 300 Prince Philip Dr.,
St John's, NF A1B 3V6.
Tel: (709) 777-7064 Fax: (709) 777-8044 E-mail: jfardy@morgan.ucs.mun.ca

FREEMAN, H.J., Gastroenterology, UBC Hospital, 2211 Wesbrook Mall,
Vancouver, BC V6T 1W5. E-mail: hugfree@shaw.ca

GAISANO, H., University Health Network, Toronto Western Hospital,
6B Fell 6-176, 399 Bathurst St., Toronto, ON M5T 2S8.
Tel: (416) 603-5949 E-mail: herbert.gaisano@utoronto.ca

GONSKA, T., Paediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children, 555 University Avenue
Toronto, ON M5G 1X8
Tel: (416) 813-7735; E-mail address: tanja.gonska@sickkids.ca

GRÉGOIRE, S., Gastroenterology, The Ottawa Hospital-General Campus,
203-311 McArthur Ave., Vanier, ON K1L 8M3.
Tel: (613) 744-8180 Fax: (613) 744-7982 E-mail: dr.gregoire@sympatico.ca

GUJRAI, N., Faculty of Pharmacy and Pharmaceutical Sciences,
#1100 Dent/Pharm Centre, University of Alberta, Edmonton, AB T6G 2N8
Tel: (780) 492-0547 E-mail: ngujral@pharmacy.ualberta.ca

GUPTA, M., 130 University Campus, Zeidler Ledcor Centre
University of Alberta, Edmonton, AB T6G2PA.
Tel: (780) 492-8245 Email: milligupta@gmail.com

GUTFREUND, K. S., Department of Medicine, 1-28B Zeidler Building,
University of Alberta, Edmonton, AB T6G 2X8.
Tel: (780) 492-0388 Fax: (780) 492-8143 E-mail: klaus.gutfreund@ualberta.ca



HABAL, F., Gastroenterology, Toronto General Hospital, 200 Elizabeth St.,
Office 9N977, Toronto, ON M5G 2C4. E-mail: flavio.habal@uhn.on.ca

HUNT, R.H., Division of Gastroenterology, McMaster University Medical Centre,
McMaster University, Room 4W8, 1200 Main St. W, Hamilton, ON L8N 3Z5.
Tel: (905) 521-2100 ext. 73219 Fax: (905) 521-5072 Cell: (905) 541-8777
GSM: 44-7785-260-430 E-mail: huntr@mcmaster.ca

JAYAKUMAR, S., University of Calgary, Rm 480075, 4th Floor South Health Campus
4448 Front Street SE, Calgary, AB T3M 1M4 Tel: 403 956 2466 or 403 956 2477
E-mail: sjayakum@ucalgary.ca

KAMATH, B., Paediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children, 555 University Avenue
Toronto, ON M5G 1X8
Tel: (416) 813-6171 E-mail address: binita.kamath@sickkids.ca

LEONARD, J., Cannon Falls Medical Center, 200 1st St SW,
Rochester, MN 55905 Tel: (507) 284-2511

LEVY, G.A., University Health Network, University of Toronto,
585 University Ave., 11-NCSB-1236, Toronto, ON M5G 2N2.
Tel: (416) 340-5166 Fax: (416) 340-3378 E-mail: glfgl2@attglobal.net

LI, Q., Department of Agricultural, Food & Nutritional Science,
University of Alberta, Room: 4-126E / 4-021 HRIF East, Edmonton,
AB T6G 2E1 Tel: (780) 492-4667 Fax: (780) 492-8855 Email: qunl@ualberta.ca

LILLY, L.B., University Health Network, 11-NCSB-1241, 585 University Ave.,
Toronto, ON M5G 2N2.
Tel: (416) 340-4629 Fax: (416) 340-3492 E-mail: les.lilly@uhn.on.ca

LING, S., Paediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children, 555 University Avenue
Toronto, ON M5G 1X8
Tel: (416) 813-8757 E-mail address: simon.ling@sickkids.ca

MA, M., Hepatology and Gastroenterology, University of Alberta,
8440-112th St., Edmonton, AB T6G 2R7.
Tel: (780) 492-8146 Fax: (780) 492-8148 E-mail: mang.ma@ualberta.ca



MACINTOSH, D.G., Gastroenterology), Dalhousie University,
Queen Elizabeth II Health Sciences Centre-Victoria General Site,
Centennial Wing, 1278 Tower Rd., Room 927, Halifax, NS B3H 2Y9.
Tel: (902) 473-3721 Fax: (902) 473-4406 E-mail: donald.macintosh@dal.ca

MASON, A. L., Division of Gastroenterology, 7-142J Katz Building,
University of Alberta, Edmonton, AB T6G 2X8
Tel: (780) 492-8176 Fax: (780) 492-1655 E-mail: andrew.mason@ualberta.ca

MAYRAND, S., Gastroenterology/Internal Medicine, MUHC-Montreal
General Hospital, D7 120-1650 av Cedar, Montreal, QC H3G 1A4.
Tel: (514) 934-8308 Fax: (514) 934-8375 E-mail: serge.mayrand@muhc.mcgill.ca

MERCER, C.D., General Surgery, Hotel Dieu Hospital, 166 Brock St.,
Kingston, ON K7L 5G2.
Tel: (613) 544-3400 Fax: (613) 546-4854 E-mail: mercerd@hdh.kari.net

MONTANO-LOZA, A. J., 120B-130 University Campus NW,
Ziedler Ledcor Centre, Edmonton, AB T6G 2X8.
Tel: (780) 248-1892 Fax: (780) 248-1895 E-mail: montanol@ualberta.ca

MOUZAKI, M., Paediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children, 555 University Avenue
Toronto, ON M5G 1X8
Email: marialena.mouzaki@sickkids.ca.

MUISE, A., Paediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children, 555 University Avenue
Toronto, ON M5G 1X8
Tel: (416) 813-6171 E-mail address: aleixo.muise@sickkids.ca

O'CONNOR, C., Paediatric Gastroenterology, Hepatology and Nutrition
The Hospital for Sick Children, 555 University Avenue
Toronto, ON M5G 1X8

PARÉ, P., Professeur agrégé de clinique, Médecine, Université Laval,
CHAUQ-Hôpital du St-Sacrement, 1050 Chemin Ste-Foy, Quebec,
PQ G1S 4L8.
Tel: (418) 682-7511 ext. 4603 Fax: (418) 682-7855 E-mail:
pierre.pare@cha.quebec.qc.ca

PATEL, D.G., Professor of Medicine, Gastroenterology, The Ottawa Hospital-
Civic Campus, A1-1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4501 Fax: (613) 761-5269 E-mail: dpatel@ottawahospital.on.ca



PATERSON, W.G., Gastroenterology/Internal Medicine, Professor of Medicine, Biology and Physiology, Hotel Dieu Hospital, Queen's University, 166 Brock St., Kingston, ON K7L 5G2.
Tel: (613) 544-3400 Fax: (613) 544-3114 E-mail: patersow@hdh.kari.net

RENNER, E. L., Director GI Transplantation, University of Toronto, Toronto General Hospital/NCSB 11C-1238, 585 University Ave, Toronto, ON M5G 2N2.
Tel: (416) 340-4800 ext. 6821 Fax: (416) 340-3126 E-mail: Eberhard.Renner@uhn.on.ca

ROMAGNUOLO, J., Division of Gastroenterology, Medical University of South Carolina (MUSC), 96 Jonathon Lucas St., CSB #210, P.O. Box 250 327, Charleston, SC 29425.
Tel: (843) 792-9902 Fax: (843) 792-8395 E-mail: romagnuo@muscd.edu

ROSTOM, A., Division of Gastroenterology, University of Ottawa, Ottawa Hospital-Civic Campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4603 Fax: (613) 761-5068 E-mail: arostom@ottawahospital.on.ca

ROWE, J.A., Assistant Professor of Department of Diagnostic Imaging, Dalhousie University, Rm 3226, Victoria Building, Queen Elizabeth II Health Sciences Centre, Capital District Health Authority, 1276 South Park Street, Halifax, N.S., B3H 2E8.
Tel: (902) 473-7770 Fax: (902) 473-2018 E-mail: jarowe@dal.ca

RUSSOS, P. G., University of Toronto Division of Gastroenterology, Director of Medical Informatics, University Health Network, Toronto General Hospital, 9N-975, 200 Elizabeth St., Toronto, ON M5G 2C4.
Tel: (416) 340-5333 Fax: (416) 340-5335

SALOOJEE, N., Gastroenterology/Internal Medicine, The Ottawa Hospital-General Campus, 501 Smyth Rd., Ottawa, ON K1H 8L6.
Tel: (613) 737-7777 ext. 76420 Fax: (613) 739-6151 E-mail: nsaloojee@ottawahospital.on.ca

SCULLY, L.J., Internal Medicine/Gastroenterology, The Ottawa Hospital-Civic Campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9.
Tel: (613) 761-4830 Fax: (613) 761-5269 E-mail: lscully@ottawahospital.on.ca

SEKAR, A.S.C., Gastroenterology, Parkdale Medical Tower, 504-1081 Carling Ave., Ottawa, ON K1Y 4G2.
Tel: (613) 729-3179 Fax: (613) 729-1026 E-mail: arnisekar@rogers.com

SHAFFER, E.A., Division of Gastroenterology, Department of Medicine, Faculty of Medicine, University of Calgary, 3330 Hospital Dr. NW, Calgary, AB T2N 4N1. E-mail: shaffer@ucalgary.ca



SIS, B., Department of Laboratory Medicine and Pathology, 24-8440 112 ST NW,
5B4 University Hospital, Edmonton, AB T6G 2B7.

Tel: (780) 407-8132 Fax: (780) 407-3009 Email: bsis@ualberta.ca

SOKOLLIK, C., Paediatric Gastroenterology, Hepatology and Nutrition

The Hospital for Sick Children, 555 University Avenue

Toronto, ON M5G 1X8

THOMPSON, W.G., Department of Medicine, University of Ottawa,

Chief of Gastroenterology, Ottawa Civic Hospital, 7 Nesbitt St.,

Ottawa, ON K2H 8C4.

Tel: (613) 761-4147 Fax: (613) 828-7300 E-mail: wgthompson@rogers.com

THOMSON, A.B.R., Division of Gastroenterology, Department of Medicine,

University of Western Ontario, London , ON E-mail: athoms47@uwo.ca

TURNBULL, G.K., Medicine, Dalhousie University,

1278 Tower Rd., Halifax, NS B3H 2Y9.

Tel: (902) 473-4140 Fax: (902) 473-4406 E-mail: turnbull@dal.ca

VANNER, S.J., Gastroenterology/Internal Medicine, Hotel Dieu Hospital,

166 Brock St., Kingston, ON K7L 5G2.

Tel: (613) 544-3400 Fax: (613) 544-3114 E-mail: vanners@hdh.ca

VALENTINO, P.L., Paediatric Gastroenterology, Hepatology and Nutrition

The Hospital for Sick Children, 555 University Avenue

Toronto, ON M5G 1X8

WATTERS, J.M., General Surgery, The Ottawa Hospital-Civic Campus,

1053 Carling Ave., Ottawa, ON K1Y 4E9.

Tel: (613) 761-4780 E-mail: jwatters@ohri.ca

WHITTAKER, J.S., Gastroenterology, 550-1144 Burrard St., Vancouver, BC V6Z 2A5.

Tel: (604) 683-6393 Fax: (604) 681-2421 E-mail: swhittaker@telus.net

WONG, F., The Toronto Hospital, General Division, 200 Elizabeth St.,

Toronto, ON M5G 2C4.

Tel: (416) 340-3834 Fax: (416) 340-5019 E-mail: florence.wong@utoronto.ca



First Principles and the CANMED Objectives

Medical expert

The discussion of complex cases provides the participants with an opportunity to comment on additional focused history and physical examination. They would provide a complete and organized assessment. Participants are encouraged to identify key features, and they develop an approach to problem-solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic base provides the means for the candidate to establish an appropriate management plan based on the best available evidence to clinical practice. Throughout, an attempt is made to develop strategies for diagnosis and development of clinical reasoning skills.

Communicator

The participants demonstrate their ability to communicate their knowledge, clinical findings, and management plan in a respectful, concise and interactive manner. When the participants play the role of examiners, they demonstrate their ability to listen actively and effectively, to ask questions in an open-ended manner, and to provide constructive, helpful feedback in a professional and non-intimidating manner.

Collaborator

The participants use the “you have a green consult card” technique of answering questions as fast as they are able, and then to interact with another health professional participant to move forward the discussion and problem solving. This helps the participants to build upon what they have already learned about the importance of collegial interaction.

Manager

Some of the material they must access demands that they use information technology effectively to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost effective management plans.

Health advocate

In the answering of the questions and case discussions, the participants are required to consider the risks, benefits, and costs and impacts of investigations and therapeutic alliances upon the patient and their loved ones.

Scholar

By committing to the pre- and post-study requirements, plus the intense three day active learning Practice Review with colleagues is a demonstration of commitment to personal education. Through the interactive nature of the discussions and the use of the “green consult card”, they reinforce their previous learning of the importance of collaborating and helping one another to learn.



Professional

The participants are coached how to interact verbally in a professional setting, being straightforward, clear and helpful. They learn to be honest when they cannot answer questions, make a diagnosis, or advance a management plan. They learn how to deal with aggressive or demotivated colleagues, how to deal with knowledge deficits, how to speculate on a missing knowledge byte by using first principals and deductive reasoning. In a safe and supportive setting they learn to seek and accept advice, to acknowledge awareness of personal limitations, and to give and take 360° feedback.

Knowledge

The basic science aspects of gastroenterology are considered in adequate detail to understand the mechanisms of disease, and the basis of investigations and treatment. In this way, the participants respect the importance of an adequate foundation in basic sciences, the basics of the design of clinical research studies to provide an evidence-based approach, the designing of clinical research studies to provide an evidence-based approach, the relevance of their management plans being patient-focused, and the need to add “compassionate” to the Three C’s of Medical Practice: competent, caring and compassionate.

“They may forget what you said, but they will never forget how you made them feel.”

Carl W. Buechner, on teaching.

“With competence, care for the patient. With compassion, care about the person.”

Alan B. R. Thomson, on being a physician.



Prologue

HREs, better known as, High Risk Examinations. After what is often two decades of study, sacrifice, long hours, dedication, ambition and drive, we who have chosen Internal Medicine, and possibly through this a subspecialty, have a HRE, the [Boards] Royal College Examinations. We have been evaluated almost daily by the sadly subjective preceptor based assessments, and now we face the fierce, competitive, winner-take-all objective testing through multiple choice questions (MCQs), and for some the equally challenging OSCE, the objective standardized clinical examination. Well we know that in the real life of providing competent, caring and compassionate care as physicians, as internists, that a patient is neither a MCQ nor an OSCE. These examinations are to be passed, a process with which we may not necessarily agree. Yet this is the game in which we have thus far invested over half of our youthful lives. So let us know the rules, follow the rules, work with the rules, and succeed. So that we may move on to do what we have been trained to do, do what we may long to do, care for our patients.

The process by which we study for clinical examinations is so different than for the MCQs: not trivia, but an approach to the big picture, with thoughtful and reasoned deduction towards a diagnosis. Not looking for the answer before us, but understanding the subtle aspects of the directed history and focused physical examination, yielding an informed series of hypotheses, a differential diagnosis to direct investigations of the highly sophisticated laboratory and imaging procedures now available to those who can wait, or pay.

This book provides clinically relevant questions of the process of taking a history and performing a physical examination, with sections on Useful background, and where available, evidence-based performance characteristics of the rendering of our clinical skills. Just for fun are included "So you want to be a such-and-such specialist!" to remind us that one of the greatest strengths we can possess to survive in these times, is to smile and even to laugh at ourselves.

Sincerely,



Emeritus Distinguished University Professor, U of A

Adjunct Professor, Western University



Acknowledgements

Patience and patients go hand in hand. So also does the interlocking of young and old, love and justice, equality and fairness. No author can have thoughts transformed into words, no teacher can make ideas become behaviour and wisdom and art, without those special people who turn our minds to the practical - of getting the job done!

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When Rebecca, Maxwell, Megan Grace, Henry, Felix, Toby and Grady ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding and kind. For what I was trying to say and to do was to make my professional life focused on the three C's - competence, caring, and compassion - and to make my very private personal life dedicated to family - to you all.



Dedication

Without the caring support from our families for our academic work, the meaning of our accomplishments would disappear.

To my loving wife, children and grandchildren, who give so much happiness and meaning to life.

May good health, happiness and Peace be yours for all the days of your lives.

Je me souviens.

A.B.R. Thomson

*

And to Noah and Zoe (Shaffer Gordon) and Jasper and Macy (Shaffer Nash) who represent the future in this 21st century.

E. A. Shaffer

*

I dedicate the Paediatric Chapter of this Textbook to Professor Anne Griffiths, Chief of the GI Division, the Hospital for Sick Children. Toronto, who managed so skillfully to create a supportive and inspiring atmosphere within our Division that makes it fun to go to work every day.

T. Gonska



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First Principles of Gastroenterology and Hepatology in Adults and Children

Volume I **GASTROENTEROLOGY**





Chapter 1: Common Symptoms and Signs in Gastroenterology

N. Saloojee

With sections authored by:

R.F. Bursey, M.C. Champion, C. Dube, J.M. Fardy, S. Grégoire,
D.G. MacIntosh, D.G. Patel, A. Rostom, N. Saloojee, L.J. Scully,
A.S.C. Sekar, W.G. Thompson and J.M. Watters



1. Introduction / *N.Saloojee, W.G. Thompson and C. Dubé*

Gastrointestinal (GI) symptoms and disease are extremely common in the general population. GI symptoms and disease will be encountered by all physicians, regardless of specialty. It is therefore important for all physicians to have a framework to approach common GI complaints.

Especially in persons with GI symptoms, taking an accurate history is the key to diagnosis and effective management. In taking the history, the first priority is not to miss serious disease, for example GI malignancy. So called “alarm symptoms” need to be sought out. Dysphagia, GI bleeding, significant weight loss, fever and pain waking the patient from sleep are examples of alarm symptoms that should prompt rapid investigation to exclude a serious GI disorder.

It is important to recognize that GI symptoms may indicate organic disease or functional disease. Organic disease refers to a well defined disorder (eg peptic ulcer disease, inflammatory bowel disease, or malignancy). Patients with functional GI disorders are more common. They have symptoms, but no objective abnormality on physical examination or diagnostic testing. The most common such disorders are irritable bowel syndrome (IBS) and functional dyspepsia (FD). The carefully taken history is often helpful in distinguishing organic from functional disease.

A good interview will include an accurate description of the symptom. This will include time of onset, location, duration, character, and radiation. Aggravating or relieving factors (eg eating or defecation), review of other GI symptoms, past history of GI disease or other illness, prior surgery and family history of GI disease should be sought.

A psychosocial history is important for a number of reasons. Functional disease is more frequent in patients with a history of traumatic life events. In patients with organic disease, anxiety or psychologic stress may worsen symptomatology (e.g. inflammatory bowel disease). This history is also important in addressing the patient's concerns. A physician cannot adequately address a patient's concerns if he or she does not know what they are.

The following is a synopsis of common GI symptoms. These notes include a description of the symptom, pathophysiologic considerations, important historical features and physical exam findings, and a brief approach to diagnosis and management. Greater detail can be found in later discussions of specific diseases. The final section of this chapter presents an approach to the examination of the abdomen.

2. Globus / *C. Dubé, W.G. Thompson and N. Saloojee*

Globus refers to the sensation of a lump or foreign body in the throat. The sensation may be intermittent or persistent. In a study of healthy volunteers, 45 % of people have experienced this at least once in their lives (1). Globus often occurs during periods of psychologic or emotional stress. Globus is present between meals, and is not food-related. Patients with this symptom swallow normally and without pain. In other words, globus is not associated with dysphagia or odynophagia.

There is no clear etiology for globus. In the majority of cases, no underlying pathology can be identified. In some cases there is an association between globus and the presence of stress, psychiatric disorders, upper esophageal sphincter dysfunction, esophageal dysmotility, or gastroesophageal reflux disease.



Evaluation of this complaint starts with the history. Ensure that the patient does not have dysphagia, odynophagia or other alarm symptoms such as weight loss. Physical examination is generally unrevealing.

Patients with persistent globus should have an ear, nose and throat (ENT) referral. Laryngoscopy is often done to rule out significant ENT pathology. Barium swallow or endoscopy may also be done to exclude significant pathology.

If investigation is negative, globus is best managed with simple reassurance. If globus is severe, a trial of proton pump inhibitor to suppress gastric acid may be given. This is aimed at reducing acid reflux that might contribute to the symptom (2). Endoscopy is often normal in patients with acid reflux. If appropriate, psychiatric consultation may be undertaken.

3. Heartburn and Regurgitation / C. Dubé, W.G. Thompson and N. Saloojee

3.1. Description

Heartburn refers to a burning sensation experienced behind the sternum. It is due to reflux of gastric acid into the esophagus. Regurgitation is the effortless return of gastric or esophageal contents into the pharynx without nausea, retching or abdominal contractions. Heartburn and regurgitation often occur concomitantly. They are symptoms of gastroesophageal reflux disease (GERD). Heartburn and regurgitation are common symptoms, with 10-20 % of the general population experiencing this at least once weekly (3). Only a minority of people with these symptoms will seek medical advice.

3.2. History

A number of points are important in taking a history. The sensation of heartburn may radiate to the neck. It is often felt after meals, (especially fatty food, spicy food, caffeine or alcohol). It may be aggravated by lying down, bending over, or straining. Unlike angina, heartburn is not worsened by exercise or physical activity. Ischemic heart disease is often misdiagnosed as GERD, and the physician must take an especially careful history to distinguish between the two common conditions. Misdiagnosing ischemic heart disease for heartburn may have serious consequences for the patient, and medicolegal issues for the physician.

It is important to note that patients may mean a variety of things when they use the term heartburn. Physicians should closely question patients as to what symptom they have when they say they have heartburn, indigestion, or dyspepsia. Symptoms associated with GERD may include chest pain, epigastric pain, nausea, globus, or less commonly odynophagia. Waterbrash may be associated. Waterbrash is spontaneous hypersalivation, thought to be due to a vagal reflex triggered by excess esophageal acid. Atypical symptoms of reflux can include chronic cough, wheeze or hoarseness.

Dysphagia may be a result from esophageal dysmotility induced by esophageal acid exposure, or it may result from a reflux induced esophageal stricture. Ongoing gastroesophageal reflux is a risk factor for esophageal cancer which can result in dysphagia, weight loss, bleeding or anemia.

The approach to investigation and management of GERD will be reviewed in the chapter "Esophagus."



4. Dysphagia / A.S.C. Sekar and N. Saloojee

4.1. Description

Dysphagia means difficulty swallowing. Dysphagia is an alarm symptom requiring prompt evaluation to exclude esophageal malignancy.

It can be classified as oropharyngeal dysphagia or esophageal dysphagia. A good history will distinguish between these two entities.

4.2. Approach to dysphagia

Oropharyngeal dysphagia is also known as “transfer” dysphagia. Patients have difficulty initiating a swallow. They may aspirate such that they cough or choke when they eat. They may have nasal regurgitation of food. Often, oropharyngeal dysphagia occurs in a patient with central nervous system pathology (eg. stroke or amyotrophic lateral sclerosis) or neuromuscular disease (eg myasthenia gravis or dermatomyositis).

Esophageal dysphagia may be due to a mechanical reason causing partial obstruction of the esophagus, or to dysmotility of the esophagus (Table 1). Less commonly, dysphagia results from extrinsic esophageal compression. Patients with esophageal dysphagia describe a sense of food or liquid sticking in the retrosternal area.

Table 1. Causes of Esophageal Dysphagia

Mechanical Lesions	Extrinsic Lesions	Motility Disorders
- Reflux stricture - Esophageal cancer - Radiation induced stricture - Post surgical anastomotic stricture - Stricture post caustic ingestion - Zenkers Diverticulum - Esophageal ring or web	- Cervical osteophyte - Goitre - Mediastinal mass - Vascular structure (aberrant subclavian artery)	- Achalasia - Scleroderma - Reflux induced dysmotility - Diffuse esophageal spasm - Hypertensive lower esophageal sphincter - Nutcracker esophagus

Certain historical points are important in evaluating esophageal dysphagia. Duration and rate of progression should be established. It is important to know if the dysphagia is to solids, liquids or both. A history of heartburn or regurgitation may point to a reflux stricture or reflux-induced esophageal dysmotility. Weight loss, bleeding or anemia could indicate esophageal malignancy. Intermittent dysphagia tends to be seen more in disorders of esophageal motility. A lower esophageal ring (Schatzki's ring) may create intermittent dysphagia. This is because the ring is flimsy, and only sometimes delays passage of food.

Food bolus obstruction may occur in a patient with dysphagia. In this situation, a bolus of food becomes impacted in the esophagus. Patients experience chest discomfort. When they swallow liquid, it is almost immediately regurgitated. The patient



will often present to the emergency department and require endoscopic removal of the food bolus. This condition is often seen in persons with eosinophilic esophagitis.

A Zenker's diverticulum is an outpouching immediately above the upper esophageal sphincter. In addition to dysphagia, patients may experience halitosis and aspiration of food retained in the diverticulum.

If a patient is suspected to have oropharyngeal dysphagia, a videofluoroscopy swallowing study (VFSS) can confirm the diagnosis. This is a test in which swallowed contrast material is radiologically visualized. Management of oropharyngeal dysphagia involves treatment of the underlying disorder if possible and dietary modification together with the helpful guidance of a speech language pathologist.

If a patient is suspected to have esophageal dysphagia, evaluation proceeds with either an endoscopy or barium swallow. Barium swallow has the advantage of being noninvasive, however biopsies cannot be taken. If a stricture is identified at endoscopy (EGD, esophagogastroduodenoscopy), multiple biopsies are necessary to establish whether it is benign or malignant.

When a barium swallow and endoscopy fail to identify any pathology, esophageal manometry may be performed to demonstrate an esophageal motility disorder.

Treatment of esophageal dysphagia depends on the underlying cause. Benign strictures due to reflux are managed with endoscopic dilation and acid suppression in the form of a proton pump inhibitor (PPI). Benign anastomotic strictures, radiation strictures and rings are similarly treated with periodic dilation. Esophageal malignancy is managed through a combination of surgery, radiation, chemotherapy and sometimes with the insertion of a palliative endoscopic stent. A small Zenker's diverticulum is generally followed, whereas larger and more symptomatic lesions may need surgery. Endoscopic management of a large Zenker's diverticulum is possible, but is not done in most centres in Canada.

Achalasia can be managed with periodic Botulinum toxin injections to the lower esophageal sphincter, endoscopic balloon dilation or surgery (myotomy). Treatment of Scleroderma esophagus is mainly with high dose proton pump inhibitor. Reflux dysmotility often responds to proton pump inhibitor. Other esophageal dysmotility disorders are sometimes managed with medication such as nitroglycerin or calcium channel blocker. The effect of such treatment is variable. Further extensive detail of these conditions is given in the chapter "Esophagus."

5. Odynophagia / N. Saloojee

5.1. Description

Odynophagia is pain that is felt while swallowing. This symptom is often present with dysphagia. The pain is generally felt in the retrosternal area. Odynophagia is pain, and should be differentiated from the burning discomfort of heartburn.

5.2. Differential diagnosis

Odynophagia implies a break in the mucosa of the esophagus. In an immunocompromised patient the most common cause is infection. The common infections that cause odynophagia are candida, herpes virus and cytomegalovirus. In an immunocompetent patient, an important cause of odynophagia is pill esophagitis. An ingested pill remains in the esophagus and dissolves there, leading to ulceration. This



can be a result of not taking the pill with enough liquid, or lying down too soon after taking the pill. Pill esophagitis is a self-limited condition that resolves without specific therapy. Other less common entities that can cause odynophagia include esophageal cancer, radiation esophagitis, and severe reflux esophagitis. Diagnosis rests on endoscopy and mucosal biopsy. Treatment depends on the underlying condition.

6. Dyspepsia / C. Dubé and N. Saloojee

6.1. Description

The term, “dyspepsia” refers to chronic or recurrent pain or discomfort centred in the upper abdomen. Patients may refer to this as “indigestion”. Various definitions for dyspepsia have been proposed. One such definition is one or more of postprandial fullness, early satiety or epigastric pain. Dyspepsia is a frequent symptom in the general population and, most persons do not seek medical attention.

6.2. Etiology

A variety of conditions can cause dyspepsia. The most common cause is “functional dyspepsia,” also known as “non ulcer dyspepsia.” Functional dyspepsia is the diagnosis in up to 60 % of cases. In such patients, no anatomic or other abnormality can be documented on upper endoscopy (EGD). The pathophysiology of functional dyspepsia is unclear. It may relate to gastric motor dysfunction, visceral hypersensitivity, psychosocial factors or in some cases it may be associated with gastritis due to an infection with *Helicobacter pylori*.

Peptic ulcer disease and atypical symptoms from gastroesophageal reflux disease (GERD) are the most common organic explanations for dyspepsia. A less common, not to be overlooked cause of dyspepsia is gastric cancer.

6.3. History and Physical

The approach to a patient with dyspepsia begins with a search for so called alarm symptoms. If present, the possibility of significant pathology increases, and investigation should take place in a timely fashion. Alarm symptoms include unintended weight loss, persistent vomiting, progressive dysphagia, odynophagia, otherwise unexplained anemia, gastrointestinal bleeding, and jaundice. Older age also increases the likelihood that dyspepsia is due to organic pathology. It has been suggested that in Canada, an age greater than 50 years be considered an alarm symptom. If the person with dyspepsia is over the age of 50, or if there are alarm symptoms at any age, EGD needs to be performed promptly.

In a young patient with no alarm symptoms, it is very unlikely that dyspepsia will be due to malignancy.

Numerous other disorders can lead to pain in the epigastrium. Careful history will often allow for identification of these. For example, the pain of biliary colic may be present in the epigastric area, but is often in the right upper quadrant as well. Irritable bowel may cause pain in the upper abdomen, but is associated with altered bowel pattern and relief of pain with defecation. As mentioned before, and to emphasize, be certain to take the appropriate history to exclude ischemic heart disease.

Physical examination is generally unhelpful. Epigastric tenderness is a common, but non-specific finding.



6.4. Investigation and Management

Investigation of dyspepsia generally entails bloodwork. This will reveal if the patient is anemic or has abnormal liver enzymes. Patients with alarm symptoms, over the age of 50 even if there are no alarm symptoms, and patients with persistent dyspepsia despite empiric trials of treatment should undergo endoscopy. If resource availability precludes a timely endoscopy, an upper GI series can be done. If a lesion is seen on the upper GI series, a prompt EGD must be arranged.

In younger patients without alarm features, non-invasive testing for *Helicobacter pylori* (*H. pylori* serology or urea breath test) is recommended. If present, *H. pylori* should be treated. The rationale is that if the patient has an ulcer, treating the infection will eliminate the problem of recurrent ulcers. Also, a minority of patients with functional dyspepsia may improve. In young patients without alarm features, another option is an empiric trial of acid suppressive (proton pump inhibitor) or prokinetic (domperidone) therapy. If these approaches fail and dyspepsia persists, endoscopy can be done.

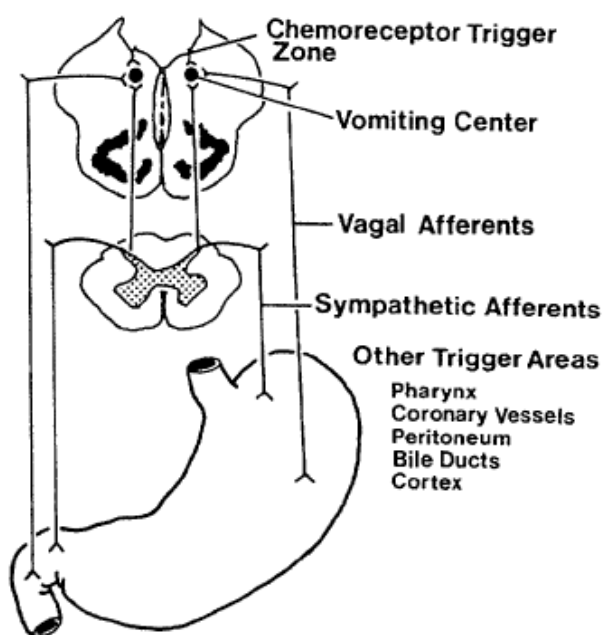
The results of the treatment of functional dyspepsia is disappointing. Some patients may respond to simple reassurance, dietary manipulation, treatment of *H. pylori*, trials of proton pump inhibitor, prokinetic or low dose tricyclic antidepressant (eg. amitriptyline 10-25 mg po once nightly).

7. Nausea and Vomiting / M.C. Champion and N. Saloojee

7.1. Description

Nausea is the unpleasant feeling of being about to vomit. Vomiting is the forceful evacuation of stomach contents through the mouth. Vomiting should be differentiated from regurgitation, which is an effortless process. Retching is differentiated from vomiting in that no gastric contents are expelled. Nausea generally precedes vomiting.

Vomiting may partially relieve nausea. Vomiting has developed as a defence mechanism, allowing the individual to expel ingested toxins or poisons.



7.2. Mechanism (Figure 1)

Figure 1. The vomiting center and chemoreceptor trigger zone control vomiting. Peripheral trigger areas send visceral afferent impulses. These excite the vomiting center into action.



Normal motor function of the upper gastrointestinal tract depends on an interplay between the central nervous system and the gut (Figure 1). The neural pathways that mediate nausea are the same as those that mediate vomiting. During nausea, there is gastric relaxation and frequent reflux of proximal duodenal contents into the stomach.

Trigger areas for vomiting exist in the pharynx, cardiac vessels, peritoneum, bile ducts, stomach and cerebral cortex. Excitation of these areas leads to activation of the vomiting centre in the medulla. This is mediated through sympathetic and parasympathetic (vagal) afferents. The chemoreceptor trigger zone exists on the floor of the fourth ventricle on the blood side of the blood-brain barrier. Neurotransmitters, peptides, drugs and toxins may activate the chemoreceptor trigger zone which in turn activates the vomiting centre.

Activation of the vomiting centre leads to forceful abdominal wall contraction, contraction of the pylorus, and relaxation of the lower esophageal sphincter. The glottis closes, and gastric contents are then forcefully expelled.

7.3. History and Differential diagnosis

The differential diagnosis of nausea and vomiting is wide. As alluded to above, nausea and vomiting may be triggered by numerous pathologies arising in many different systems. A good history is therefore critical. Such a history will include inquiry into the timing of the nausea and vomiting. Associated gastrointestinal symptoms such as abdominal pain or diarrhea should be sought. Associated non gastrointestinal symptoms such as headache, chest pain or vertigo are important. As always, obtain the past medical history, past surgical history, family history, and list of medications.

Further questions will suggest themselves as one searches for the specific cause. Table 2 presents a list of more common causes. This list is not exhaustive.



Table 2. Causes of Nausea and Vomiting

➤ Disorders of the Gut	➤ Psychiatric disorders
○ Mechanical Obstruction	○ Psychogenic vomiting
○ Gastrointestinal Malignancy	○ Anorexia Nervosa
○ Peptic Ulcer Disease	○ Bulimia
○ Cholecystitis	○ Anxiety / Depression
○ Pancreatitis	
○ Hepatitis	➤ Endocrine causes
○ Gastroenteritis	○ Diabetic Ketoacidosis
○ Crohn disease	○ Hyperthyroidism
○ Functional Gastrointestinal disorders	○ Addison's disease
○ Chronic Intestinal Pseudoobstruction	○ Hyperparathyroidism
○ Gastroparesis	○ Hypoparathyroidism
➤ CNS disorders	➤ Cardiac disease
○ Migraine	○ Acute Myocardial Infarction
○ CNS Malignancy	○ Congestive Heart Failure
○ Abscess	
○ Meningitis	➤ Infections
○ Cerebrovascular Accident	➤ Medications, Drug Withdrawal
○ Hydrocephalus	➤ Vestibular disorders
	➤ Uremia
	➤ Pregnancy
	➤ Chronic Pain

Given the wide differential, patients with nausea and vomiting should have a complete physical examination. Attention should be paid to signs of volume depletion, and to clues as to the cause of these symptoms.

7.4. Investigation and Management

Investigations ordered depend on the severity of the nausea and vomiting and whether a specific cause is suggested by clinical evaluation. Potential tests include bloodwork, diagnostic imaging of the abdomen and CNS, and endoscopy.

Management rests on treatment of the underlying disorder and correction of fluid and electrolyte imbalance. A number of medications may be used for their antiemetic action. These include antihistamines such as diphenhydramine, phenothiazines, and gastric prokinetics (domperidone, metoclopramide). Domperidone is generally preferred over metoclopramide as it does not cross the blood-brain barrier and therefore does not cause CNS side effects. Ondansetron is a serotonin antagonist used primarily in chemotherapy-induced nausea and vomiting.



8. Anorexia / M.C. Champion and N. Saloojee

8.1. Description

Anorexia is a loss of, or lack of appetite. Anorexia is a common and non-specific symptoms. It can be a presenting feature of serious pathology such as malignancy. Alternatively, it may arise from a psychologic or functional disorder.

8.2. History and Physical

A thorough history is needed due to the non-specific nature of this symptom. A calorie count may be helpful to assess the actual intake of food. Any weight loss that has occurred should be documented. Physical examination is often normal.

8.4. Differential Diagnosis

Many diseases feature a loss of appetite. These include gastrointestinal pathology, malignancy, chronic renal failure, and congestive heart failure. Psychiatric illnesses such as depression, anxiety, and anorexia nervosa should be considered.

8.5. Approach to Investigation and Management

Choice of investigations for anorexia depends on the severity of illness and whether specific clues are suggested by history and physical. If no organic disease is discovered, psychiatric problems may be present.

9. Gas and Bloating / W.G. Thompson and N. Saloojee

9.1. Description

Patients describing excess gas may be experiencing belching, flatulence, or bloating. Excessive belching or burping is sometimes associated with aerophagia (air swallowing). A degree of aerophagia is physiological, but it may become exaggerated in some patients. Borborygmi is the name given to the noises generated as air and fluid gurgle through the gut. Flatulence is a physiologic phenomenon due to the production of gas by colonic bacteria. Bloating is a perception of abdominal distension. These symptoms often occur together.

9.2. Aerophagia

Commonly, aerophagia is an unwanted but learned habit. Other mechanisms of aerophagia include gum chewing, drinking carbonated drinks, and rapid eating. Stomach gas has the same composition as the atmosphere.

Belching or burping is a physiologic mechanism to relieve gastric overdistention with gas. It occurs after a large meal or as a result of aerophagia. Excess belching or burping is rarely a manifestation of significant pathology. It is generally not investigated further unless accompanied by other, more concerning, symptoms.

9.3. Flatulence

Flatulence is a physiologic process. Normally, the gut contains 100 to 200 mL of gas. An average person on a normal diet emits between 500 mL and 1500 mL per day. Excess flatulence is a subjective concern that is defined by the patient's perception. Hydrogen, carbon dioxide, methane and swallowed nitrogen comprise 99% of colonic gas. The remaining 1% consists of trace gases that often have a strong odour. Such



gases include hydrogen sulphide, ammonia, skatole, indole and volatile fatty acids. Most emitted gas originates in the colon. Some carbohydrates such as cellulose are not assimilated in the small intestine. They arrive intact in the colon. Here, resident bacteria digest them to produce hydrogen, carbon dioxide, methane and trace gases. Intestinal microbiota differs from person to person. Some bacteria produce hydrogen, while others consume it. Differing intestinal organisms can be an explanation for excess flatulence.

Excess flatulence is rarely a sign of serious disease. If symptoms such as weight loss or diarrhea are present, investigations to exclude malabsorption may be undertaken. If a patient is concerned about flatus, treatment may include dietary alteration, simethicone (an agent which causes gas bubbles to break), beano (an agent which absorbs gas), or bismuth. On occasion a trial of antibiotic may be given if small bowel bacterial overgrowth is suspected.

9.4. Bloating

9.4.1. Description

Patients experiencing bloating and distention are often convinced that it is due to excess intestinal gas. Despite visible distention in these patients, abdominal x-rays and computerized tomography (CT) show no increase in bowel gas: gas volume in such individuals is not abnormal. Flatulence may temporarily relieve the perception of bloating.

Gut hypersensitivity may explain the sensation of abdominal bloating. The hypersensitive gut feels full with smaller than usual amounts of gas and fluid and abdominal muscles relax to accommodate the perceived distention. Abdominal girth of female irritable bowel syndrome (IBS) patients complaining of distention may increase 3–4 cm over an eight-hour day. CT has demonstrated increased abdominal girth despite unchanged gas content or distribution. There were no corresponding changes in control subjects.

When patients deliberately protrude their abdomens, the configuration is different from when they are bloated, so a conscious mechanism poorly explains increased abdominal girth.

The reality of the phenomenon of bloating is indisputable, however the mechanism remains a mystery.

9.4.2. Clinical Features

Occasionally, bloating occurs in about 30% of adults and is frequent in 10%. Amongst those with functional disorders such as irritable bowel syndrome or functional dyspepsia, the figures are much higher. Bloating is often the most troublesome symptom of these conditions. Often, the abdomen is flat upon awakening, but distends progressively during the day. The distention often disappears with sleep. Patients complain of the need to loosen their clothing. Bloating may occur quickly, even over just a minute. It is often aggravated by eating and relieved by lying down. Menstrual periods and stress may worsen bloating in some persons.



9.4.3. Differential Diagnosis

When assessing a patient with bloating and visible abdominal distension, the physician should exclude conditions such as ileus, bowel obstruction, ascites, or intrabdominal tumour. Ileus is a condition in which intestinal motility is reduced. The small and large bowel dilate. This can lead to abdominal distention. Ileus can occur due to medication such as narcotics. It is often seen in the postoperative state. A patient with a bowel obstruction will also have a visibly distended abdomen.

The abdomen can be distended by the presence of fluid in the peritoneal cavity. This condition is called ascites. Rarely, a large tumour in the peritoneal cavity can lead to abdominal distention. Generally these conditions can be separated out with a history and physical as other signs and symptoms are present. If necessary, imaging with abdominal X ray or ultrasound is definitive.

On its own, bloating is not a symptom of organic disease, and should not prompt investigation.

10. Constipation / C. Dubé, W.G. Thompson and N. Saloojee

10.1. Description

Constipation is also known as obstipation. A precise definition of constipation is elusive due to the variability of what constitutes a normal bowel pattern. Ninety five percent or more of the population have between three movements per day and three movements per week. Some physicians consider that fewer than three movements a week without discomfort or dissatisfaction is normal. Most would agree that hard bowel movements that are difficult to pass constitute constipation even if they occur as often as daily.

The most common terms which patients use to describe constipation are “straining”, hard stools” and the “ inability to have a bowel movement”. Therefore, constipation is a symptom that does not always correlate with infrequent passage of bowel movements.

Constipation is best understood as persistent symptoms of difficult evacuation. This may include straining, stools that are excessively hard, unproductive urges, infrequent bowel movements, or a feeling of incomplete evacuation, often defecation.

10.2. Mechanism

Many conditions can result in constipation. The most common kind of constipation is that associated with irritable bowel syndrome (Table 3). Constipation may be due to primary colonic conditions. Examples are an obstructing colon cancer or idiopathic slow-transit constipation.

Constipation may also be caused by systemic diseases. For example, endocrine disorders (diabetes mellitus, hypothyroidism), metabolic disturbances (hypo- or hypercalcemia), neurologic disorders (multiple sclerosis, Parkinson’s disease), muscular disease (systemic sclerosis, myotonic dystrophy), or medications (opiates, anticholinergic agents).

Proper defecation requires normal transit through the proximal colon, an intact gastrocolic response to a meal, and normal mechanisms of defecation. The gastrocolic response is simply an increase in colonic motility triggered by gastric distention. This reflex is responsible for the urge to defecate after a meal. Defecation requires an intact



defecation reflex. In this reflex, stool in the rectum triggers an urge to defecate. Coordinated relaxation of the puborectalis and external anal sphincter muscles must occur.

Table 3. Some causes of chronic constipation

➤ Primary diseases of the colon ○ Stricture ○ Cancer ○ Anal fissure ○ Irritable bowel syndrome ○ Idiopathic slow-transit constipation	➤ Pelvic floor dyssynergia
➤ Pharmacologic ○ Opiates ○ Antidepressants ○ Anticholinergic agents ○ Calcium channel blockers ○ Iron ○ Laxative abuse	➤ Metabolic disturbances ○ Hypercalcemia ○ Hypothyroidism ○ Diabetes mellitus
	➤ Neurologic and muscular disorders ○ Parkinson's disease ○ Spinal cord lesion ○ Multiple sclerosis ○ Autonomic neuropathy ○ Hirschsprung's disease ○ Systemic sclerosis (Scleroderma) ○ Myotonic dystrophy
➤ Pregnancy	

10.3. Important Points on History and Physical Examination

Taking a good dietary history is important to help manage the person with constipation. This involves an assessment of daily fibre intake, fluid consumption and meal patterns. Many constipated patients do not eat breakfast. As mentioned, colonic motility increases after meals as part of the gastrocolic reflex.

Physical activity stimulates colonic motility. Therefore one should inquire about exercise. Physical impairments leading to impaired mobility will contribute to constipation.

The list of medications should be reviewed. A history of prolonged intake of cathartics, often in the form of herbal remedies or teas, should be sought. Prolonged use of stimulant laxatives can sometimes lead to permanent impairment of colonic motility.

Symptoms such as bloating, abdominal pain relieved with defecation, and alternation of constipation with diarrhea should be sought. These symptoms suggest a diagnosis of irritable bowel syndrome. Stress incontinence suggests a problem with pelvic floor musculature. Weight loss or rectal bleeding raise the possibility of an obstructing colon cancer. Some persons with constipation may leak fluid stool around the inspissated stools, leading to “overslow diarrhea.”

There may be the presence of abdominal distension or palpable stools, but the physical examination of patients with constipation is generally unrevealing. Digital rectal examination (DRE) is useful to identify fissures or hemorrhoids. These may cause constipation, since the patient tries to avoid pain induced by defecation. Fissures or hemorrhoids may also result from constipation. A lax anal sphincter may sometimes



suggest a neurologic disorder. The presence of stools in the rectum on DRE may sometimes suggest an impaired defecation reflex.

10.4. Approach to Diagnosis

Constipation is a common symptom. Many patients, particularly those that are younger or those with milder symptoms will need minimal or no investigation.

If investigation is deemed necessary, bloodwork including hemoglobin, inflammatory markers such as erythrocyte sedimentation rate and c reactive protein, blood sugar, thyroid function tests and serum calcium may be done. Inflammatory markers may be elevated in persons with Crohn disease. Crohn's is an inflammatory bowel disease which may sometimes

lead to colonic stricture. Lower endoscopy with either sigmoidoscopy or colonoscopy may be done to rule out structural lesions such as a colonic stricture, malignancy or anal fissure. Endoscopic testing may also detect melanosis coli, a disorder in which there is hyperpigmentation of the colonic mucosa due to chronic use of laxatives. If a patient is over 40 years of age or if alarm symptoms (such as rectal bleeding or weight loss) are present, colonoscopy would be indicated as opposed to sigmoidoscopy. Sigmoidoscopy does not assess the more proximal colon. Alternate tests to assess the structure of the colon include air contrast barium enema or CT colonography. CT colonography is also known as virtual CT and provides radiologic images of the interior of the colon. This test does not allow for biopsy or other intervention, but may be done if colonoscopy cannot be performed or is not readily available.

Occasionally other tests are done. A gut transit study may be revealing. Twenty radiopaque markers are ingested and daily plain abdominal x-rays are taken. If 80% of the markers have disappeared in five days, the transit time is said to be normal. When the transit time is longer than 5 days, the position of the markers may help distinguish slow colonic transit from an anorectal disorder: if remaining markers are seen throughout the colon, slow colonic transit is present. If remaining markers are all in the rectum, an anorectal disorder is present. Anorectal manometry and defecography, are then required.

10.5. Approach to Management

In the majority of patients, a specific disorder is not diagnosed. In these cases, management includes education as to the great variability of bowel habits among the general population. Reassurance is sometimes all that is required.

Where further intervention is needed, dietary changes can be made. This includes the intake of at least three meals a day and adequate amounts of liquids. While no data proves the efficacy of increased fluid intake, 6 to 8 cups per day of water are often recommended. A high fibre intake can be achieved with increased dietary fibre or a commercial fibre product. This increases stool bulk and frequency of bowel movement. The recommended amount of dietary fibre is 20 to 35 g/day. High doses only cause adverse effects, and are not recommended. Regular exercise is often helpful, as it stimulates colonic motility.

Chronic severe constipation may require the use of osmotic agents such as magnesium, lactulose or polyethylene glycol solution. The long-term use of stimulant laxatives such as bisacodyl or senna should be avoided.



More details about this important and common problem are given in the chapter “Colon”.

11. Diarrhea / W.G. Thompson and N. Saloojee

11.1. Description

Diarrhea is defined as bowel movements that are too frequent, too loose or both. Three or more bowel movements per day, or a stool weight of over 200 grams / day is generally considered to be abnormal. In clinical practice, stool weight is rarely measured. Diarrhea is frequently accompanied by urgency. It is important to determine if the patient is using the word “diarrhea” when in fact they have fecal incontinence.

11.2. Mechanism

The four mechanisms of diarrhea are osmotic, secretory, inflammatory and rapid transit. In many instances of diarrhea, two or more of these four mechanisms are at work. Therefore, these mechanisms provide a framework for understanding diarrhea, however they are seldom of great help when approaching a patient in clinical practice. In clinical practice, an anatomical approach is much easier and more useful (please see the chapter on Small Intestine).

If the osmotic pressure of intestinal contents is higher than that of the serum, fluid is drawn into the lumen of the intestinal tract and osmotic diarrhea results. This may result from malabsorption of fat (e.g. celiac disease) or of lactose (e.g. in intestinal lactase deficiency).

Certain laxatives, such as lactulose and magnesium hydroxide, exert their cathartic effect largely through osmosis. Certain artificial sweeteners, such as sorbitol and mannitol, have a similar effect. Beware of diabetic candies causing diarrhea. Characteristically, osmotic diarrhea ceases when the patient fasts or sleeps.

Secretory diarrhea occurs when there is a net secretion of water into the intestinal lumen. This may occur with bacterial toxins, such as those produced by *E. coli* or *Vibrio cholerae*. It may occur with hormones, such as vasoactive intestinal polypeptide (VIP). Excess VIP is produced by some pancreatic islet cell tumours. In these rare tumours, VIP provokes adenylate cyclase activity in the enterocyte (intestinal epithelial cell). The result is increased cyclic AMP and intestinal secretion. A similar effect may occur as a result of excess bile salts in the colon. Secretory diarrhea does not diminish with fasting, and the patient will be up at night-time to have bowel motion.

Exudative diarrhea results from direct damage to the small or large intestinal mucosa. This interferes with the absorption of sodium salts and water and is complicated by exudation of serum proteins, blood and pus. Infectious or inflammatory disorders of the gut cause this kind of diarrhea.

Acceleration of intestinal transit may result in diarrhea. An example of this is diarrhea related to hyperthyroidism. The rapid flow impairs the ability of the gut to absorb water, resulting in diarrhea.

11.3. Important Points on History and Physical Exam

The duration of diarrhea is important. If diarrhea has been present for less than two weeks, it is categorized as being acute. Acute diarrhea is almost always due to an



infection or food poisoning. Chronic diarrhea, defined as lasting over 2 weeks, has many potential etiologies and often requires investigation.

Knowing the volume of diarrhea can provide a clue to the cause. Distal colonic pathology generally leads to a small volume diarrhea. Small bowel or proximal colonic pathology generally leads to a large volume diarrhea. Patients may have difficulty in categorizing the volume of diarrhea, and asking them to describe their stool volume as “little squirts” or “big gushes” may be helpful.

Further history includes knowing the characteristics of the diarrhea, such as frequency and consistency. Associated symptoms such as rectal bleeding, weight loss, and abdominal pain should be elicited. Foul smelling, floating or oily stool may indicate fat malabsorption. The presence of intermittent normal or constipated bowel movements suggests irritable bowel syndrome. A thorough medication history is necessary. Recent antibiotic use is of particular importance since this is a risk factor for *Clostridium difficile*, a common cause of diarrhea. Other questions include travel history, exposure to individuals with diarrhea, and sexual practices which might lead to immune deficiency (e.g. HIV/AIDS).

There are many causes of diarrhea, some of which are summarized in Table 4. This list is not exhaustive. Each of these causes will suggest further questions to the interviewer. Physical exam is generally more useful in assessing the severity of diarrhea, rather than finding a cause. Volume status is best determined by looking for changes in pulse and blood pressure.

Table 4. Differential Diagnosis of Diarrhea

➤ Acute Diarrhea	
○ Infection	○ Initial Presentation of Chronic Diarrhea
○ Food Poisoning	
➤ Chronic Diarrhea	
➤ Gastric	➤ Pancreas
– Dumping syndrome	– Chronic pancreatitis
	– Islet cell tumours (e.g. VIPoma)
➤ Small intestine	➤ Drugs
– Celiac disease	– Antibiotics
– Lymphoma	– Alcohol
– Whipple’s disease	– Laxatives
– Parasitic infection (ex Giardia lamblia)	– Nonsteroidal anti-inflammatories
– Bacterial overgrowth	– Sorbitol, fructose
– Bile salt malabsorption	– Many others
– Diabetic Autonomic Neuropathy	
– Short Bowel Syndrome	➤ Metabolic/Endocrine
	– Hyperthyroidism
➤ Large bowel	– Addison’s disease
– Villous adenoma / Colon cancer	– Diabetes



- Inflammatory bowel disease (ulcerative colitis, Crohn disease)
- Irritable bowel
- Functional diarrhea
- HIV related infections
- Carcinoid syndrome

11.5. Investigation and Management

Acute diarrhea is self-limiting and may not need investigation. If it is more severe, investigation focuses on searching for an infection through stool tests for culture and sensitivity, ova and parasites and *Clostridium difficile* toxin. Viral studies are important in infants.

As noted, the differential diagnosis of chronic diarrhea is long. Testing will vary depending on the individual case, case, but may include bloodwork, stool testing, gastroscopy and small bowel biopsy, colonoscopy and biopsy, and imaging of the small bowel and abdomen.

Practice points

- Gastrointestinal complaints are common in the general population
- Fear of underlying malignancy is a common reason for a complaint to come to medical attention
- Functional GI disorders are common
- Thorough and careful history-taking is crucial in gastroenterology. This includes family history for such disorders as malignancy, celiac disease, IBD, and liver disease
- Alarm symptoms such as weight loss, bleeding, dysphagia should lead to prompt investigation for organic pathology
- The history may lead to a differential diagnosis (increasing pre-test probability of a physical finding), so that additional care and the use of supplemental tests will be used on physical examination
- Physical examination involves much more than just the abdomen. It should include a thorough examination of all parts of the body, looking for extraintestinal signs such as may occur in persons with cirrhosis, celiac disease, inflammatory bowel disease, and nutritional deficiencies

12. Malnutrition / D.G. Patel

12.1. Description

Nutrition may be defined as the process by which an organism utilizes food. This complex process involves ingestion, digestion, absorption, transport, utilization and excretion. Any alteration in one or many of these factors can produce malnutrition. Globally, primary malnutrition due to lack of food is the most common cause. Malnutrition in a developed country such as Canada may be due to inadequate intake of nutrients, malabsorption and/or the hypercatabolism accompanying a critical illness. Protein-energy malnutrition is increasingly recognized in eating disorders such as anorexia nervosa.



12.2. Mechanism

More common reasons for malnutrition include the following.

- Lack of food intake due to anorexia, depression or symptoms exacerbated by food intake (dysphagia, odynophagia, nausea, vomiting or abdominal pain)
- Maldigestion. Examples include pancreatic disease and bile salt deficiency due to cholestatic hepatobiliary disease or ileal disease
- Malabsorption. For example, mucosal disease of the small intestine or loss of intestinal surface area due to resection
- Excessive loss of nutrients. For example, protein-losing enteropathy seen in many intestinal disorders
- Medications. For example, cholestyramine used for bile salt induced diarrhea can worsen steatorrhea in the case of an extensive ileal resection
- Alcoholism. Alcoholics rarely consume a well-balanced diet. They depend heavily on “empty” calories from alcohol. Protein and vitamin deficiencies, particularly of the B-complex group, are extremely common. Alcohol is a toxic agent that even in the presence of adequate nutritional intake can produce damage to the pancreas, liver and small bowel mucosa, aggravating malnutrition

12.3. Signs of Malnutrition

- Weight loss
- Muscle wasting. Particularly evident in the temporal area and dorsum of the hand between the thumb and index finger. It suggests protein-calorie deficiency
- Signs of fat soluble vitamin (ADEK) deficiency. Decreased visual acuity, low bone mass, and easy bruising
- Cheilitis. Fissures at corners of mouth due to riboflavin (B2), iron deficiency.
- Glossitis. Due to B12, folate or iron deficiency
- Hepatomegaly. Fatty liver is a common finding in protein malnutrition or alcoholism.
- Peripheral neuropathy. Decreased position sense, decreased vibration sense or ataxia may result from B12 deficiency
- Anemia. Can be due to iron, folate or B12 deficiency. Can be due to anemia of chronic disease
- Peripheral edema (Hypoalbuminemia)

13. Acute Abdominal Pain / J.M. Watters and N. Saloojee

13.1. Description

Acute abdominal pain refers to pain that has been present for a short period of time, generally less than 24 hours. The term *acute abdomen* is best used to describe abdominal pain severe enough to suggest a serious intraabdominal condition. Although not entirely accurate, acute abdomen is sometimes used synonymously with peritonitis (peritoneal inflammation). Since some patients with an acute abdomen require resuscitation and early surgical treatment, it is important to assess the patient and establish a plan of management as soon as possible. The initial goal if the patient has an acute abdomen is not necessarily to make a definitive diagnosis, but rather to identify if the patient requires prompt surgical intervention.



13.2. Mechanism

Acute abdominal pain may be referred to the abdominal wall from intraabdominal organs (visceral pain) or may involve direct stimulation of the somatic nerves in the abdominal wall (somatic pain). Peritonitis results in somatic pain.

Visceral pain arises from such things as tension in the bowel wall (e.g., distension or vigorous contraction), mesenteric traction, or irritation of the mucosa or serosa of the bowel (e.g., chemical irritation, bacterial contamination, ischemia). Foregut pain is typically epigastric in location, midgut pain is central, and hindgut pain is felt in the lower abdomen. Organs that are bilateral give rise to visceral pain that is predominantly felt on one or the other side of the body.

Somatic pain is more precise in location than visceral pain. That is the main difference between the two. Somatic pain corresponds more directly to the anatomic site of the underlying pathology. Somatic pain occurs with stimulation of pain receptors in the peritoneum and abdominal wall.

Occasionally, pain is referred to the abdomen from extra-abdominal sites (e.g. lower lobe pneumonia). Unusually, acute abdominal pain is a feature of systemic disease (e.g. diabetic ketoacidosis).

13.3. History

The history should focus on the chronology, location, intensity and character of the pain. Aggravating and relieving factors should be sought. As always, inquire about associated symptoms, past medical and surgical history, medications, family and social history (including smoking, alcohol and substance abuse).

Severe pain of sudden onset may suggest a catastrophic event (e.g. perforation of an ulcer, intestinal ischemia, or rupture of an aortic aneurysm). Pain that occurs episodically is sometimes referred to as “colic”. Colicky pain corresponds to peristaltic waves. It eases or disappears between waves. One example is the intermittent, mid-abdominal pain of uncomplicated small bowel obstruction. Another is the intermittent flank pain radiating anteriorly to the groin that accompanying ureteric obstruction from a renal stone. Biliary “colic”

is a misnomer, in that biliary pain is typically steady. It is usually felt in the epigastrium or right upper quadrant.

As mentioned visceral pain is poorly localized as compared to somatic pain. Nevertheless, the initial location of pain can provide a clue as to the origin. Also, radiation of pain may provide important clues to diagnosis. Irritation of the diaphragm, from peritonitis, for example, may cause shoulder tip pain. Biliary tract pain may radiate to the right scapular region. Pain arising from retroperitoneal structures may be perceived in the back (e.g. pancreatitis, leaking abdominal aortic aneurysm).

The character and subsequent evolution of acute abdominal pain may give a clue as to the site and nature of the underlying pathology. For example, pain with movement (e.g. riding in a car or walking) suggests the presence of peritonitis.

13.4. Associated Symptoms

Anorexia, nausea and vomiting are more common in diseases of the gastrointestinal tract but are not specific to a particular disorder. Abdominal distention and obstipation may suggest intestinal obstruction. Bloody diarrhea may arise from severely inflamed, ulcerated



or infarcted bowel. Jaundice points to a hepatobiliary problem. In women, an accurate menstrual history is important. Urinary symptoms may suggest a genitourinary diagnosis (e.g. pyelonephritis, renal stones).

13.5 Physical Examination

In some patients with acute and severe abdominal pain, analgesics are delayed until after the physical exam. This generally applies to a subset of such patients presenting for evaluation in the emergency department. Analgesia may impair the sensitivity of physical examination when signs are subtle. Medication should be given promptly once the assessment has been completed. It should be given if the physical exam will be unavoidably delayed.

The physical exam begins with an evaluation of blood pressure, pulse and respiratory rate. Abdominal pathology may lead to systemic effects such as hypotension, tachycardia, or tachypnea. A careful physical examination will also identify pertinent extra-abdominal findings such as jaundice or lymphadenopathy.

Examination of the abdomen is performed with the patient supine. The steps are inspection, auscultation, palpation and percussion. Inspection of the abdomen should note any distention, mass, hernia, or scar. Of note is that the patient with peritonitis typically lies immobile. This is because any movement increases peritoneal irritation and pain.

Unlike examination of other systems, auscultation is often performed before palpation. Palpation can stimulate intestinal peristalsis and alter the result of auscultation. Auscultation may reveal a range of bowel sounds. A silent abdomen indicates an ileus or lack of intestinal peristalsis. Causes of ileus include the postoperative state, medications such as narcotics, or peritonitis. Hyperactive bowel sounds may be heard when a bowel obstruction is present. Bruits are sounds created by turbulent flow through a stenotic artery. When present, they suggest vascular disease.

Gentleness is the key to abdominal palpation. Palpation detects and localizes tenderness, muscle guarding, rigidity and masses. Palpation should begin in an area away from where pain is experienced, progressing to the area of pain last. Involuntary guarding and rebound tenderness are signs of peritonitis. Guarding refers to contraction of abdominal wall muscles when the abdomen is palpated. Guarding is only important if muscle contraction is involuntary. Involuntary guarding occurs as a protective mechanism when peritoneal inflammation (peritonitis) is present. Voluntary guarding occurs when a patient tenses abdominal wall muscles in response to that abdominal wall pressure. It is a meaningless finding that is commonly seen. Guarding may be localized (e.g. uncomplicated appendicitis) or generalized throughout the abdomen (e.g. perforated appendicitis with diffuse contamination of the peritoneal cavity). In some instances of peritonitis, the muscles are in a state of continuous contraction. They are rigid or “board-like”, even without palpation. In subtle situations, peritonitis is suggested by the triggering of pain in the area of suspected pathology (e.g., appendicitis) through palpation elsewhere on the abdominal wall, by having the patient cough or by gently shaking the pelvis.

Gentle percussion is also a very useful way to assess peritoneal irritation, as well as to assess the nature of abdominal distention. Rebound tenderness, another sign of



peritonitis, is elicited by deeply palpating the area of concern and then suddenly releasing the abdominal wall. Severe pain felt on release of the abdominal wall is rebound tenderness. This manoeuvre can be very distressing to the patient with peritonitis, so it is often not done. Rectal and pelvic examinations should be carried out and recorded by at least one examiner. The sites for inguinal and femoral hernias should be specifically examined. Femoral pulses should be palpated.

13.6. Differential Diagnosis

The list of causes of abdominal pain is long. Table 5 provides a list of common or important conditions to consider. The list is not meant to be complete. Intra-abdominal conditions requiring surgery (open or laparoscopic) are the most common causes of an acute abdomen. Some conditions require immediate surgery (e.g. ruptured abdominal aneurysm). They must always be included in the differential diagnosis, therefore, and confirmed or excluded promptly. In other instances, the specific diagnosis and the need for surgery may take some time to establish. The likelihood of specific diagnoses varies to an extent with the age of the patient. Clinical presentations are more likely to be atypical in the elderly and in patients with coexisting conditions (such as diabetes or stroke). Particular care must be taken to not overlook an important intra-abdominal process in such patients.

One must always consider in the differential diagnosis: (1) intra-abdominal conditions for which surgery is not indicated (e.g. acute pancreatitis, (2) extra-abdominal (e.g. pneumonia) or systemic conditions (e.g. diabetic ketoacidosis) that can be accompanied by acute abdominal pain.

Table 5. Differential Diagnosis of Acute Abdominal Pain

○ Peptic Ulcer Disease	○ Bowel obstruction
○ Mesenteric ischemia/infarction	○ Diverticulitis
○ Gastroenteritis	○ Ruptured Abdominal Aortic Aneurysm
○ Cholecystitis	○ Incarcerated hernia
○ Pancreatitis	○ Hepatitis
○ Appendicitis	○ Pyelonephritis / Cystitis
○ Functional Conditions (eg. irritable bowel syndrome, non ulcer dyspepsia)	○ Gynaecologic conditions (ex. pelvic inflammatory disease, ruptured ectopic pregnancy)
○ Inflammatory Bowel Disease	○ Extra abdominal and Systemic Causes

13.7. Investigations

In many instances, a careful history and physical examination provide the clinical diagnosis. Complete blood count (CBC), serum amylase or lipase, electrolytes, creatinine, liver enzymes, glucose and urinalysis are routine. Other blood work is obtained as indicated. Pregnancy testing should be done when appropriate. Chest and plain abdominal x-rays are obtained routinely unless the diagnosis is clear (e.g. appendicitis). The presence of free peritoneal air indicates a



perforated viscus. Abdominal x-rays can also provide information about the pattern of bowel gas (e.g. intestinal obstruction), edema and pneumatosis of the bowel wall, retroperitoneal structures (e.g. pancreatic calcification), and bony structures (e.g. fractures, bone metastases).

More sophisticated diagnostic imaging is often valuable. Ultrasound is very useful in the diagnosis of biliary tract disease (gallstones), abdominal aortic aneurysm, gynecologic disease and is often used in suspected appendicitis. Increasingly, abdominal CT scanning is being used, often obviating the need for more invasive or uncomfortable studies.

Other imaging modalities that may be ordered depending on the case include intravenous pyelography to assess the genitourinary tract or mesenteric angiography. The choice of investigation should be discussed with a radiologist.

Endoscopy (gastroscopy or colonoscopy) may be indicated in some cases. Laparoscopy has an important diagnostic role, as well as allowing definitive surgical therapy (e.g. appendectomy, omental patch of a perforated duodenal ulcer).

13.8. Approach to Management

A reasonably specific diagnosis or focused differential can usually be established early on. This is the basis for determining further management. In some instances (e.g. possible appendicitis), careful observation with repeated examination and selected imaging studies (e.g., ultrasound) allow a diagnosis to be reached. In some individuals, acute abdominal pain of mild to moderate severity resolves without a confirmed diagnosis. In patients with more serious conditions, intravenous fluid administration, other supportive measures and monitoring must be instituted following rapid initial assessment, even before a specific diagnosis can be made. In such individuals, diagnostic and therapeutic manoeuvres must proceed in a coordinated and efficient manner. Occasionally, patients with an acute abdomen, typically those who are unstable despite resuscitation or who have obvious generalized peritonitis, require urgent CT scan or ultrasound of the abdomen, or even laparotomy without a definitive preoperative diagnosis.

14. Chronic Abdominal Pain / W.G. Thompson and N. Saloojee

14.1. Description

As discussed below, there is a wide differential to chronic abdominal pain. In many cases however, no objective abnormality can be found. Such patients are said to have functional abdominal pain. Ten percent of children suffer recurrent abdominal pain and approximately 20% of adults have abdominal pain at least six times per year unrelated to menstruation. Functional abdominal pain syndrome is formally described as pain present continuously or near continuously for 6 months or more in which there is no relationship of the pain to eating, defecation, menses and in which no organic pathology can be found. Patients not strictly meeting this duration of pain may still be said to have functional abdominal pain.

14.2. Mechanisms and Causes

Functional abdominal pain is regarded as being related to dysfunction of the brain-gut axis: pain is perceived in the abdominal region in the absence of pathology. The central



nervous system and psychosocial stressors combine to lead to a heightened experience of pain.

Of course, chronic abdominal pain may be caused by many organic diseases. The pain of peptic ulcer disease may be food related and may improve with antacid. Most ulcers are related to Non Steroidal Anti inflammatory Drugs (NSAID) or *H. pylori* infection.

Intermittent obstruction of the cystic duct by a gallstone is known as biliary colic. Characteristically, patients experience significant episodic right upper quadrant (RUQ) and sometimes epigastric pain after meals. The pain may last hours in duration. However it subsides spontaneously and the patient is systemically well. Cholecystitis refers to a more long lasting, continuous pain in the same area due to impaction of a stone in the cystic duct. Subsequent dilation and inflammation of the gallbladder occurs. Such patients may have fever or be systemically unwell. Obstruction of the common bile duct with a stone (choledocholithiasis) results in pain and jaundice. The presence of fever in such a patient indicates infection due to stasis of material in the biliary tree (cholangitis).

Other causes of chronic or recurrent abdominal pain include chronic pancreatitis, intra abdominal neoplasms, inflammatory bowel disease, mesenteric ischemia, partial bowel obstruction, adhesions, renal colic and gynaecologic disorders.

As mentioned, functional abdominal pain is unrelated to eating, defecation or menses. Irritable bowel syndrome, is an almost identical disorder but is distinguished by disordered defecation. Functional abdominal pain may be due to a normal perception of abnormal gut motility or an abnormal perception of normal gut motility. It may not be due to the gut at all in that patients frequently have accompanying psychosocial difficulties.

14.3. Important Historical Points and Physical Examination Features

When chronic abdominal pain relates to a bodily function (defecation, eating, micturition or menstruation) investigation should focus upon the involved system.

Functional pain is more frequent in those who have had recent conflicts, have experienced a death in the family, or have become overly concerned with fatal illness. There may be a history of traumatic life events. Depression and anxiety are frequent. Patients with functional abdominal pain do not have alarm symptoms such as fever, weight loss, or rectal bleeding. Physical examination and lab tests are normal.

14.4. Diagnosis and Management

Diagnostic testing for chronic abdominal pain is similar to that for acute abdominal pain. Investigation involves a combination of bloodwork, urinalysis, diagnostic imaging and endoscopic testing. Management of organic causes of the chronic abdominal pain is directed at the underlying disease process.

For patients with functional abdominal pain, the physician's responsibility is to reassure the patient that no serious disease exists. A strong patient-physician relationship is needed. Where such a relationship does not exist, the patient may consult many doctors without satisfaction. The focus is to help the patient manage the pain, rather than cure it. It is important to investigate to a degree to reassure both patient and physician that the diagnosis is correct. However, it is also important not to continually repeat investigations in the belief something is being missed. Drugs,



especially narcotics, should be used with restraint. Some individuals benefit from low-dose antidepressants, as in other chronic pain syndromes. These patients test our skill in the art rather than the science of medicine.

15. Jaundice / L.J. Scully and N. Saloojee

15.1. Description

A state characterized by increased serum bilirubin levels (hyperbilirubinemia) and a yellow appearance due to deposition of bile pigment in the skin and mucus membranes.

15.2. Mechanism

Bilirubin is a waste product of hemoglobin metabolism. Interruption of the breakdown pathway at any of a number of steps, or a marked increase in load due to red blood cell destruction, results in an increase in serum bilirubin and if high enough, clinical jaundice. Under normal circumstances, senescent red blood cells are taken up and destroyed in the reticuloendothelial system. Through a number of steps the heme molecule of hemoglobin is converted to bilirubin which is, tightly bound to albumin, and transported in the plasma to the liver cells. Hepatocytes take up bilirubin, conjugate it to glucuronide and excrete the bilirubin diglucuronide in bile into the duodenum. In the bowel, bacteria break down bilirubin to urobilinogen, 80% of which is excreted in the feces, contributing to the normal stool colour. The remaining 20% of urobilinogen is reabsorbed and excreted in bile and urine (enterohepatic circulation of urobilinogen).

Functional defects in bilirubin metabolism or anatomic obstruction to excretion into the biliary system will result in an increase in serum bilirubin and jaundice. A large increase in the breakdown products of hemoglobin alone (e.g. hemolytic anemia) will cause an increase in serum unconjugated bilirubin. If the problem lies after the uptake and conjugation step, the increase is in serum conjugated bilirubin. In adults, aside from hemolysis or the common benign unconjugated hyperbilirubinemia of Gilbert's syndrome, most patients with jaundice have a conjugated hyperbilirubinemia. Causes of jaundice are usually classified as: (1) hemolysis; (2) genetic defects in bilirubin handling; (3) hepatocellular disease; and (4) obstruction or cholestasis.

15.3. Clinical Presentation

Clinical jaundice is detected when the serum bilirubin level reaches 2–4 mg/dL (40–80 $\mu\text{mol/L}$). Jaundice is usually preceded by a few days of pale stools (as excretion of bilirubin into the intestine is decreased) and dark urine (due to increased glomerular filtration of conjugated bilirubin). Jaundice is usually first detected in the sclera, although the bilirubin is actually deposited in the overlying conjunctival membranes. Yellow skin without scleral icterus should suggest carotenemia (excess intake of foods high in carotene) or the ingestion of such drugs as quinacrine.

Patients with jaundice due to a hepatocellular cause (e.g. viral hepatitis) often have nausea, anorexia, hepatomegaly and right upper quadrant discomfort. Patients with jaundice due to a cholestasis often experience pruritis, presumably from deposition of bile salts in the skin. Physical exam may reveal an abdominal mass such as a dilated gallbladder. Other historical points to ask include inquiring about viral hepatitis risk



factors (e.g. IV drug use, prior transfusions), history of alcohol abuse, medications, and family history of liver disease.

The end stage of liver disease of any cause is cirrhosis of the liver. Such patients have a small, shrunken and nodular liver. Signs or so-called stigmata of chronic liver disease may be found. These include spider nevi, gynecomastia, palmar erythema, Dupuytren's contracture, signs of portal hypertension (ascites, splenomegaly, dilated periumbilical veins) and asterix (flapping of the outstretched hands, a sign of hepatic encephalopathy).

15.4. Approach to Diagnosis

Initially, the evaluation of jaundice is to determine whether it is primarily due to conjugated or unconjugated hyperbilirubinemia (Figure 2). Serum bilirubin can be fractionated from total bilirubin into conjugated and unconjugated. The presence of bile in the urine determined by a test strip at the bedside confirms that the bilirubin rise is predominantly in the conjugated form. If the

bilirubin is primarily unconjugated, hemolysis or genetic defects are implicated. A blood smear showing schistocytes or fragmented red cells confirms hemolysis. In adults, Gilbert's syndrome is an inherited genetic disorder of impaired bilirubin conjugation. Particularly at times of physiologic stress, a mild unconjugated hyperbilirubinemia may occur. The disorder is innocuous and follows a benign natural history.

If the hyperbilirubinemia is conjugated, liver enzyme tests (AST, ALT, GGT and alkaline phosphatase) will help determine if the jaundice is primarily due to hepatocellular damage (high AST and ALT) or obstruction/cholestasis (high GGT and alkaline phosphatase). Transaminases (AST/ALT) are released by damaged hepatocytes. Also check the patient's INR and albumin concentration, as these are markers of synthetic function of the liver and reflect a more chronic underlying disease process.

Cholestatic jaundice requires an ultrasound as the best, first test. Dilation of intra- and/or extrahepatic bile ducts indicates an anatomic problem. In this case, the cholestasis is caused by an extrahepatic problem (e.g. pancreatic neoplasm compressing common bile duct or stones in the common bile duct). Lack of biliary dilation indicates intrahepatic cholestasis (e.g. medication adverse effect).

Further tests such as viral serology, markers for other liver diseases, further liver imaging, endoscopic retrograde cholangiopancreatography (ERCP), MRI of the biliary area (MRCP), CT scan of the abdomen, and liver biopsy are ordered as needed.



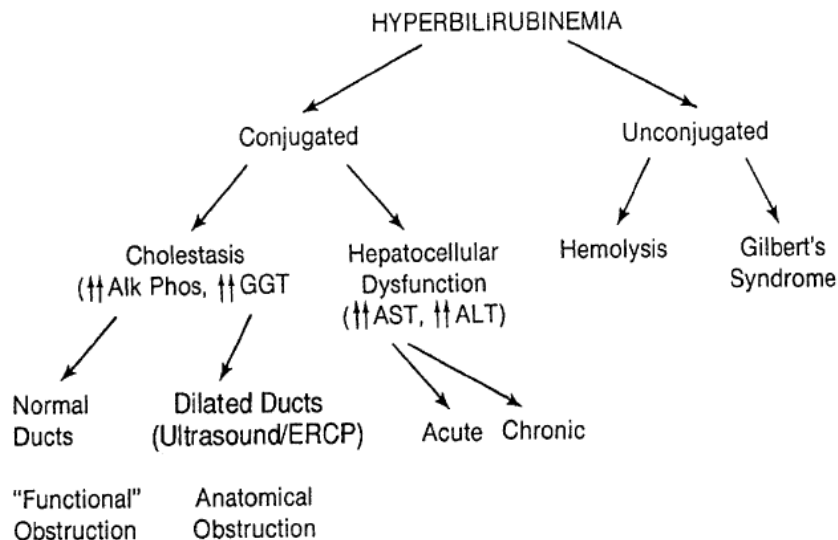


Figure 2. Approach to hyperbilirubinemia.

15.5. Management

Management of the specific disorders causing jaundice is contained in the chapters on the hepatobiliary and pancreatic systems. In general, hepatotoxins (e.g. alcohol, medication) should be withdrawn, biliary obstruction should be relieved if present, and therapy for the underlying disorder instituted where possible.

16. Ascites in Chronic Liver Disease / L.J. Scully and N.Saloojee

16.1. Definition

Ascites is the accumulation of free fluid in the peritoneal cavity.

16.2. Mechanisms

With significant liver disease (cirrhosis), ascites is a result of activation of the renin-angiotensin-aldosterone system and portal hypertension. Renin-angiotensin-aldosterone activation leads to sodium and water retention. Increased portal pressure leads to transudation of fluid from the capillaries in the portal system to the peritoneal cavity. Ascites may also occur in patients without liver disease. Intra-abdominal malignancy or chronic peritoneal infection (e.g. tuberculosis) can lead to ascites as a result of protein rich fluid being actively secreted.

16.3. Signs and Symptoms

Ascites most commonly presents with increasing abdominal girth. There is often an uncomfortable feeling of distention. Sometimes, there is nausea and anorexia. Diaphragmatic elevation or a pleural effusion (ascites fluid tracking into pleural space) can lead to shortness of breath. Ankle edema may accompany ascites. Clinical examination reveals a distended abdomen and bulging flanks on inspection. "Shifting



dullness” or a “fluid thrill” may be elicited. Smaller amounts of fluid may be detected on ultrasound when clinical signs are absent. One should look for other signs of portal hypertension, such as dilated abdominal wall veins or splenomegaly.

16.4. Differential Diagnosis

Newly developed ascites must have a diagnostic aspiration (paracentesis) to determine the albumin level, cell count and cytology. The fluid should be clear and straw coloured. If the fluid is bloody, chronic infection (e.g. tuberculosis) or malignancy should be sought. Determining the etiology of ascites hinges on the serum ascites albumin gradient (SAAG). The gradient is calculated by subtracting the ascites albumin from the serum albumin. If the gradient is high (>11 g/L), then the ascites is due to portal hypertension. If the gradient is low (≤ 11 g/L), then the ascites is not from portal hypertension. The likeliest cause of low gradient ascites is malignancy. A low gradient results from ascites that is high in protein, so that the ascites albumin level is close to that of the serum.

Ascitic fluid may become infected, in which case the white blood cell count will be elevated (>250 neutrophils/uL) in the fluid. Bacterial infection of ascites fluid can be due to a perforation in the GI tract (e.g. perforated appendix) or it can be a spontaneous occurrence (spontaneous bacterial peritonitis).

16.5. Approach to Management

Management of ascites begins with salt restriction. Most cases also require addition of a diuretic such as spironolactone and/or furosemide. If ascitic fluid reaccumulates despite these measures, aspiration of large quantities of ascites fluid or large volume paracentesis may be necessary. Six to eight litres can be safely removed at a time. If ascites remains uncontrolled, options include repeated large volume paracentesis, transjugular intrahepatic portosystemic stent shunt (TIPS) or liver transplant.

This topic is covered extensively in the chapter “Ascites”.

17. Gastrointestinal Bleeding / A. Rostom, C. Dubé and N. Saloojee

17.1. Description

Gastrointestinal (GI) bleeding may be referred to as upper, lower, obscure or occult. Upper GI bleeding commonly presents with hematemesis (vomiting of red blood), coffee-ground emesis and/or melena (black, tarry stools). The black colour of melena is the result of degradation of blood by intestinal bacteria. In comparison, hematochezia (bright red or maroon coloured blood per rectum) is usually a sign of lower GI bleeding. It is important to note that a very brisk upper GI bleed can lead to hematochezia as blood passes rapidly through the gut and is not degraded. Upper GI bleeding occurs proximal to the ligament of Treitz. Small bowel bleeding occurs from the ligament of Treitz to the distal ileum. Lower GI bleeding occurs from the terminal ileum and colon.

Occult bleeding is bleeding that is not apparent to the patient. The quantity of bleeding is small, so that the colour of stools is not altered. Patients may present with a positive fecal occult blood test (FOBT) result and/or iron-deficiency anemia (IDA). Chronic loss of small amounts of blood can eventually lead to significant IDA. Obscure bleeding is



defined as bleeding of unknown origin that persists or recurs after negative initial endoscopies (colonoscopy and upper endoscopy). Most commonly, the source of obscure bleeding is the small bowel. Obscure bleeding may be overt (i.e., hematemesis, melena or hematochezia), or may be occult such as persistent IDA. The important causes of upper and lower GI bleeding are presented in Tables 3 and 4 respectively.

Table 6. Causes of Upper GI Bleeding

Common	Less Common
○ Peptic Ulcer Disease : Gastric Ulcer, Duodenal Ulcer ○ Esophageal Varices ○ Mallory-Weiss Tear ○ Neoplasm : Esophageal cancer, Gastric Cancer, Lymphoma	○ Esophagitis ○ Portal Hypertensive Gastropathy ○ Vascular : angiodysplasia, gastric antral vascular ectasia (GAVE; “watermelon” stomach), Dieulafoy lesion) ○ Aortoenteric Fistula ○ Hemobilia ○ Crohn disease

Table 7. Causes of Lower GI Bleeding

Common	Less Common
○ Diverticular bleed ○ Angiodysplasia ○ Colon Cancer ○ Ischemic Colitis ○ Inflammatory Bowel Disease	○ Radiation Proctitis ○ Post-polypectomy bleeding

17.2. Approach to Diagnosis and Management

The initial evaluation of the patient with acute GI bleeding involves assessment of the “ABCs” (Airway, Breathing, and Circulation). Patients with upper GI bleeding are at risk of airway compromise from aspiration of vomited blood. Another risk factor for some patients is a reduced level of consciousness due to shock or hepatic encephalopathy. Some patients may require supplemental oxygen or even intubation for airway protection and/or assisted breathing. During the assessment of the hemodynamic status, IV access is crucial. In a significant GI bleed, two large bore peripheral IVs (18 gauge or greater) are placed for fluid and blood product restoration. At this stage, blood should be drawn for typing and cross-matching. Bloodwork should include CBC, INR, electrolytes, urea, creatinine, as well as albumin and liver enzymes.

It is important to remember that, hemoglobin (Hb) and hematocrit (Hct) may not be low at presentation. These measures reflect the red blood cell concentration. Over the ensuing 36–48



hours, most of the volume deficit will be repaired by the movement of fluid from the extravascular into the intravascular space. Only at these later times will the Hb and Hct reflect the true degree of blood loss. Furthermore, if a patient presents with an acute GI bleed and the initial Hb is low, one should expect the Hb to continue to decline and so transfusion should be considered. Some patients, in particular those with GI malignancies, may have had chronic occult bleeding prior to their acute presentation. The result is hypochromia and microcytosis from iron deficiency. Coagulopathy, due to medications (e.g. warfarin) or liver dysfunction, should be corrected. An elevated blood urea nitrogen (BUN) value in the presence of a normal creatinine may be a sign of upper GI bleeding. The elevated BUN is due to blood being absorbed from the proximal small bowel.

Pharmacotherapy for GI bleeding includes intravenous proton pump inhibitors in cases of suspected bleeding from peptic ulcer disease and intravenous administration of somatostatin analogs (octreotide) in suspected cases of esophageal variceal bleeding. Because of the seriousness of upper GI bleeding, and the not-uncommon delay in obtaining an endoscopy for purposes of diagnosis and endoscopic hemostatic therapy, pharmacotherapy is often given on initial presentation, before the cause of bleeding has been definitively determined.

In acute GI bleeding, symptoms associated with blood loss include weakness, diaphoresis, pre-syncope, and syncope. Patients with a chronic, slow bleed may present with iron deficiency anemia. Signs and symptoms include pallor, fatigue, and dyspnea. In a predisposed individual, anemia can lead to congestive heart failure or angina. In all cases of GI bleeding, information should be gathered about medication use, in particular the intake of NSAIDs, Aspirin (ASA) or anticoagulants. Other important data includes a prior history of peptic ulcer disease, history of abdominal surgery (e.g. vascular grafts raise the suspicion of aorto-enteric fistulas), and a history of chronic liver disease or alcohol abuse. Look for signs of chronic liver disease on physical examination. The hemodynamic status should be interpreted in light of the patient's abilities to compensate for hypovolemia. In a young and fit adult, the presence of a resting or orthostatic tachycardia should be interpreted as a sign of significant volume loss, while the loss of an equivalent blood volume in an elderly or debilitated subject would more likely be manifested by hypotension or shock.

Once supportive measures have been undertaken, the patient should be assessed with a view towards identifying the source of bleeding (ie. upper or lower). Bright red emesis is suggestive of bleeding from esophageal varices or of a brisk upper GI source. In a duodenal bleed, blood may or may not reflux into the stomach. Therefore, the absence of hematemesis, coffee ground emesis or a bloody aspirate from nasogastric suction does not rule out an upper GI bleed. The pigmentation of the stool will depend on the length of time in transit along the bowel. In an upper GI bleed, transit time is usually longer than a lower bleed. Therefore, an upper GI or proximal small bowel bleed usually leads to melena. Conversely, a lower GI bleed generally leads to hematochezia. In determining the likely source of bleeding, the clinician needs to interpret the patient's manifestations of bleeding in conjunction with the hemodynamic status. Blood originating from the left colon typically is bright red. However, hematochezia associated with hemodynamic instability raises the suspicion of a brisk upper GI bleed. Similarly, while the passage of melena is most commonly associated with an upper GI



source, dark burgundy or black stools can sometimes be encountered in proximal colonic bleeds. In the absence of spontaneous passage of stools, a digital rectal examination to determine the stool color will be most informative.

Under certain circumstances it may be difficult to determine if the GI bleed, particularly if it is significant, is of upper or lower origin. It is then safest to proceed on the assumption of an

upper GI bleed, and to arrange for early upper endoscopy. Many causes of upper GI bleeding are amenable to endoscopic therapy. If the bleed is due to a peptic ulcer, upper endoscopy allows stratification of rebleed risk based on the appearance of the ulcer. In a suspected upper GI bleed, the timing of upper endoscopy varies. Early upper endoscopy is done if there are signs of a brisk bleed, a variceal bleed is suspected, the patient is older or has numerous comorbidities.

Most lower GI bleeds stop spontaneously, so the treatment is mainly supportive. If a lower GI bleed does not stop, angiography should be pursued to localize the source of bleeding and possibly embolize the source. If these measures fail to stop a lower GI bleed, surgery may become necessary. Colonoscopy has little utility in an active lower GI bleed since blood obscures visualization. The role of colonoscopy in lower GI bleeding is mainly diagnostic, once bleeding has slowed and bowel cleansing can be achieved.

In the case of a GI bleed where upper endoscopy and colonoscopy are negative, small bowel investigations may become necessary. Radiologic options include a small bowel follow through or CT enterography (protocol to look at small bowel). Wireless capsule endoscopy involves ingestion of a pill sized camera to take pictures of the small bowel. Enteroscopy involves a long scope inserted from the mouth to examine the proximal small bowel. Balloon enteroscopy is a newer endoscopic technique in which total endoscopic examination of the small bowel is possible.

18. Abdominal Mass / S. Grégoire and N. Saloojee

18.1. Description

When an abdominal mass is discovered on physical examination, one must define its nature. Using a systematic approach often permits the identification of the mass before the use of sophisticated tests.

18.2. Important Points in History and Physical Examination

Important clues in the history and general physical examination may help to identify the enlarged viscus. For example, in a young patient presenting with diarrhea, weight loss and abdominal pain, finding a right lower quadrant mass would suggest inflammatory bowel disease. However, an abdominal mass may be discovered during physical examination of an asymptomatic individual. Certain observations made during the abdominal examination may be helpful (See also Section 20).

18.2.1. Inspection

Where is the mass located? A practical approach is to divide the abdomen into four quadrants (See Section 20.1). Starting from the principle that an abdominal mass originates from an organ, surface anatomy may suggest which one is enlarged. A mass seen in the left lower quadrant, for example, could be of colonic or ovarian origin but, unless there is situs



inversus, one would not consider an appendiceal abscess. Does the mass move with respiration? In the upper abdomen a mobile intraabdominal mass will move downward with inspiration, while a more fixed organ (e.g. aorta, pancreas) or an abdominal wall mass (e.g. hematoma of the rectus muscle) will not.

18.2.2. Auscultation

Careful auscultation for bowel sounds, bruit or rub over an abdominal mass is part of the systematic approach.

18.2.3. Defining the Contour and Surface of the Mass

This is achieved by inspection, percussion and palpation. Is the organ air filled (e.g. stomach) or fluid-filled? Is it a well-defined mass (e.g. liver, spleen) or are its borders difficult to define (e.g. matted loops of small bowel)? Is the surface regular? An enlarged liver due to fatty infiltration may have a smooth surface. What is the consistency of the mass? Firm, hard or soft? Is it pulsatile to suggest an aortic aneurysm? In the absence of ascites, ballottement of an organ situated in either upper quadrant more likely identifies an enlarged kidney (more posterior structure) than hepatomegaly or splenomegaly.

18.3. Differential Diagnosis

The following suggests an approach to the differential diagnosis of an abdominal mass located in each quadrant:

18.3.1. Right Upper Quadrant

This location suggests liver, right kidney, gallbladder and, less commonly, a colon or gastroduodenal mass. A pancreatic mass is rarely palpable.

Liver: As a subdiaphragmatic organ, the liver moves downward with inspiration. This anterior organ has an easily palpable lower border, which permits assessment of its consistency. An enlarged left lobe can usually be felt in the epigastric area.

Right kidney: The kidney may protrude anteriorly when enlarged and be difficult to differentiate from a Riedel's lobe of the liver. It may be balloted.

Gallbladder: This oval-shaped organ moves downward with inspiration and is usually smooth and regular.

Colon: Colon masses are deep and ill-defined, and do not move with respiration. High-pitched bowel sounds suggest obstruction.

18.3.2. Left Upper Quadrant

Location in the left upper quadrant suggests spleen or left kidney. Less commonly, a colonic (splenic flexure) or gastric mass can be felt. A pancreatic mass is rarely palpable.

Spleen: This anterior organ moves downward with inspiration. Since it has an oblique longitudinal axis, it extends toward the right lower quadrant when enlarged. It has a medial notch and the edge is sharp.

Left kidney: Its more posterior position and the presence of ballottement helps distinguish the left kidney from the spleen.



Colon, pancreas, stomach: It is practically impossible to differentiate masses in these organs by physical examination. The history helps but often one must resort to radiology or endoscopy.

18.3.3. Right Lower Quadrant

A mass in this area has its origin either in the lower GI tract (colon, distal small bowel, appendix) or in a pelvic structure (ovary, uterus, fallopian tube).

Lower GI tract: These deeper organs are usually ill-defined. Clinical context is important. Inflammatory bowel disease usually would be associated with pain on palpation but carcinoma of the cecum would be painless.

Pelvic organs: Bimanual palpation is the preferred method.

18.3.4. Left Lower Quadrant

As with a right lower quadrant mass, the differential diagnosis here is between lower GI (in this quadrant the sigmoid colon) and pelvic origin. Pelvic examination may help differentiate the two.

18.4. Approach to Diagnosis

To complete the assessment of an abdominal mass, one may choose among several different investigational tools. The use of specific tests depends on availability and on the organ studied. Generally, ultrasound is useful. This noninvasive, safe, cheap and widely available method identifies the mass and provides information on its origin and nature. Ultrasound may also be used to direct a biopsy. Other noninvasive modalities are CT scan and MRI. Hollow organs may be demonstrated radiographically through the use of contrast media (e.g., air contrast barium enema, upper GI series, intravenous pyelogram, endoscopic retrograde cholangiopancreatography [ERCP]). Sometimes, laparotomy or laparoscopy will be necessary to make the diagnosis.

19. Proctalgia Fugax / W.G. Thompson and N. Saloojee

19.1. Description

Proctalgia fugax is a sudden severe pain in the anus lasting several seconds or minutes and then disappearing completely.

19.2. Mechanism

The pathophysiology of proctalgia fugax is uncertain. Although some observations suggest a rectal motility disorder, the symptom appears more likely to result from spasm of the skeletal muscle of the pelvic floor (specifically, the puborectalis).

19.3. History and Physical Examination

Proctalgia fugax occurs in about 14% of adults and is somewhat more common in females than males. The pain may be excruciating, but since it is so short-lived patients seldom report it to their physician. In 90% of instances it lasts less than five minutes and in many cases less than a minute. About one third of patients suffer attacks following defecation. A small minority report attacks following sexual activity. There are no physical signs.



19.4. Differential Diagnosis

Perianal disease may cause pain but it usually accompanies, rather than follows, defecation. One should be particularly careful to exclude the presence of an anal fissure, which may be difficult to see on anal inspection. Pain originating from the coccyx may be accompanied by coccygeal tenderness both externally and from within the rectum. An acute attack of anal pain lasting several hours may indicate a thrombosed hemorrhoid.

19.5. Management

Beyond reassurance, there is no specific treatment.

20. Examination of the Abdomen / *R.F. Bursey, J.M. Fardy, D.G. MacIntosh and N. Saloojee*

Examination of the abdomen is an important component of the clinical assessment of anyone presenting with suspected disease of the gastrointestinal tract. As in all other parts of the examination, care must be taken to show respect and concern for the patient while ensuring an appropriate and thorough examination. While performing the examination it is useful to keep in mind the concepts of sensitivity and specificity. How confident can we be that a suspected physical finding is in fact present and has clinical significance? For example, how sensitive and specific is our bedside examination for hepatomegaly? What is the clinical significance of an epigastric bruit heard in a thin 20-year-old female versus a 55-year-old hypertensive, obese male? In the following sections we will describe an appropriate sequential examination of the abdomen and highlight some of the potential pitfalls of this process.

20.1. Inspection

Start from the usual position to the right side of the supine patient. The patient should not have a full bladder. Ensure that the abdomen is exposed from the costal margin to symphysis pubis. Positioning is important. The patient should keep his or her arms by the sides or folded across the chest. Ensure the patient does not have his or her legs crossed. When describing the location of an abnormality it is useful to divide the abdomen into four quadrants. Imagine a perpendicular line through the umbilicus from the xiphoid process to the symphysis pubis. A horizontal line through the umbilicus then allows the abdomen to be divided into 4 areas: the left upper, right upper, left lower and right lower quadrants (Figure 3). On occasion it may be helpful to divide the abdomen into 9 regions with the spaces marked by vertical lines through the left and right mid-clavicular lines and horizontal lines passing through the subcostal margins and anterior iliac crests (Figure 4).

The overall appearance of the abdomen can be described as scaphoid (markedly concave), protruberant, or obese. The location of any surgical scars noted. One should examine the skin for cutaneous lesions, vascular markings, dilated veins and striae. Note any pulsation that could indicate an aneurysm. Note the movement of the abdominal wall with respiration. Normally the abdominal wall will rise with inspiration. Occasionally organomegaly or a mass will be visible. It is helpful to look at the abdomen from the foot of the bed as well.



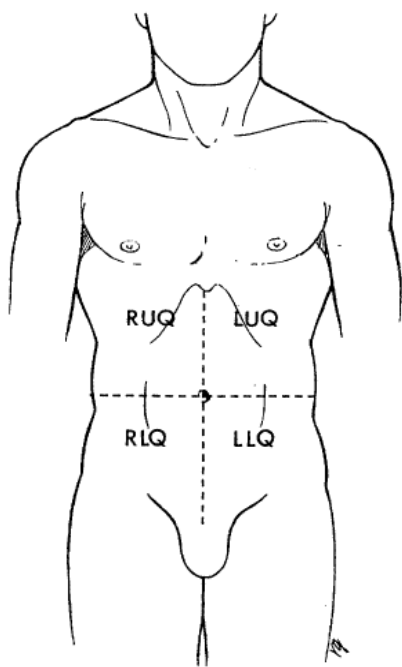


Figure 3. Division of the abdomen into four quadrants: the left upper quadrant, right upper quadrant, left lower quadrant and right lower quadrant.

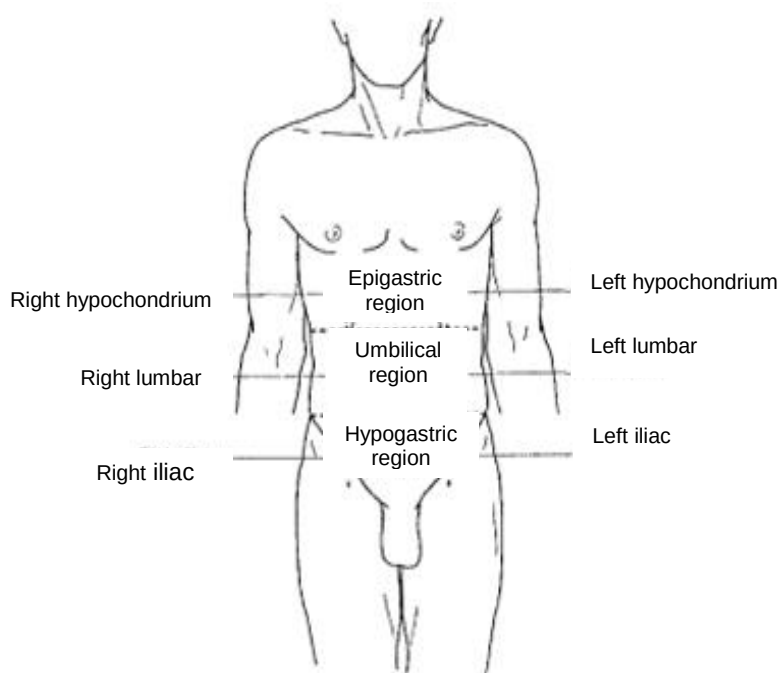


Figure 4. Division of the abdomen into nine regions.

20.2. Auscultation

It is useful to auscultate the abdomen for bowel sounds and bruits prior to palpation or percussion. Palpation or percussion will stimulate peristalsis and may mask vascular bruits. When listening for vascular bruits it is useful to keep in mind Figure 4. Bruits are vascular sounds created by turbulent flow and may indicate partial arterial occlusion. Arterial bruits are usually heard only during systole and best heard with the diaphragm of the stethoscope, as they are high pitched. Listen for the aorta in the epigastrium. Renal bruits may be heard midway between the xiphoid process and the umbilicus, 2 cm away from the midline. Listen for iliac bruits halfway between the umbilicus and the inguinal ligament. One should listen over the inguinal ligament for femoral bruits as well.

About 20% of normal persons will have a vascular bruit, so that the auscultation of an abdominal bruit has to be placed within the clinical context.

A venous hum is a rare sound, best heard overlying the portal vein. This is found in an area approximated by an ellipse between the umbilicus and the midclavicular line where it crosses the right subcostal margin. A venous hum can occur in portal venous hypertension of any cause. There are, however, no studies to suggest this is a helpful finding in routine examination.

Friction rubs are a rare sound indicating inflammation of the peritoneal surface of an organ. They are grating in quality and vary with respiration. They may occur over a



liver tumour. However, even with careful auscultation of patients with known liver tumours, fewer than 10% are found to have a rub.

20.2.1. Bowel Sounds

Bowel sounds should be listened for prior to palpation or percussion, but the yield of this examination is low. The diaphragm of the stethoscope should be placed on the abdomen. Listening in one spot, such as the right lower quadrant, is generally sufficient since bowel sounds are transmitted widely through the abdomen. Rushes of very high pitched bowel sounds coinciding with crampy pain may indicate hyperperistalsis and acute small bowel obstruction. Complete absence of bowel sounds may indicate an ileus or peritonitis.

20.3. Palpation

Palpation of the abdomen should be done in an orderly sequence with the patient in the supine position. Light palpation should be done in all four quadrants, assessing for areas of potential tenderness. If the patient complains of pain, palpate that area last. With one hand, using the pads of the fingertips, palpate in a gentle, circular motion. If no areas of obvious tenderness are elicited, then deep palpation is performed. This is again done in all four quadrants, however use both hands. One hand is placed on the abdominal wall. The second hand is placed over top of the first. It is thought that using one hand for deep palpation may increase the risk of missing a mass. The accuracy of this has not been tested.

Involuntary guarding and rebound tenderness are signs of peritoneal inflammation (peritonitis). Guarding refers to contraction of abdominal wall muscles when the abdomen is palpated. Guarding is only important if muscle contraction is involuntary. Involuntary guarding occurs as a protective mechanism when peritonitis is present. Voluntary guarding occurs when a patient tenses abdominal wall muscles in response to that abdominal wall pressure. It is a meaningless finding that is commonly seen. Guarding may be localized (e.g. uncomplicated appendicitis) or generalized throughout the abdomen (e.g. perforated appendicitis with diffuse contamination of the peritoneal cavity). In some instances of peritonitis, the muscles are in a state of continuous contraction. They are rigid or “board-like” even without palpation. In subtle situations, peritonitis is suggested by the triggering of pain in the area of suspected pathology (e.g., appendicitis) through palpation elsewhere on the abdominal wall, by having the patient cough or by gently shaking the pelvis.

Rebound tenderness, another sign of peritonitis, is elicited by deeply palpating the area of concern and then suddenly releasing the abdominal wall. Severe pain felt on release of the abdominal wall is rebound tenderness. This manoeuvre can be very distressing to the patient with peritonitis, so it is often not done. The sites for inguinal and femoral hernias should be specifically examined. Femoral pulses should be palpated.

The techniques of palpation of liver and spleen are discussed in Sections 20.5 and 20.6.



20.4. Percussion

Percussion of the abdomen will detect the presence of bowel gas. It is useful in defining organomegaly and the presence of free intra-abdominal fluid (ascites), as discussed below.

20.5. Examination of the Liver

First, inspect for a right upper quadrant mass. The examiner should look for stigmata of chronic liver disease (section 15.3). Next, palpate for the lower edge of the liver.

To palpate the liver edge, start in the right lower quadrant of the abdomen. The edge of an enlarged liver may be missed by starting too high in the abdomen. The patient is asked to breathe deeply and slowly, in order to bring the liver edge down to the examining fingertips of the right hand. The examiner moves the right hand in a cephalad direction about 2 cm with each expiration. If the edge is not felt, no further examination is required.

The liver, if palpable, is normally smooth and regular. Note any firmness, irregularity or nodularity to suggest an abnormal liver. Interobserver agreement about such characteristics is poor, even among experts. Note any tenderness. When the liver edge is palpable, trace the edge working laterally to medially. If the liver edge is palpated, the liver span should be measured by percussion. Start by percussing in the right midclavicular line in an area of tympany. Percuss in a cephalad direction in the right midclavicular line until an area of dullness is encountered. This is the lower border of the liver. Percuss for the upper border starting in the right midclavicular line in the third intercostal space. Move down one interspace at a time until the percussion note changes from resonant to dull. To confirm the change of percussion note strike the third and fourth fingers laid in adjacent interspaces. The note on the top finger should be resonant and on the lower dull. This is the upper border of the liver. Measure the distance between the upper and lower percussion edges in the mid-clavicular line. Percussion typically underestimates the true vertical span on the liver.

The scratch test has been used to find the lower liver margin. The diaphragm of the stethoscope is placed at the right costal margin in the midclavicular line. A finger moves up the abdomen in the mid-clavicular line, scratching gently and with consistent pressure. When the liver edge is reached, there is a sudden increase in the scratching sound heard through the stethoscope. In one comparative study the scratch test was not felt to offer any advantage over the techniques of palpation and percussion.

What is the significance of a palpable liver edge? One review suggested that a palpable liver is not necessarily enlarged or diseased. When clinical examination is compared to nuclear medicine scanning, about one-half of palpable livers are not enlarged. The inability to feel a liver edge does not rule out hepatomegaly, but does reduce its likelihood. What is the normal percussion span? Only one study has been done to establish the normal span. Castell examined 116 healthy subjects using firm percussion. The mean span in the mid-clavicular line was 7 cm in women and 10.5 cm in men (8 ± 2 cm in women and 11 ± 2 cm in men is considered to be normal).



The following nomograms were developed to predict estimated liver dullness in a normal population using firm percussion technique. Male liver dullness equals $(0.032 \times \text{weight in pounds}) + (0.183 \times \text{height in inches}) - 7.86$. The female liver dullness equals $(0.027 \times \text{weight in pounds}) + (0.22 \times \text{height in inches}) - 10.75$. The 95% confidence intervals were ± 2.64 cm. Therefore a 5 ft. 10 in., 175 lb. male would have an estimated liver span of 10.2 cm (range 7.6–12.8) and a 5 ft. 5 in., 130 lb. female would have an estimated liver span of 7.1 cm (4.5–9.7 cm) by this formula. These formulae are not used in day to day clinical practice.

Unlike the kidney in the left upper quadrant, the spleen moves downward and medially with inspiration, and does not have a notch.

20.6. Examination of the Spleen

The normal spleen is a curved, wedge-shaped organ located beneath the rib cage in the upper left quadrant. The spleen lies beneath the left tenth rib and normally weighs about 150 g. It is approximately 12 cm in length, 7 cm in width and 3 cm in thickness. The normal spleen usually cannot be palpated, but as it enlarges it descends below the rib cage and across the abdomen toward the right lower quadrant. An enlarged spleen may have a palpable notch along its medial edge. Examination of the spleen should begin with observation of the left upper quadrant for an obvious mass, though such a mass is quite uncommon.

The examiner should then proceed with percussion over the area of the spleen to look for evidence of dullness, implying splenic enlargement. The two most useful methods are percussion over Traube's space and Castell's sign. The surface markings for Traube's space are the left sixth rib, the left midaxillary line and the left costal margin. An enlarged spleen may cause dullness over Traube's space. Percussion should be carried out at one or more levels of Traube's space from medial to lateral. This maneuver has a sensitivity and specificity between 60 and 70% for splenic enlargement. The sensitivity and specificity increases to approximately 80% in non-obese patients who are fasting.

Castell's method involves percussion in the lowest intercostal space in the left anterior axillary line. In normal individuals this area is resonant on percussion and remains resonant on inspiration. In patients with mild splenic enlargement this area will be resonant on percussion and become dull on maximal inspiration. This method has a sensitivity and specificity of approximately 80% for detection of splenic enlargement and is helpful for detection of a minimally enlarged spleen that may not be palpable.

Palpation of the spleen should begin in the right lower quadrant and proceed toward the left upper quadrant in order to follow the path of splenic enlargement. Palpation should initially be carried out in the supine position with a bimanual technique using the left hand to gently lift the lowermost portion of the left rib cage anteriorly. The fingertips of the right hand are used to palpate gently for the spleen tip on inspiration. The hand is moved from the right lower quadrant, advancing toward the left upper quadrant. If the spleen is not palpated in the supine position, the patient should be moved into the right lateral decubitus position and again with bimanual technique the spleen tip should be sought using the fingertips of the right hand on inspiration. This technique has a sensitivity of about 70% and specificity of 90% for splenic enlargement.



20.7. Examination for Suspected Ascites

The presence of ascites, free fluid within the abdominal cavity, is always due to an underlying pathological process (see section 16). Potential causes include cirrhosis, severe right-sided heart failure, primary intra-abdominal malignancy, peritoneal metastases, chronic infection such as tuberculosis, and lymphatic obstruction. It is easy to identify large-volume ascites clinically, but the sensitivity of the examination techniques falls with lower volumes of fluid. Ultrasound, which can detect as little as 100 mL of free fluid, is the gold standard against which the clinical diagnostic maneuvers are compared.

An approach involves inspection for bulging flanks, palpation for the presence or absence of fluid waves, and percussion to demonstrate shifting dullness. Bulging flanks are suggestive of ascites since fluid sinks with gravity, while gas filled bowel loops float to the top. Adipose tissue in the flanks may be occasionally mistaken for free fluid.

To demonstrate a fluid wave it is necessary to enlist the aid of the patient or another individual. With the patient in the supine position, the examiner places one palm on the patient's flank. The patient or an assistant places a hand on the mid-abdomen. This is to apply sufficient pressure to dampen any wave that may pass through adipose tissue in the anterior abdominal wall. The examiner then briskly taps the opposite flank. If fluid is present, a shock wave will be felt with the palpating hand. The sensitivity of this technique is approximately 50% but it has a specificity of greater than 80%.

To test for shifting dullness, percuss from resonance in the mid-abdomen to dullness in the flanks. The area of transition is then marked and the patient rolled to the opposite side. For example, if flank dullness is demonstrated on the left then the patient should be rolled onto the right side. One should allow approximately 30 seconds for the fluid to move between the mesentery and loops of bowel into the inferior portion of the abdomen. The previous area of dullness in the left flank should now be resonant. It does not matter which side one chooses to start with. In three separate studies shifting dullness had a sensitivity that ranged from 60–88% and a specificity that ranged from 56–90%. In one study involving six gastroenterologists and 50 hospitalized alcoholic patients, the overall agreement was 75% for the presence or absence of ascites and reached 95% among senior physicians (i.e. experienced). The absence of a fluid wave, shifting dullness or peripheral edema is also useful in ruling out the presence of ascites.

21. Oral-Cutaneous Manifestations of GI Disease / N. Saloojee

21.1. Description

A number of gastrointestinal disorders are associated with oral or cutaneous manifestations. Some of the more common of these are presented here.

21.2. Specific Disorders

1. Glossitis. Inflammation of the tongue which can occur in a number of conditions. Seen in nutritional deficiencies such as iron or B12 deficiency. The tongue is smooth and can be enlarged.
2. Oral thrush. Candidiasis involving the oropharynx. When seen in association with dysphagia, the patient likely has esophageal candidiasis.



3. Cutaneous manifestations of Inflammatory Bowel Disease (IBD). Aphthous ulcers may occur in the oral mucosa of patients with IBD. Generally these lesions follow the course of the disease. They are seen when the intestinal disease is active.

Erythema Nodosum is a panniculitis or inflammation of subcutaneous fat that has multiple associations, one of which is IBD. Red, tender, nodular lesions occur on the anterior tibial area. These lesions follow the course of the intestinal disease.

Pyoderma Gangrenosum is an ulcerating, tender lesion with a dusky border. It often occurs on the anterior tibial area or around a stoma site. Lesions can progress rapidly. Lesions sometimes follow the course of the intestinal disease, however not always.

4. Hereditary Hemorrhagic Telangiectasia (HHT) or Osler-Weber-Rendu Syndrome. This disorder is characterized by vascular lesions including telangiectasias and arteriovenous malformations. Such lesions occur in the brain, lung and GI tract. Clinical manifestations include epistaxis and GI bleeding. Numerous telangiectasias occur on the lips.

5. CREST. This syndrome is an acronym for calcinosis, raynauds, esophageal dysfunction, sclerodactyly and telangiactasia. Patients experience dysphagia and reflux symptoms. Calcinosis is a deposition of calcium in the soft tissue, often around the elbows. Raynauds is a discolouration of fingers due to vasospasm that often results from exposure to cold. In sclerodactyly, the skin of the fingers becomes tightened and waxy. Telangiactasia occur on the chest and back.

6. A number of polyposis syndromes have cutaneous manifestations. Gardner's syndrome is a form of Familial Adenomatous Polyposis, patients develop hundreds to thousands of colonic polyps at a young age. Colon cancer is inevitable without colectomy, generally by age 40. Many patients develop epidermoid cysts of the face, scalp and extremities. Multiple unerupted supernumerary teeth may be seen.

Peutz-Jeghers syndrome is characterized by hamartomatous polyps, mucocutaneous hyperpigmentation and an elevated risk of various cancers.

7. Dermatitis Herpetiformis is a pruritic, vesicular rash. It may be seen on the scalp, shoulders, elbows, knees or buttocks. It is associated with celiac disease. The skin lesions usually respond to the introduction of a gluten free diet.

8. Cutaneous disorders of liver disease. As noted previously, patients with liver disease may become jaundiced. In cirrhosis, palmar erythema, telangiactasia, and caput medusa (dilated periumbilical veins) may also be seen. Patients with hemochromatosis, a condition of iron overload, may develop a bronze discolouration of the skin. Xanthomas, deposits of yellowish, cholesterol rich material, develop on the trunk and face of patients with primary biliary cirrhosis.



22. Extraintestinal changes seen in patients with GI disease

Provided through the courtesy of Dr. John McKaigney, University of Alberta

Case 1 – Scleroderma

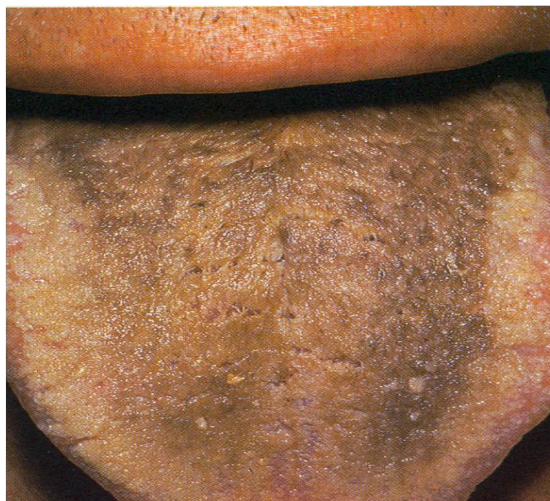
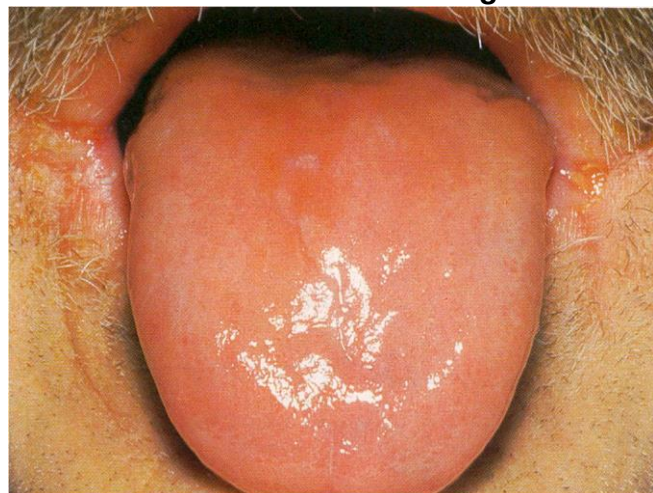
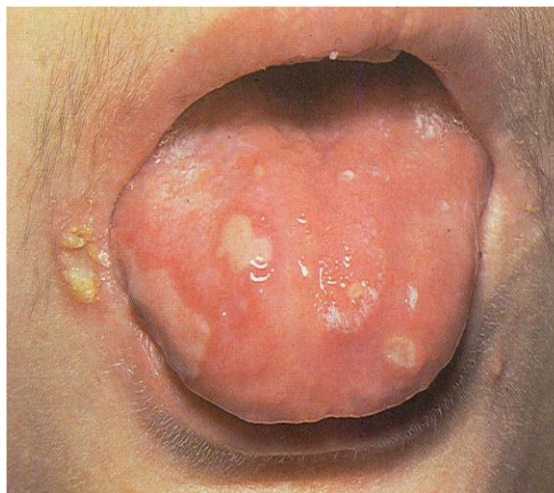
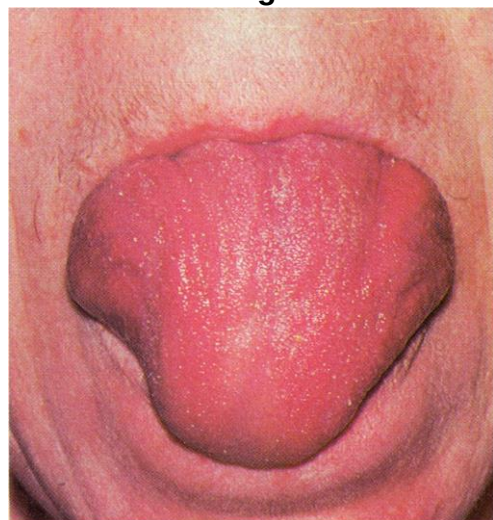


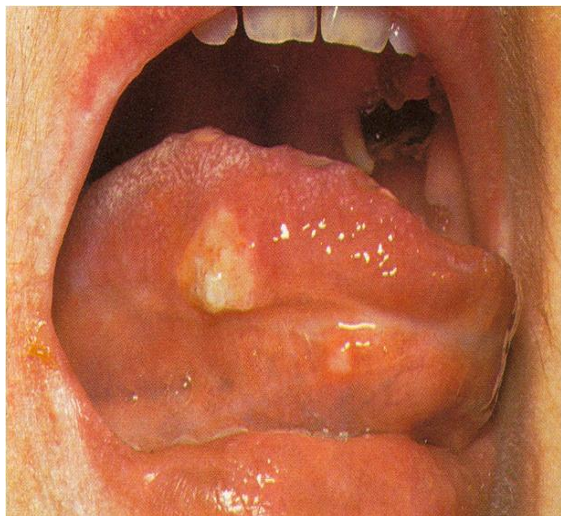
Case 2 - Peutz-Jegher's syndrome



Case 3 - Crohn disease



Case 4 - Osler-Weber-Rendu**Case 5 - Black Tongue—Bismuth Licorice, Fungal infection, Post antibiotic****Case 6 - Canker Sores and Angular Cheilosis****Case 7 – Glossitis****Case 8 – Macroglossia**

Case 9 - Behçet's syndrome—Oral and genital ulceration**Case 10 - Anterior uveitis****Case 11 – Xanthelasmata****Case 12 – Dermatomyositis****Case 13 - Acanthosis nigricans**

Case 14 - Spider angioma syndrome



Case 15 - Blue rubber bleb nevus



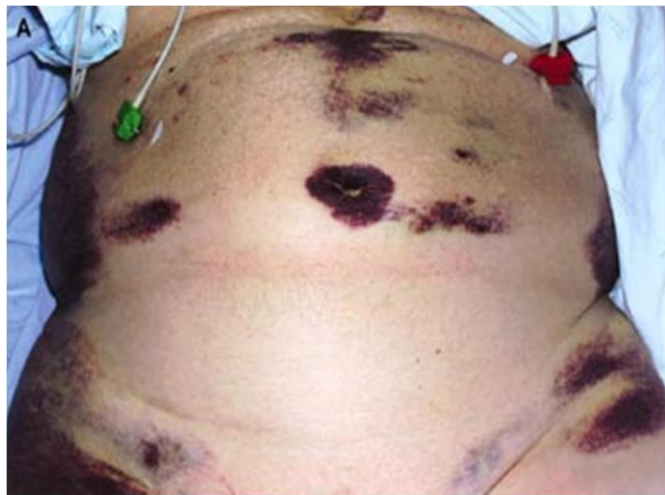
Case 16 - Leukocytoclastic vasculitis



Case 17 - Dermatitis herpetiformis



Case 18 - Cullen's sign



Case 19 - Grey Turner's sign (Flank Hemorrhage) again in acute pancreatitis



Case 20 - Erythema nodosum



Case 21 - Pyoderma gangrenosum



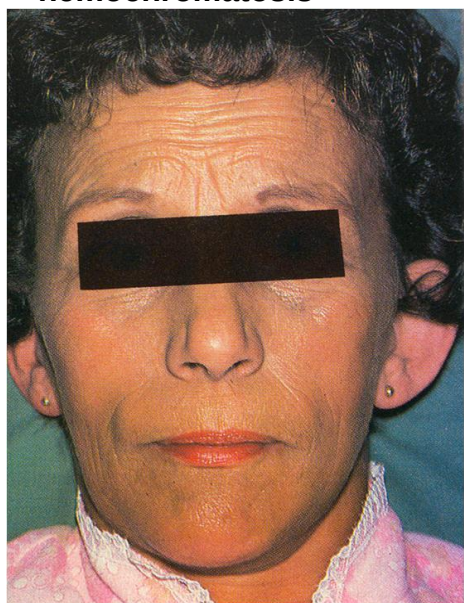
Case 22 - Ascitic abdomen with caput medusa veins



Case 23 - Caput medusa type and umbilical hernia

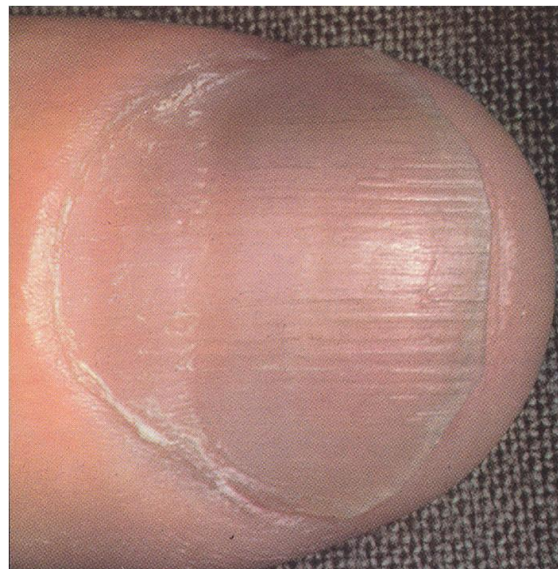


**Case 24 - Skin pigmentation
—hemochromatosis**



Case 25 – Carotenemia



Case 26 - Palmar erythema**Case 27 – Dupuytren's****Case 28 - White nails****Case 29 - Beau's lines****Case 30 - Nail pitting-psoriasis****Case 31 -
Psoriatic Nails**

Case 32 - Calcinosis crest syndrome**Case 33 – Scleroderma**



First Principles of Gastroenterology and Hepatology in Adults and Children – Volume I
A. B. R. Thomson, E. A. Shaffer and T. Gonska

Chapter 2: Esophagus

W.G. Paterson, S. Mayrand and C.D. Mercer



1. Introduction

The esophagus is a hollow muscular organ whose primary function is to propel into the stomach the food or fluid bolus that it receives from the pharynx. Symptoms of esophageal disease are among the most commonly encountered in gastroenterology. Fortunately, most symptoms are due to benign disease that can be easily remedied. The physician must be on the lookout, however, for the more serious disorders, which can present with a similar spectrum of symptoms. This chapter will focus on the pathophysiology, diagnosis and management of the more common esophageal disorders. Rare diseases involving the esophagus will be dealt with only briefly.

2. Anatomy

2.1. Muscular Anatomy

The esophagus is a hollow muscular tube closed proximally by the upper esophageal sphincter (UES) and distally by the lower esophageal sphincter (LES). The UES consists predominantly of the cricopharyngeus and the caudal fibers of the inferior pharyngeal constrictor muscles. The UES forms a transverse slit at the C5–C6 vertebral level due to surrounding bony structures and cartilage. In the proximal one-quarter to one-third of the esophagus, the muscle is striated. There is then a transition zone of variable length where there is a mixture of both smooth and striated muscle. The distal one-half to one-third of the esophageal body and LES are composed of smooth muscle. The LES is located at the junction between the esophagus and stomach, usually localized at or just below the diaphragmatic hiatus. With careful dissection, the LES can be identified as an area of thickened circular smooth muscle consisting of two components, namely, semi-circular “clasp” fibers on the lesser curvature, and “sling-like” muscle bundles on the greater curvature that merge with the long oblique gastric muscle fibers.

2.2. Innervation

The motor innervation of the esophagus is via the vagus nerves. The cell bodies of the vagal efferent fibers innervating the UES and the proximal striated-muscle esophagus arise in the nucleus ambiguus, whereas fibers destined for the distal smooth-muscle segment and the LES originate in the dorsal motor nucleus. The esophagus and LES also receive sympathetic nerve supply (both motor and sensory) arising from spinal segments T1–T10. Sensory innervation is also carried via the vagus and consists of bipolar nerves that have their cell bodies in the nodose ganglion and project from there to the brainstem.

2.3. Blood Supply

Arterial blood supply to the UES and cervical esophagus is via branches of the inferior thyroid artery. Most of the thoracic esophagus is supplied by paired aortic esophageal arteries or terminal branches of bronchial arteries. The LES and the most distal segment of the esophagus are supplied by the left gastric artery and by a branch of the left phrenic artery. Venous drainage is via an extensive submucosal plexus that drains into the superior vena cava from the proximal esophagus and into the azygous system from the mid-esophagus. In the distal esophagus, collaterals from the left gastric vein (a branch of the portal vein) and the azygos interconnect in the submucosa. This



connection between the portal and systemic venous systems is clinically important; when there is portal hypertension, variceal dilation can occur in this area. These submucosal esophageal varices can be the source of major gastrointestinal hemorrhage.

2.4. Lymphatic Drainage

In the proximal third of the esophagus, lymphatics drain into the deep cervical lymph nodes, whereas in the middle third, drainage is into the superior and posterior mediastinal nodes. The distal-third lymphatics follow the left gastric artery to the gastric and celiac lymph nodes. There is considerable interconnection among these three drainage regions.

2.5. Histology

The wall of the esophagus consists of mucosa, submucosa and muscularis propria. Unlike other areas of the gut, it does not have a distinct serosal covering, but is covered by a thin layer of loose connective tissue. The mucosa consists of stratified squamous epithelium in all regions of the esophagus except the LES, where both squamous and columnar epithelium may coexist. Beneath the epithelium are the lamina propria and the longitudinally oriented muscularis mucosa. The submucosa contains connective tissue as well as lymphocytes, plasma cells and nerve cells (Meissner's plexus). The muscularis propria consists of an inner circular and an outer longitudinal muscle layer. The circular muscle layer provides the sequential peristaltic contraction that propels the food bolus toward the stomach. Between the circular and longitudinal muscle layers lies another nerve plexus called the myenteric or Auerbach's plexus, which mediates much of the intrinsic nervous control of esophageal motor function.

3. Physiology

The major function of the esophagus is to propel swallowed food or fluid into the stomach. This is carried out by sequential or "peristaltic" contraction of the esophageal body in concert with appropriately timed relaxation of the upper and lower esophageal sphincters. The esophagus also clears any refluxed gastric contents back into the stomach and takes part in such reflex activities as vomiting and belching.

3.1. Deglutition: Primary Peristalsis

The act of deglutition is a complex reflex activity. The initial phase is under voluntary control. Food is chewed, mixed with saliva and formed into an appropriately sized bolus before being thrust to the posterior pharynx by the tongue. Once the bolus reaches the posterior pharynx, receptors are activated that initiate the involuntary phase of deglutition. This involves the carefully sequenced contraction of myriad head and neck muscles. The food bolus is rapidly engulfed and pushed toward the esophagus by the pharyngeal constrictor muscles. Simultaneously there is activation of muscles that lift the palate and close off and elevate the larynx in order to prevent misdirection of the bolus. Almost immediately upon activation of this reflex, the UES opens just long enough to allow the food bolus to pass through; it then rapidly shuts to prevent retrograde passage of the bolus. The oropharyngeal phase is thus completed and the esophageal phase takes over. This involves two major phenomena: (1) the sequential



contraction of the circular muscle of the esophageal body, which results in a contractile wave that migrates toward the stomach; and (2) the relaxation and opening of the LES, which allows the bolus to pass. The peristaltic sequence and associated UES and LES relaxation induced by swallowing are termed *primary peristalsis*. These can be assessed manometrically using an intraluminal tube to measure pressures. The typical sequence seen during primary peristalsis is depicted in Figure 1. *Secondary peristalsis* refers to a peristaltic sequence that occurs in response to distention of the esophagus. This is a localized peristaltic wave that usually begins just above the area of distention. It is associated with LES relaxation, but not with UES relaxation or deglutition.

3.2. Upper Esophageal Sphincter Function

The UES serves as a pressure barrier to prevent retrograde flow of esophageal contents and the entry of air into the esophagus during inspiration. This high pressure zone is created by tonic contraction of the UES muscles, which is produced by tonic neuronal discharge of vagal lower motor neurons. With deglutition this neuronal discharge ceases temporarily and permits relaxation of the UES. UES opening will not occur with relaxation of the muscles alone; it requires elevation and anterior displacement of the larynx, which is mediated by contraction of the suprahyoid muscles. Relaxation lasts for only one second and is followed by a post-relaxation contraction (Figure 1).

3.3. Esophageal Body Peristalsis

There is a fundamental difference in the control mechanisms of peristalsis between the upper (striated-muscle) esophagus and the lower (smooth-muscle) esophagus. In the striated-muscle segment, peristalsis is produced by sequential firing of vagal lower motor neurons so that upper segments contract first and more aboral segments subsequently. In the smooth-muscle segment, the vagal preganglionic efferent fibers have some role in the aboral sequencing of contraction, but intrinsic neurons are also capable of evoking peristalsis independently of the extrinsic nervous system. Transection of vagal motor fibers to the esophagus in experimental animals will abolish primary peristalsis throughout the esophagus; however, in this setting, distention-induced or secondary peristalsis will be maintained in the smooth-muscle but not in the striated-muscle segment. Furthermore, if vagal efferent fibers are stimulated electrically (Figure 2), a simultaneous contraction will be produced in the striated-muscle esophagus that begins with the onset of the electrical stimulus, lasts throughout the stimulus, and ends abruptly when the stimulus is terminated. In the smooth-muscle esophagus, however, the response to vagal efferent nerve stimulation is quite different, in that the onset of contractions is delayed relative to the onset of the stimulus. The latency to onset of the contraction increases in the more distal segments of the esophagus (i.e., the evoked contractions are peristaltic).

This experimental observation indicates that intrinsic neuromuscular mechanisms exist and can mediate peristalsis on their own. Further evidence for this mechanism is found in studies where strips of esophageal circular smooth muscle are stimulated electrically in vitro. The latency to contraction after stimulation is shortest in the strips taken from the proximal smooth-muscle segment and increases progressively in the more distal strips.



This latency gradient of contraction is clearly important in the production of esophageal peristalsis. Although the exact mechanisms are unclear, initial or deglutitive inhibition is important. With primary or secondary peristalsis, a wave of neurally mediated inhibition initially spreads rapidly down the esophagus. This is caused by the release of the inhibitory neurotransmitter nitric oxide, which produces hyperpolarization (inhibition) of the circular smooth muscle. It is only after recovery from the initial hyperpolarization that esophageal muscle contraction (which is mediated primarily by cholinergic neurons) can occur. Thus, the duration of this initial inhibition is important with respect to the differential timing of the subsequent contraction. Derangements of the mechanisms behind this latency gradient lead to nonperistaltic contractions and dysphagia. Such derangements could result from problems with either the intrinsic neural mechanisms (enteric nervous system) or the central neuronal sequencing.

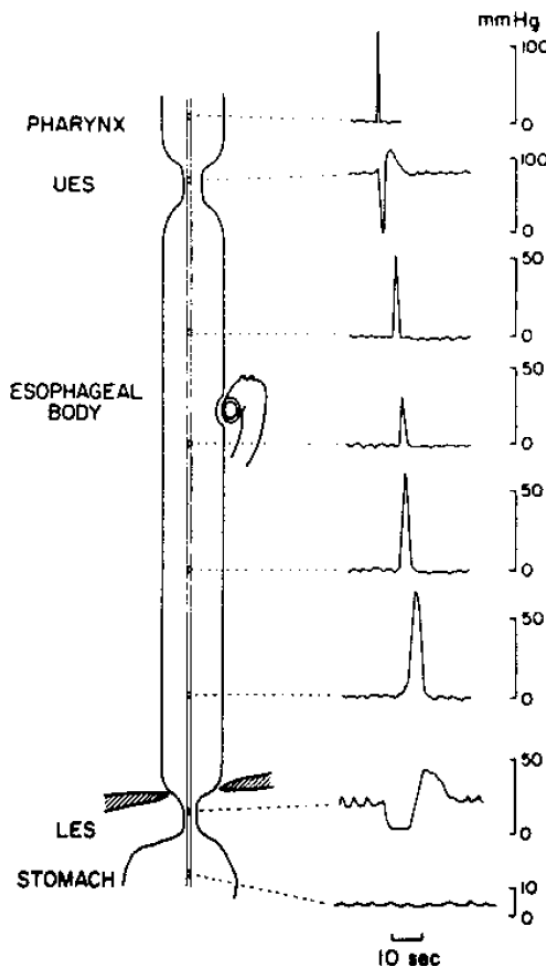


Figure 1. Schematic representation of primary peristalsis as recorded by intraluminal manometry. Swallowing is marked by a rapid pharyngeal contraction coincident with abrupt relaxation of the UES. This is followed by postrelaxation contraction of the UES and sequential contraction of the esophageal body, which produces a pressure wave that migrates toward the stomach. A swallowed food bolus is pushed in front of this migrating contraction wave. The LES relaxes within 1 to 2 seconds of the onset of



swallowing and remains relaxed until the esophageal pressure wave has reached the distal esophagus. LES pressure then recovers and is followed by a postrelaxation contraction, which occurs in continuity with the distal esophageal contraction.

Source: Goyal RK, Paterson WG. Esophageal motility. In: Wood JD (ed.), Handbook of physiology: motility and circulation, vol. 4. Washington, DC: American Physiological Society, 1989. Used with permission.

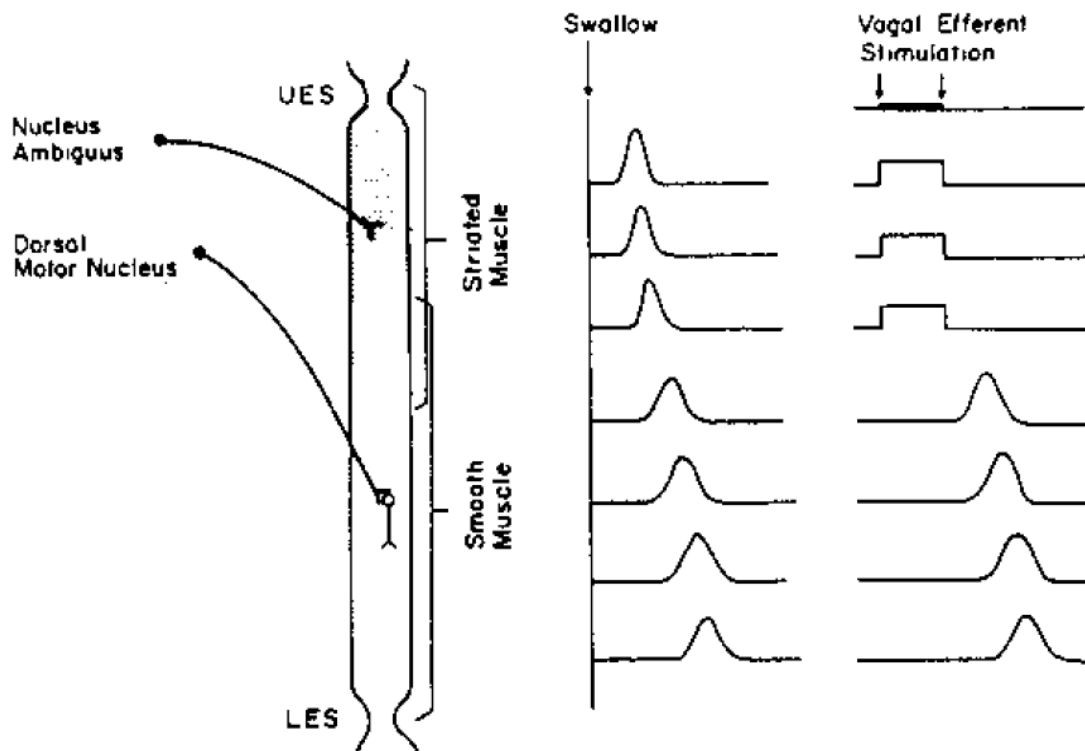


Figure 2. Schematic representation of esophageal peristaltic contractions as evoked by swallowing and vagal efferent nerve stimulation. Swallowing evokes sequential esophageal contractions that pass smoothly from the striated- to the smooth-muscle segment. Electrical stimulation of the distal cut end of a vagus nerve, which simultaneously activates all vagal efferent fibers, evokes peristaltic contractions only in the smooth-muscle segment of the esophagus. In the striated-muscle esophagus, vagal stimulation causes simultaneous contractions that occur only during the period of stimulation. This demonstrates that the striated-muscle esophagus is dependent on central neuronal sequencing for its peristaltic contraction, whereas intrinsic neuronal mechanisms are capable of producing a peristaltic sequence in the smooth-muscle segment.

Source: Goyal RK, Paterson WG. Esophageal Motility. In: Wood JD (ed.), Handbook of physiology: motility and circulation, vol. 4. Washington, DC: American Physiological Society, 1989. Used with permission.



3.4. Lower Esophageal Sphincter Function

The LES is an intraluminal high-pressure zone caused by tonic contraction of a region of physiologically distinct circular smooth muscle at the junction of the esophagus and stomach. This results in a pressure barrier that separates the esophagus from the stomach and serves to prevent reflux of gastric contents up into the esophagus. In normal individuals, resting LES pressure averages between 10 and 35 mmHg above intragastric pressure. Patients with very feeble resting LES pressure are prone to develop gastroesophageal reflux disease (GERD). Unlike that of the UES, the resting tone of the LES is primarily due to myogenic factors that result in tonic contraction of the sphincter. Extrinsic innervation as well as circulating hormones can modify the resting tone; however, the muscle fibers themselves have inherent properties that result in their being tonically contracted.

At the time of deglutition or when the esophagus is distended, the LES promptly relaxes. Swallow-induced LES relaxation is mediated by vagal efferent fibers that synapse on inhibitory neurons of the myenteric plexus. The predominant inhibitory neurotransmitter released from these intrinsic neurons is nitric oxide. LES relaxation usually lasts about five to seven seconds, and is sufficient to abolish the gastroesophageal pressure barrier. This permits the food bolus to pass unimpeded from the esophagus to the stomach. The LES also relaxes to permit belching or vomiting. Inadequate LES relaxation is seen in achalasia and results in dysphagia.

4. Symptoms and Signs of Esophageal Diseases

4.1. Symptoms

4.1.1. Dysphagia

The sensation of food sticking during swallowing is a manifestation of impaired transit of food through the mouth, pharynx or esophagus. It is important to differentiate oropharyngeal (“transfer”) dysphagia from esophageal dysphagia. If the patient has problems getting the bolus out of the mouth, then one can be certain of an oropharyngeal cause; if the food sticks retrosternally, an esophageal cause is indicated. Some patients, however, will sense food sticking at the level of the suprasternal notch when the actual obstruction is the distal esophagus. Thus, it can be difficult to determine the site of the problem when patients refer their dysphagia to the suprasternal notch or throat area. With these patients it is important to elicit any ancillary symptoms of oropharyngeal-type dysphagia, such as choking or nasal regurgitation. It may also be helpful to observe the patient swallowing in an attempt to determine the timing of the symptom; with esophageal dysphagia referred to the suprasternal notch, the sensation of dysphagia onsets several seconds after swallowing begins.

The history can also be used to help differentiate structural from functional (i.e., motility disorders) causes of dysphagia. Dysphagia that is episodic and occurs with both liquids and solids from the outset suggests a motor disorder, whereas when the dysphagia is initially for solids such as meat and bread, and then progresses with time to semisolids and liquids, one should suspect a structural cause (e.g., stricture). If such a progression is rapid and associated with significant weight loss, a malignant stricture is suspected. Associated symptoms help determine the etiology of dysphagia. For instance, a reflux-induced stricture should be suspected if the dysphagia is associated with heartburn or regurgitation, esophageal cancer if there is associated mid-back pain



and weight loss, a motor disorder such as diffuse esophageal spasm if there is angina-like chest pain, and a “scleroderma esophagus” if there is arthralgia, skin changes or Raynaud’s phenomenon.

4.1.2. Odynophagia

This refers to the sensation of pain on swallowing. Local inflammation or neoplasia in the mouth and pharynx can produce such pain. When the pain is retrosternal, one should suspect nonreflux-induced forms of esophagitis, such as infection, radiation or pill-induced (chemical) injury. Less commonly it occurs with esophageal cancer, a deep esophageal ulcer (e.g., Barrett’s ulcer) or esophageal motor disorders.

4.1.3. Heartburn or Pyrosis

The sensation here is one of retrosternal burning. Typically it begins in the low retrosternal area and radiates up to the throat. It may be precipitated by bending over or lying down, and usually begins shortly after consuming certain foods or beverages. It is often associated with regurgitation of acidic material into the back of the throat. “Heartburn” with these features indicates gastroesophageal reflux. This very common symptom has been experienced at one time or another by over one-third of the population and therefore does not necessarily indicate serious disease. Many patients will complain of “heartburn,” but this should not be taken at face value: this term is used by some patients to describe unrelated symptomatology. It is therefore important to have patients describe exactly what they mean by the term *heartburn*.

4.1.4. Regurgitation

This refers to the spontaneous appearance of food or fluid in the back of the throat or in the mouth. Some patients describe this symptom as “vomiting”; therefore it is important to determine whether there is associated nausea, retching, etc., when patients present with “vomiting.” The taste and consistency of the regurgitated material is an important historical detail. Regurgitation of acidic or bile-stained fluid indicates gastroesophageal reflux. Regurgitation of undigested food or stagnant fluid devoid of an acidic taste indicates an esophageal transport problem (e.g., achalasia). (With achlorhydria, such as occurs with pernicious anemia, gastric contents also lack acid.) In motor disorders and mechanical obstruction of the esophagus, food may become stuck and then rather quickly will be regurgitated if it does not pass through into the stomach. Some patients regurgitate food back into their mouths after a meal only to chew and swallow it all over again. This is called *rumination* and, although a rarity in humans, it is a normal physiological event in certain animals.

4.1.5. Nonheartburn Chest Pain

This may also be an indication of esophageal disease. Chest pain, and in particular mid-dorsal pain, is seen in advanced esophageal cancer. The most common type of nonheartburn esophageal chest pain, however, is a pain that is qualitatively similar to the pain of ischemic heart disease (so-called “noncardiac chest pain”). This pain can be squeezing or crushing and can radiate into the jaw or arms. Unlike ischemic heart pain, angina-like chest pain of esophageal origin is not predictably elicited by



exertion and often occurs spontaneously, in relationship to meals or in the middle of the night. It may be associated with other more typical esophageal symptoms. Clearly, patients with this type of pain need to have ischemic heart disease excluded. Once this is done, many will be found to have either gastroesophageal reflux or some form of esophageal motor or sensory disorder.

4.1.6. Waterbrash

The sudden appearance of copious amounts of saliva in the mouth must be differentiated from regurgitation of fluid. With waterbrash, acid reflux into the esophagus stimulates hypersalivation via a (cholinergic) neural reflex.

4.1.7. Bleeding

This may be a symptom of certain esophageal diseases. Mucosal laceration in the region of the gastroesophageal junction (*Mallory-Weiss tear*), as a consequence of retching or vomiting, is a common cause of upper gastrointestinal tract bleeding. Esophageal varices can cause massive hematemesis and melena. Deep esophageal ulcers may also bleed massively, but this is uncommon. Usually the bleeding from ulcerative lesions of the esophagus or esophageal cancer is occult. When the patient does present with hematemesis or melena from esophagitis, the rate of bleeding is usually slow; therefore, significant hemodynamic compromise is uncommon.

4.1.8. Respiratory/Laryngeal Symptoms

These may be a manifestation of esophageal disease or oropharyngeal swallowing disorders. Aspiration at the time of swallowing will cause coughing, choking and eventual hoarseness. In addition, patients with motor disorders or gastroesophageal reflux disease (GERD) may regurgitate esophageal or gastric contents up into the larynx and subsequently aspirate. These patients may present with pneumonia, chronic cough, wheezing, hoarseness or laryngitis. Gastroesophageal reflux might also trigger coughing and wheezing via a vagovagal reflex.

4.2. Signs

It is uncommon for esophageal disease to be associated with specific physical findings. Signs of weight loss and malnutrition can be found if the esophageal problem is so severe that adequate caloric intake is not maintained. There may be signs of metastatic disease (e.g., hepatomegaly, supraclavicular lymphadenopathy) in esophageal cancer. Patients with GERD rarely have respiratory tract signs such as wheezing, hoarseness or lung consolidation. It is important to look for signs of connective tissue disease (especially scleroderma) in patients with reflux symptoms or dysphagia.

The physical examination is more often helpful in patients with oropharyngeal dysphagia. Careful examination of the head and neck for structural and neurologic abnormalities is mandatory. It is also important to look for more generalized neurologic or connective tissue abnormalities. Observing the patient swallow is also useful when oropharyngeal dysphagia is present.



5. Investigations Used in the Diagnosis of Esophageal Disease

A number of tests are available to facilitate the diagnosis of patients with suspected esophageal disease. The choice of which diagnostic test to use depends on the patient presentation and the question(s) to be answered.

5.1. Barium X-ray

This most commonly used method of investigating the esophagus evaluates both structural lesions and motor disorders. It is most useful in evaluating patients with dysphagia. Proper communication between physician and radiologist is vital. Videotaping the barium swallow (“video-fluoroscopy swallowing study”) allows for playback and slow-motion review. This is very helpful in assessing the rapid events of the oropharyngeal phase of swallowing. Use of marshmallows, barium-coated cookies and different consistencies of barium further assesses swallowing disorders, as delays in transport may not be apparent with simple liquid barium. The disadvantage of barium x-rays is that they are relatively insensitive in detecting mucosal disease. If a patient is suspected of having an esophageal perforation, a water soluble contrast agent (Gastrografin) should be used in place of barium.

5.2. Endoscopy with Mucosal Biopsy and Brush Cytology

Fiberoptic endoscopy directly visualizes the esophageal mucosa as well as other areas of the upper gastrointestinal tract. Its direct view is superior to barium x-rays for assessing mucosal disease of the esophagus. Furthermore, pinch biopsies and/or brush cytology of specific lesions are easily obtained through the endoscope. Microscopic evidence of esophagitis may be found even when the mucosa looks grossly normal. Endoscopy is the single most useful test in the evaluation of patients with reflux symptoms, as it permits one to establish the presence or absence of esophagitis (Figure 3) or Barrett’s esophagus (Section 7.3). Endoscopy gives little reliable information regarding esophageal function.

5.3. Endoscopic Ultrasound

This technique combines ultrasonography with endoscopy by placing an ultrasound transducer at the end of a video endoscope. It is particularly useful in staging esophageal cancer in that it is the most sensitive imaging technique for determining the depth of invasion through the esophageal wall and involvement of region lymph nodes.



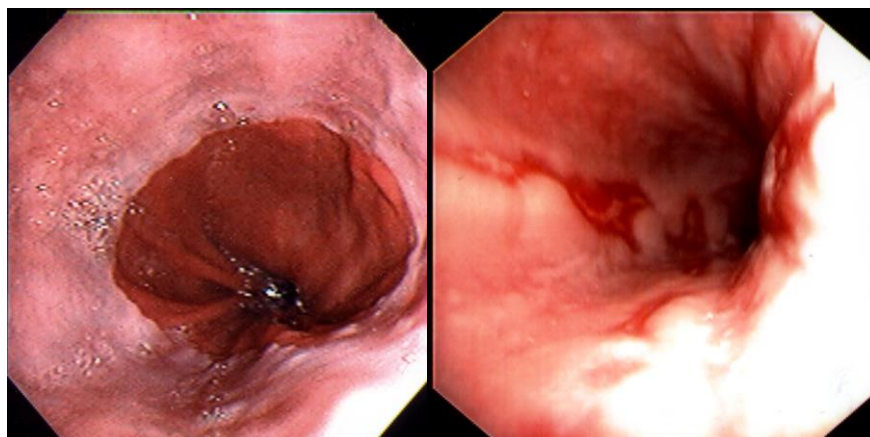


Figure 3. Endoscopic view of normal distal esophagus (left) and from a patient with reflux esophagitis (right). Note linear superficial ulcerations with normal appearing esophageal mucosa in between.

5.4. Esophageal Manometry

This involves recording intraluminal pressures at multiple sites along the esophagus (Figure 1). The most commonly used method involves a perfused multilumen catheter bundle with side holes at 5 cm intervals. Each catheter is connected to a pressure transducer, which in turn is attached to a physiograph. LES pressure and swallow-induced LES relaxation are measured, as are pressure responses to swallowing at several esophageal sites. Pharyngeal peristalsis and UES function can also be measured. Esophageal manometry is the “gold standard” in the assessment of esophageal motor disorders. Motor dysfunction, however, may be intermittent and therefore not detected at the time of the study. Manometry may be combined with provocative tests (acid perfusion, balloon distention and/or pharmacological stimulation of the esophagus with bethanechol or edrophonium) in an attempt to evoke abnormal contractions and reproduce the patient’s chest pain (Section 11). In recent years, the introduction of “high resolution” manometry has allowed for more detailed recording and analysis of esophageal motor function. Using multiple pressure sensors spaced at 1 cm intervals, the pressure profile from pharynx to stomach can be assessed simultaneously. Sophisticated software converts the data to contour plots using different colours to depict pressure variations, thereby facilitating detection of motor disorders. The technique can be combined with simultaneous intraluminal impedance recording, so that bolus transit can be simultaneously measured and correlated with motor function. This powerful methodology enhances the detection of esophageal motor disorders, but is quite expensive.

5.5. Ambulatory Esophageal pH Monitoring

This is performed using a pH electrode passed via the nose into the distal esophagus, which continuously records intraluminal pH over a 24-hour period. Acid reflux events can be identified by an abrupt drop in pH to < 4 . The results of this test are



compared to a healthy control population to determine whether an abnormal degree of gastroesophageal acid reflux is present. The test is most useful, however, in determining whether atypical symptoms coincide with acid reflux events (Figure 4), and in objectively assessing the response to therapy in patients with refractory symptoms. Recently, wireless pH electrodes, which are clipped to the distal esophageal mucosa endoscopically, have been introduced. These are better tolerated and allow for longer recording intervals (e.g. 48-72 hours), which increases diagnostic yield. In addition, combined pH and impedance recording catheters are being used at some centres, and are useful in detecting non-acid or weakly acidic reflux events that may be responsible for refractory symptoms in a small subset of patients.

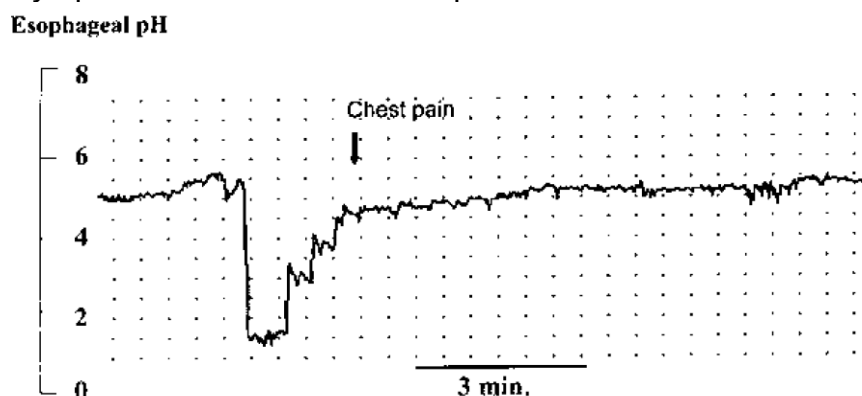


Figure 4. Extract from an intraesophageal 24-hour pH study in a patient with unexplained chestpain. Note that intraluminal pH abruptly drops, indicating a gastroesophageal acid reflux event. This is followed shortly thereafter by the patient's recording chest pain.

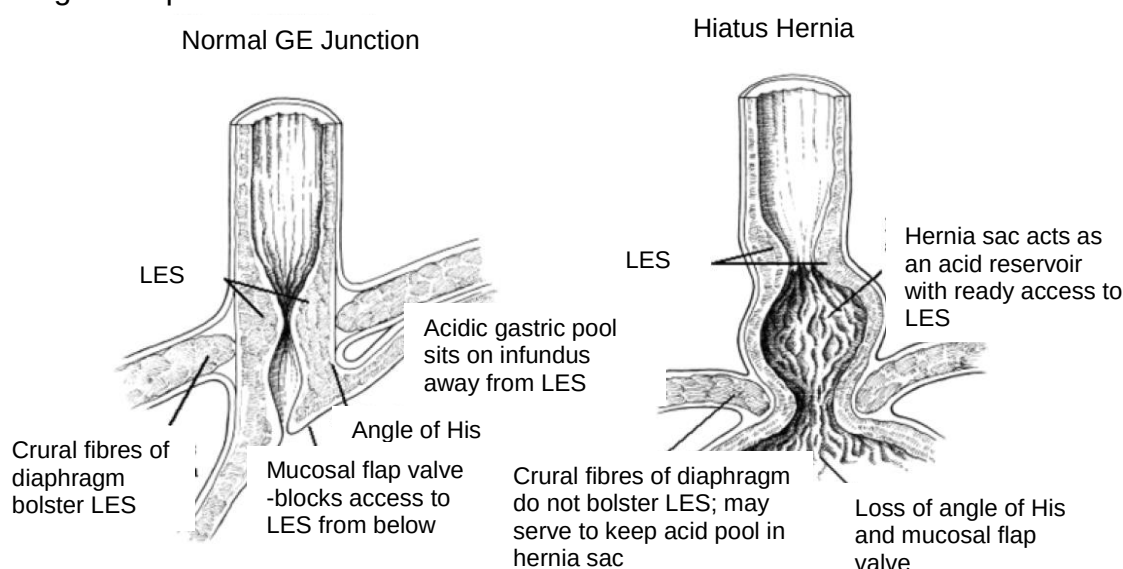


Figure 5. Sliding hiatus hernia (right) in comparison to normal anatomy of the gastroesophageal junction (left). Also depicted are the various mechanisms whereby a hiatus hernia can predispose to GERD. (Reproduced from Paterson WG, Zhang Y. The lower esophageal sphincter. *Clinical & Investigative Medicine*, 2002; 25; 47-53, with permission.)



6. Anatomic Variants

6.1. Congenital Anomalies

Embryologically the gastrointestinal and respiratory tracts start out as a single tube; however, by the second month of gestation they have completely divided. Problems with this process lead to various congenital anomalies, the most common being tracheoesophageal fistula with esophageal atresia. In 85–90% of cases, the proximal esophagus ends in a blind pouch while the distal esophagus consists of a blind pouch in continuity with the stomach. Neonates with this abnormality develop immediate aspiration with feeding. There is no air in the bowel on x-ray films of the abdomen, contrary to what is observed in those with fistulas involving the distal esophagus. In 1–2% of cases there is an “H-type” fistula with atresia. The patient presents with repeated pulmonary infections and abdominal distention. The latter is caused by air getting into the gastrointestinal tract via the fistula when the infant cries. Because the H-type fistula may be very small, the condition may go unnoticed until adulthood, when it is detected during the investigation of recurrent pulmonary infections. Some of these fistulas may close spontaneously but produce paraesophageal inflammation and ultimately localized esophageal stricture formation.



Figure 6. Barium contrast study of a paraesophageal-type hiatus hernia. Note that unlike in a sliding hiatus hernia depicted in Figure 5, the gastroesophageal (GE) junction has maintained its normal position at the hiatus, but a large portion of the gastric fundus has migrated up through the hiatus alongside the distal esophagus. The herniated portion of the stomach is compressing the distal esophagus.

Treatment of esophageal fistulas (with or without atresia) is surgical. The prognosis is now quite good and mortality is usually related to coexistent congenital malformations. It



is important to remember that many of these patients will have gastroesophageal reflux as well as abnormal esophageal peristalsis following surgery, which may cause significant long-term problems.

Congenital esophageal stenosis is a rare anomaly that is also probably related to abnormal differentiation of the gastrointestinal and respiratory tracts, as resected specimens have been found to have pulmonary epithelium and/or bronchial remnants. Sequestered pulmonary remnants with connections to the esophagus but not associated with stenosis have also been described.

6.2. Hiatus Hernia

The majority of hiatus hernias are acquired. Rarely, a hiatus hernia can be caused by a congenitally short esophagus. Hiatus hernias can be divided into two types: (1) sliding and (2) paraesophageal (Figures 5 and 6, respectively). A *sliding hiatus hernia* refers to the condition where a circumferential cuff of cardia and proximal stomach migrates up through the diaphragmatic hiatus and into the thorax. This may reduce and reform spontaneously. These hernias are very common and increase in incidence with advancing age. Generally they are of no clinical significance, despite the fact that many patients and physicians persist in attributing a wide variety of symptoms to them. Large hiatus hernias may be associated with iron deficiency anemia that is presumably caused by recurrent superficial ischemic ulcerations at the site where the diaphragm exerts pressure on the herniated stomach ("Cameron's" ulcers). If no other source of GI blood loss is discovered after thorough investigation, and patients continue to be iron-deficient despite supplementation and antiulcer treatment, surgical correction of the hernia should be performed.

The etiology of the sliding hiatus hernia is obscure. Certainly there is laxity and dilation of the diaphragmatic hiatus and associated laxity of the phrenoesophageal ligament; however, these may well be secondary and not primary pathophysiologic factors. In some cases, persistent gastroesophageal reflux may result in inflammation and consequent esophageal shortening, which in turn leads to the development of a hiatus hernia.

A sliding hiatus hernia is often seen in association with GERD; the precise role of the hernia in the pathogenesis of the reflux remains uncertain. The majority of people with hiatus hernias do not have significant reflux disease, and occasionally patients with severe reflux esophagitis will not have a hiatus hernia. It appears that a hiatus hernia may contribute to gastroesophageal reflux (see Figure 5), but it is most unlikely that this is the prime etiologic factor. A hiatus hernia may contribute to GERD by providing a reservoir of gastric acid that has ready access to the distal esophagus whenever the LES relaxes.

Paraesophageal hiatus hernias are uncommon. These consist of the fundus of the stomach migrating through the hiatus alongside the esophagus without any displacement of the gastroesophageal junction. Although these hernias may be asymptomatic, many surgeons believe that they should be treated surgically when the diagnosis is made because the herniated portion may become strangulated and infarcted. However, a recent study suggests that observation alone is a valid option. Paraesophageal hernias may also cause dysphagia by compressing the distal esophagus (Figure 6). The treatment consists of reduction of the herniated stomach into



the abdomen, elimination of the hernia sac and closure of the herniated defect by reapproximating the crura. Whether or not an anti-reflux procedure (i.e. fundoplication) should be added is debatable. On occasion, both types of hiatus hernias can coexist in the same patient (mixed hiatus hernia).

7. Gastroesophageal Reflux Disease (GERD)

GERD is the most common condition to affect the esophagus, with roughly 5 million Canadians experiencing heartburn or acid regurgitation, the cardinal symptoms of GERD, at least once per week. The disease spectrum ranges from patients with heartburn and other reflux symptoms without morphologic evidence of esophagitis (the so-called endoscopy-negative reflux disease) to patients with deep ulcer, stricture or Barrett's epithelium. Everyone has some degree of gastroesophageal reflux; it becomes pathological only when associated with troublesome symptoms or complications. Fortunately, the vast majority of patients suffering from GERD have an easily controlled disorder. At the other end of the spectrum, there are patients who develop severe damage to the esophagus. Some will develop Barrett's metaplasia as a consequence of gastroesophageal reflux, which in turn predisposes them to adenocarcinoma.

7.1. Pathophysiology

GERD results from the reflux of gastric contents into the esophageal lumen. Early pathogenesis concepts focused on anatomic factors: reflux was considered a mechanical problem, related to the development of a hiatus hernia. We now know, however, that a hiatus hernia can occur without GERD, and conversely, GERD can occur without a hiatus hernia. Many factors are involved in the pathogenesis of GERD.

7.1.1. Barriers to Gastroesophageal Reflux

By far the most important barrier to gastroesophageal reflux is the LES. Factors such as the intra-abdominal location of the sphincter, extrinsic compression exerted by the diaphragmatic crura and the angle of His (which forms a "mucosal flap valve") may augment this barrier but plays a less significant role than the LES itself (Figure 5). Some patients developing reflux esophagitis have feeble LES tone, but in most, resting LES pressure is normal or only slightly impaired. Gastroesophageal reflux occurs by three major mechanisms, as outlined in Figure 7.



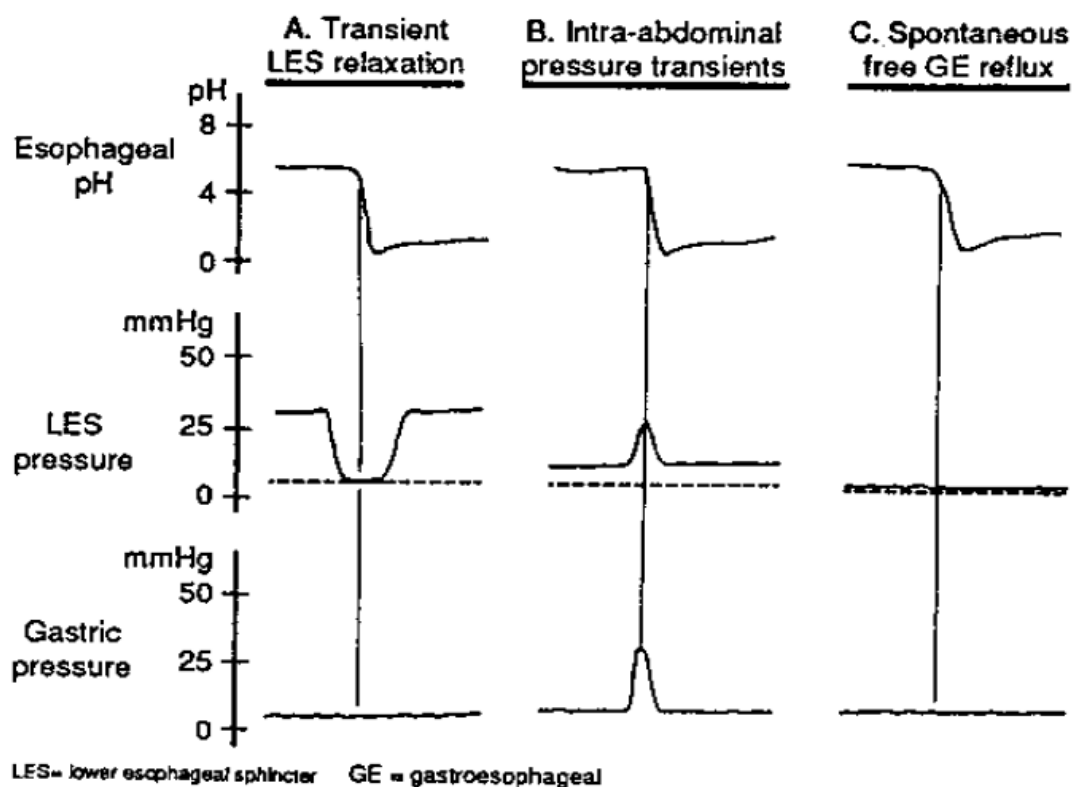


Figure 7. Schematic representation of three different mechanisms of gastroesophageal (GE) reflux.

A. Transient LES relaxation refers to the sudden occurrence of LES relaxation that causes obliteration of the gastroesophageal pressure barrier and permits gastric contents to reflux up into the esophagus. The reflux event is marked by the sudden drop in esophageal pH. These transient LES relaxations are sometimes related to incomplete or failed peristalsis but may also occur in isolation.

B. Intra-abdominal pressure transients are sudden increases in intragastric pressure caused by coughing, sneezing or deep inspiration. The increased intragastric pressure overcomes the LES pressure and results in reflux.

C. Spontaneous free reflux occurs when there is very low or nonexistent LES pressure, which permits spontaneous reflux across the gastroesophageal junction. In healthy volunteers without GERD, virtually all reflux episodes are due to transient LES relaxation. In patients with reflux esophagitis, approximately two-thirds of the reflux episodes are due to transient LES relaxation. The remaining one-third are caused by either intra-abdominal pressure transients or spontaneous free gastroesophageal reflux. Source: Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *The New England Journal of Medicine* 1982; 307:1547–1552. Used with permission.

7.1.2. Esophageal Clearance

Once reflux occurs, the duration of insult to the esophageal mucosa depends on the rapidity with which the esophagus clears this material. Once the initial (primary)



peristaltic wave has passed, the bolus (a portion of which frequently remains) is cleared by one or two secondary peristaltic waves. The remaining small adherent acidic residue is then neutralized by saliva, which is carried down by successive swallows. Disorders of salivation or esophageal motor function will impair this clearance mechanism and predispose to the development of GERD. Patients with severe GERD may have frequent prolonged nighttime reflux episodes because during sleep, peristalsis seldom occurs and salivary flow virtually ceases. Hence the contact time of refluxed material with the esophagus is markedly increased.

7.1.3. Gastroduodenal Factors

In some patients delayed gastric emptying further predisposes to the development of GERD. Bile salts and pancreatic enzymes, if refluxed back into the stomach, can in turn reflux into the esophagus and may inflict worse damage than when gastric juice is refluxed alone. Such reflux into the stomach and then the esophagus may be significant after gastric surgery, when the pylorus is destroyed. Whenever there is increased gastric pressure or an increase in gastric contents, there is greater likelihood that reflux will occur when the sphincter barrier becomes deficient. Furthermore, distention of the proximal stomach is a potent stimulus for transient LES relaxation via a vago-vagal reflex.

7.1.4. Mucosal Resistance

The degree of damage to esophageal mucosa depends not only on the composition of the refluxed material and the amount and duration of reflux, but also on defensive factors within the mucosa itself. These include protective secretions from esophageal glands, the integrity of tight junctions between adjacent epithelial cells and esophageal blood flow. Certain patients are more susceptible to the development of actual mucosal damage, for reasons that are not clear.

7.2. Clinical Features

Most patients present with heartburn and acid regurgitation that onset after eating certain foods or following various postural maneuvers (e.g., bending over, lying flat). Frequency varies from once a week or less to daily episodes with disruption of sleep. Other presenting symptoms include waterbrash, angina-like chest pain, dysphagia and various respiratory symptoms (hoarseness, throat discomfort, cough, wheezing). The dysphagia may be due to the development of a reflux-induced stricture, loss of compliance of the esophageal wall secondary to inflammation, or to abnormal motility induced by the refluxed acid. Odynophagia is rarely a symptom of GERD and should alert the physician to another diagnosis such as infectious esophagitis.

Reflux symptoms are common during pregnancy because of increased intra-abdominal pressures and the LES-relaxant effect of progesterone. Physical examination in patients with GERD rarely reveals associated physical signs. In severe cases with stricture formation there may be weight loss secondary to decreased caloric intake. Patients with GERD secondary to scleroderma may have the physical findings associated with this disease.



7.3. Diagnosis

In the vast majority of patients, GERD can be diagnosed from the history alone and treated without further investigation. Some specialists believe that all patients with longstanding symptomatic gastroesophageal reflux should undergo endoscopy. The argument in favour of this approach is that Barrett's esophagus will be found in about 5-10% of patients with GERD symptoms for more than 5 years. This identifies those at increased risk for the development of adenocarcinoma (Section 7.5.2). Such an approach is of unproven benefit, however, and is almost certainly not cost-effective. Less than half the patients undergoing endoscopy for reflux symptoms will have erosive esophagitis. The remainder have non-erosive reflux disease ("NERD"). Endoscopic biopsy in these patients may detect microscopic evidence of esophagitis (hyperplasia of the basal zone layer, elongation of the papillae, inflammatory cell infiltration, dilated intercellular spaces).

In patients with atypical or multiple symptoms, or typical symptoms that don't respond to empiric treatment, a 24-hour pH reflux study may be necessary to establish that the symptom(s) are in fact due to acid reflux (Figure 4). It is important to first rule out ischemic heart disease if the presenting symptom is angina-like chest pain. In general, patients who present with symptoms of complicated GERD (i.e., dysphagia, bleeding or respiratory symptoms) require investigation. If dysphagia is present, an upper GI endoscopy, with or without initial barium x-ray study, should be performed. It may be reasonable to forgo further testing in patients with heartburn and dysphagia that completely resolve with proton pump inhibitor therapy.

Esophageal manometry has little role to play in the routine assessment of patients with GERD. It may be useful in the assessment of patients with atypical chest pain, and can be combined with an acid perfusion (Bernstein) test as well as with other provocative tests. It is recommended that manometry be performed prior to surgical intervention, because patients with significant underlying motor disorders of the esophagus (e.g., scleroderma) often develop severe dysphagia following an antireflux procedure.

7.4. Treatment

7.4.1. Medical Treatment

The treatment of GERD is directed toward the abnormal pathophysiology. The ideal therapeutic agent would be one that restores barrier function of the gastroesophageal junction. Unfortunately, at present there are no pharmacological agents that are capable of doing this well. The GABAB receptor agonist baclofen has been shown to decrease the frequency of transient LES relaxations and thereby reduce GE reflux. This drug is limited by side effects and is not yet approved for use in GERD. Prokinetic agents can increase LES pressure and improve gastric emptying and esophageal clearance, but unfortunately these drugs have fairly limited efficacy in the treatment of GERD. The one showing the most promise (cisapride) has been withdrawn from the market because of cardiac side effects.

Because of these limitations, acid suppression remains the main pharmacological approach to the treatment of GERD. It is well documented that acid and pepsin (if in an acid milieu) are the predominant constituents of refluxed gastric juice that damage the esophageal mucosa. Over the counter antacids and alginates in



liquid or tablet form can alleviate heartburn symptoms when taken on an as-needed basis, and are commonly used by patients as self-medication.

Both histamine-2 receptor antagonists and proton pump inhibitors have been shown to improve symptoms and heal reflux esophagitis. The efficacy of the proton pump inhibitors is far superior to histamine-2 receptor antagonists in this regard, therefore these agents have become the mainstay of treatment for reflux disease. With a once or twice daily proton pump inhibitor treatment regimen, one can expect symptom resolution and/or healing of esophagitis in over 90% of patients.

Although the level of evidence for efficacy is not strong, certain lifestyle modifications should be considered in the management of GERD. Elevating the head of the bed on 4"-6" blocks and avoiding sleeping in the right lateral position have been shown to decrease nocturnal acid exposure. These maneuvers should be considered in patients with nocturnal reflux symptoms. Avoiding specific foods, drugs or activities may also help. Reflux is more likely to occur after large, fatty meals, especially if the patient becomes recumbent too soon after food ingestion. Certain drugs with smooth muscle-relaxing effects (e.g., calcium channel blockers, nitrates and drugs with anticholinergic effects) can decrease resting LES pressure or delay gastric emptying, and therefore may exacerbate GERD. Obesity also predisposes to GERD, therefore weight loss should be encouraged in obese patients.

GERD is a chronic relapsing condition that usually requires long-term treatment. As a general rule the physician should use the simplest, least expensive and least potent therapeutic regime that will keep the patient's symptoms in check.

7.4.2. Antireflux Surgery

Although several different surgical procedures have been used to treat GERD, the most popular one is the "Nissen fundoplication," originally described by the Swiss Rudolf Nissen in 1955 (Figure 8). Some expert surgeons have reported that this 360-degree gastric wrap can produce long-term control of reflux symptoms in > 90% of patients. However, more recent reports suggest that reflux symptoms eventually recur in up to 30% of patients. The Nissen fundoplication was first performed laparoscopically in 1991, and when compared to the open procedure, this approach results in reduced postoperative pain, hospital stay and recovery period, with similar functional outcome. Surgical therapy improves the LES barrier and is recommended for patients with proven gastroesophageal reflux whose symptoms respond inadequately to medical therapy, or who cannot or will not take the required medication. Ideal patients for the Nissen fundoplication are young and have an incompetent LES with normal esophageal peristaltic contraction amplitude, esophagitis documented by endoscopy and/or endoscopic biopsy and 24-hour esophageal pH monitoring demonstrating frequent reflux. Patients who should not be considered for surgical therapy include those who refuse testing, have certain primary esophageal motility disorders, have not responded initially to a trial of proton pump inhibitors, or who have normal 24-hour pH tests.



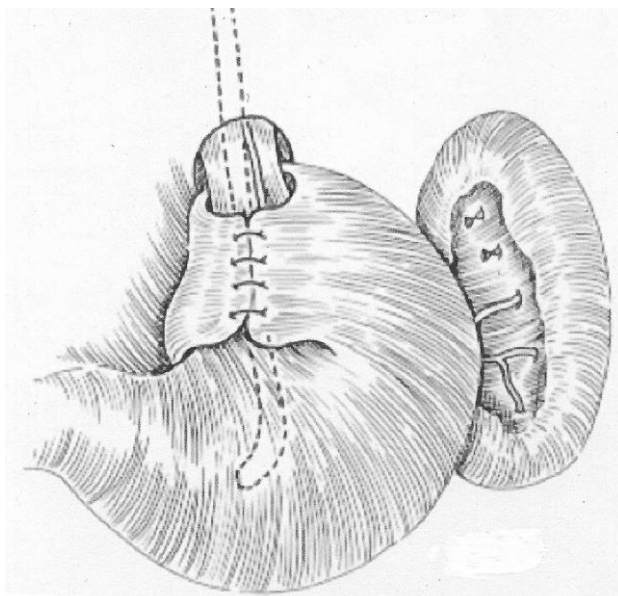


Figure 8. Diagram of completed Nissen fundoplication. The hiatus hernia is reduced into the abdomen and the fundus of the stomach wrapped around the distal esophagus. This serves to bolster the pressure barrier at the gastroesophageal junction and change the anatomy in such a way that the acid pool no longer accumulates near the LES. Spleen is seen on right.

Careful diagnostic evaluation is required in all patients prior to antireflux surgery. Endoscopy determines the presence and severity of esophagitis and excludes Barrett's esophagus, while 24-hour esophageal pH monitoring objectively documents the frequency and duration of reflux and ensures that pathological reflux is present and responsible for the patient's symptoms. pH monitoring is a particularly important test in those patients who do not have endoscopic evidence of esophagitis. Manometry identifies the location and tone of the LES and rules out primary motility disorders of the esophagus, which might contraindicate an anti-reflux operation.

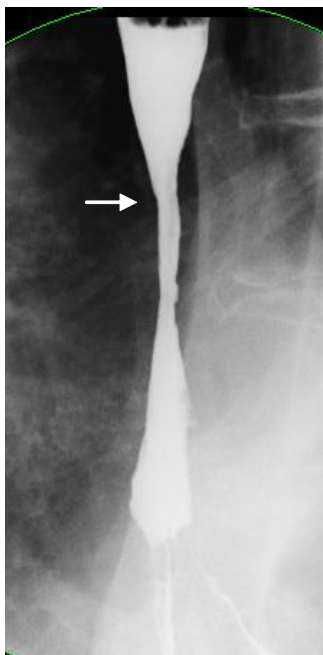
The principles of the operation are to: (1) reduce and fix the LES into the positive pressure environment of the abdomen; (2) augment the LES pressure; and (3) close the diaphragmatic hiatus around the esophagus to prevent the wrap from migrating into the chest postoperatively. Obesity, very large paraesophageal hiatal hernias, shortened esophagus and re-do antireflux surgery are relative contraindications to laparoscopic anti-reflux surgery, particularly early in a surgeon's laparoscopic career. Overall operative mortality for first-time operations is $\leq 0.5\%$. Between 10 and 20% of patients develop significant problems with dysphagia and/or gas-bloat symptoms after surgery. Inability to belch or vomit may also occur. In most cases these problems resolve with time.

7.5. Complicated GERD

7.5.1. Peptic Stricture

Chronic GERD may lead to peptic stricture formation (Figure 9). This is a fibrous stricture related to collagen deposition that occurs in the course of repair of esophagitis. Patients are usually asymptomatic until the luminal narrowing has reached 12–14 mm.





At this point dysphagia to solids occurs. As the stricture progresses, the dysphagia gradually progresses to semisolids and then liquids. Treatment of peptic strictures involves peroral dilation, using either mercury-filled rubber bougies, rigid dilators passed over guidewires, or balloons passed through endoscopes. In close to 50% of patients one or two dilation sessions prove adequate, and no further dilations are required because ongoing medical treatment of the reflux is successful. In others, the stricture recurs and periodic dilations are required to maintain luminal patency. In patients who are otherwise healthy, consideration should be given to antireflux surgery if frequent dilations are required to maintain luminal patency. The success rate of antireflux surgery is lower in such patients with peptic stricture. Strictures are less likely to recur following dilation if the patient is treated with a proton pump inhibitor. For this reason, long-term treatment with a proton pump inhibitor is indicated in patients with peptic

stricture.

Figure 9. Barium swallow radiograph in a patient with a tight peptic stricture (arrow).

7.5.2. Barrett's Esophagus

In this condition the squamous epithelium of the distal esophagus is replaced by columnar epithelium with intestinal metaplasia (Figure 10). Deep ulcers as well as strictures at the new squamocolumnar junction may also develop. Severe hemorrhage may complicate the deep ulcers. This condition occurs in approximately 10% of patients with chronic GERD, although recent prospective studies in which careful biopsies were performed from the region of the gastroesophageal junction suggest that the incidence is may be higher.

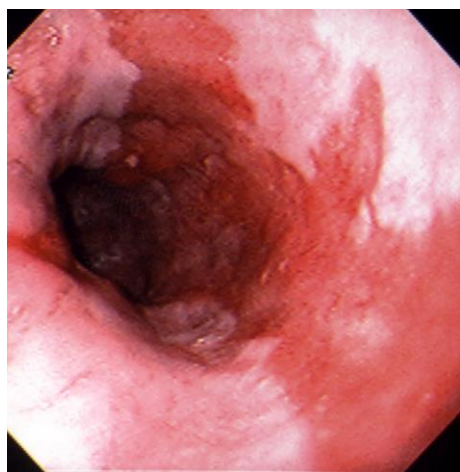


Figure 10. Endoscopic appearance of Barrett's esophagus. Note that broad tongues of columnar-type epithelium extend up from the gastroesophageal junction into the esophageal body that is normally lined with squamous epithelium. Histology reveals an intestinal-type metaplasia with goblet cells.



Barrett's epithelium is a premalignant condition. At the time of initial presentation, up to 10% of patients found to have Barrett's esophagus will have coexistent adenocarcinoma arising in the Barrett's epithelium. This number gives an exaggerated impression of the magnitude of risk, because Barrett's esophagus patients with cancer are more likely to seek medical attention. The true incidence of adenocarcinoma developing in Barrett's epithelium is only about 1 case for every 200 patient-years of follow-up. This nevertheless represents about a 30- to 40-fold increase over the risk faced by the general population. For this reason current guidelines recommend that periodic (i.e., every 2-3 years) endoscopy and mucosal biopsy should be performed in order to detect precancerous lesions or early cancer. Most patients will develop severe dysplasia before frank invasive carcinoma occurs. Thus, if patients are found to have severe dysplasia or early mucosal carcinoma, esophageal resection should be considered in order to prevent the development of invasive carcinoma. Recently, photodynamic therapy, radiofrequency ablation and endoscopic mucosal resection have been introduced as effective, less invasive alternatives to surgery in patients with severe dysplasia or intramucosal carcinoma complicating Barrett's esophagus.

7.5.3. Respiratory Complications

In some patients the refluxed gastric contents may get past the UES and into the larynx and lungs. This may produce asthma, recurrent chest infections, chronic cough and laryngitis. In addition, gastroesophageal reflux may trigger broncho-spasm or cough via a neural reflex. GERD with aspiration is more commonly seen in the paediatric age group; when present, antireflux surgery should be performed unless there is a well-documented response to medical therapy.

8. Nonreflux-Induced Esophagitis

8.1. Infectious Esophagitis

Bacteria rarely cause primary esophageal infection, although the esophagus can be involved secondarily by direct extension from the lung. The two most common forms of infectious esophagitis are caused by *Candida* and herpes viruses. Other viruses (e.g., CMV, HIV) and fungi can also cause esophagitis; however, this is uncommon and almost invariably associated with immunosuppression.

8.1.1. Candida Esophagitis

This is by far the most common form of infectious esophagitis. Usually there is a predisposing cause, such as diabetes mellitus, recent antibiotic therapy or some form of immunocompromise. The patient may be asymptomatic. Not all patients will have associated oral thrush. More commonly, however, patients present with odynophagia, retrosternal chest pain and/or dysphagia. Severe cases can be complicated by bleeding, a stricture and sinus tract formation with secondary lung abscess. Barium x-rays may reveal an irregular granular or even cobblestone appearance to the esophageal mucosa, but in many patients the barium esophagogram is unremarkable; for this reason, endoscopy with biopsy and brushing are required to make the diagnosis. The typical endoscopic appearance is the presence of small raised whitish plaques (Figure 11).





Figure 11. Endoscopic appearance of *Candida* esophagitis. Note the small white plaques adherent to the esophageal mucosa.

When the plaques are removed the underlying mucosa is seen to be erythematous and friable. Specimens obtained by biopsy or brush cytology should be examined microscopically for the presence of typical *Candida* yeast with pseudohyphae formation. Mild cases of *Candida* esophagitis can be treated with oral nystatin (luminal treatment); however, more extensive disease, especially if the patient is immunocompromised, may require systemic treatment with fluconazole.

Amphotericin B is required if there is evidence of systemic spread.

8.1.2. Herpes Simplex Esophagitis

Next to *Candida*, this is the most common form of infectious esophagitis. The clinical presentation is much the same as with *Candida* esophagitis. There may also be constitutional symptoms of a viral upper respiratory tract infection preceding the esophageal symptoms. Herpetic mouth or skin lesions may also develop. This infection occurs most frequently in immunosuppressed patients, but also develops sporadically in healthy young adults. Endoscopy with biopsy and brush cytology is required to confirm the diagnosis. The pathognomonic finding is the eosinophilic “Cowdry’s Type A” intranuclear inclusion body. Herpetic esophagitis is self-limiting in immunocompetent individuals; specific treatment is not indicated. Symptoms of odynophagia often respond to a combination of antacids mixed with viscous Xylocaine®. In severely immunocompromised patients, intravenous acyclovir treatment should be instituted.

8.2. Eosinophilic (Allergic) Esophagitis

In recent years there has been increasing recognition of so-called allergic or eosinophilic esophagitis. It used to be felt that this was largely restricted to the paediatric population, however, adults of all ages are now being diagnosed with this disease. It is most common in young adult men. The typical presentation is recurrent solid food dysphagia and often food bolus obstructions. Barium swallow x-ray and endoscopy may show little or no change. Proximal esophageal strictures or a diffuse small caliber esophagus is a clue to this disease when seen on barium x-ray. Endoscopically (Figure 12) one often sees subtle longitudinal furrowing of the esophageal mucosa, transverse ridges or corrugation or whitish papules or plaques that have the appearance of candida esophagitis. The latter actually represent small eosinophilic abscesses. Another characteristic feature is fragility of the esophageal mucosa, such that bits of mucosa often tear away when passing the endoscope through the esophageal lumen. The diagnosis requires mucosal biopsy, which shows intense infiltration of eosinophils into the squamous mucosa. More than 15 eosinophils per high-powered field confirms the diagnosis.



Although food allergy may trigger this disorder, it is also possible that inhaled allergens may result in indirect involvement of the esophagus as part of the allergic response. It is also possible that swallowed mucus-containing inhaled allergens are responsible. A majority of these patients have a history of allergic disease such as asthma, skin atopy or allergic rhinitis. In general, allergy testing is usually unhelpful. In the paediatric population, exclusion diets and/or elemental diets have been reported to be beneficial. Currently, the preferred treatment in adults is either topical steroids (fluticasone, which is swallowed rather than inhaled) or the leukotriene inhibitor montelukast sodium.

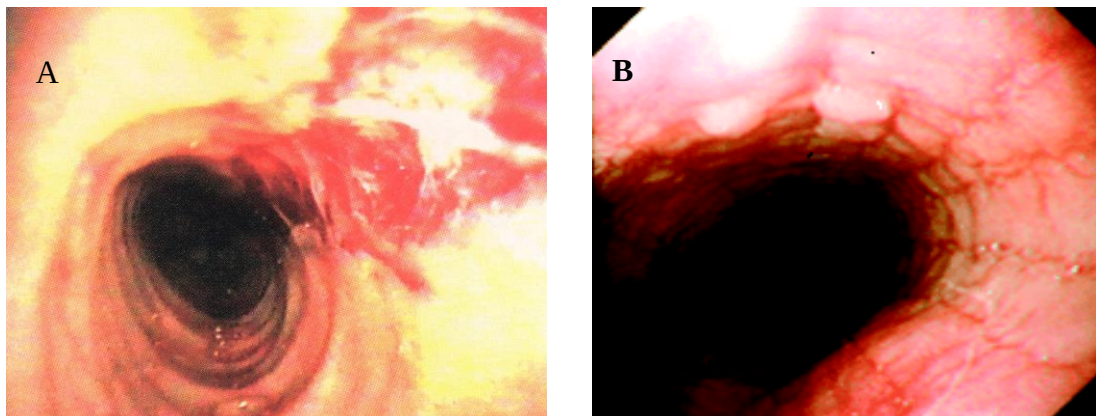


Figure 12. Endoscopic features of eosinophilic esophagitis. A) Note transverse ridges (“trachealization”) and mucosal trauma (top right). The latter is caused by trauma from passage of the endoscope, due to mucosal fragility and subtle luminal narrowing. B) Longitudinal furrowing and corrugation.

8.3. Esophagitis Associated with Immune-Mediated Disease

Rarely, esophagitis can occur in association with Crohn disease or Behçet’s syndrome. The typical lesion is scattered aphthous-type ulcerations, although severe transmural involvement with stricture formation can occur. The esophagus can also be severely involved in pemphigoid, pemphigus, epidermolysis bullosa and lichen planus. Esophagitis occurs in as many as one-third of patients who develop chronic graft-versus-host disease after bone marrow transplantation. The typical lesion is a generalized epithelial desquamation of the upper and middle esophagus. There may be associated ring-like narrowings or strictures due to submucosal fibrosis. A nonspecific esophageal motor disorder may also develop and result in superimposed reflux esophagitis because of poor esophageal clearing. Sarcoidosis also rarely causes esophageal inflammation.

8.4. Chemical-Induced Esophagitis

8.4.1. Caustic Chemical Ingestion

Strong acids or alkalis ingested accidentally or as a suicide attempt cause marked esophagitis. Alkali tends to be more injurious to the esophageal mucosa than acid and produces liquefaction necrosis as well as thermal burns (due to heat release when the alkali is hydrated by gut secretions). Acids tend to produce superficial



coagulation necrosis and eschar formation. Typically the patient develops immediate chest pain and odynophagia. Oral burns also may produce local pain and drooling. There may be respiratory symptoms such as stridor, dyspnea and hoarseness if the airway is contaminated. Symptoms alone do not permit accurate prediction of the presence or absence of esophageal injury; therefore early diagnostic endoscopy should be considered in most patients. Clearly, endoscopy should not be performed if there is evidence of esophageal perforation. In the management of these patients, it is imperative to maintain an adequate airway. Oral intake must be stopped and intravenous fluids administered. Empiric treatment classically has involved antibiotics and corticosteroids, but there is no good evidence documenting the efficacy of this approach. Patients who survive the acute phase of the injury are at risk of developing strictures because of the intense collagen deposition associated with healing. This often requires repeated esophageal dilation to maintain luminal patency.

Lye-induced injury increases the risk of developing squamous cell carcinoma of the esophagus. Typically there is a 30- to 50-year lag time before the development of cancer. For this reason any patient with previous lye injury and new esophageal symptoms should be promptly investigated. The extent of the risk is such that most experts do not recommend periodic endoscopic surveillance.

8.4.2. Pill-Induced Esophagitis

A large number of oral agents can cause localized esophageal injury. The antibiotic doxycycline and the anticholinergic emepronium bromide are two of the most common culprits. Nonsteroidal anti-inflammatory drugs and slow-release forms of potassium chloride are also frequently implicated. Patients with this type of injury typically take their medication with a small amount of water and then immediately lie down to go to bed. They may then wake up several hours later with severe retrosternal chest pain and odynophagia. Capsules and tablets are notorious for being transported through the esophagus quite poorly unless adequate amounts of fluid are ingested at the same time. This is an important point to remember in counselling all patients who take medicines at bedtime. Rarely, the medication becomes lodged and causes a deep esophageal ulcer with perforation. More commonly the ulceration is superficial and heals in a few weeks. Late stricture formation may occur. Patients with esophageal motility disorders are particularly prone to this complication. The bisphosphonate alendronate sodium has also been reported to rarely cause esophageal ulceration, but the mechanism of this injury is unclear.

8.5. Radiation-Induced Esophagitis

When included in the field of irradiation, the esophagus becomes inflamed in up to 80% of patients receiving therapeutic radiation for cancer. The risk of esophagitis is greater if there is concomitant chemotherapy. The patients typically develop chest pain, dysphagia and odynophagia shortly after the initiation of therapy. This can be a serious problem in such patients, who are often already severely malnourished. Late stricture formation is a well recognized complication.

9. Disorders of the Oropharyngeal Phase of Deglutition

A variety of structural and functional disorders can disrupt the oropharyngeal phase of deglutition and result in oropharyngeal or “transfer”-type dysphagia (Table 1).



In the assessment of these patients it is important to exclude disorders for which specific treatment is available. The most important investigation is a carefully performed video fluoroscopic study of the swallowing mechanism. In addition to the usual barium studies, it is helpful to observe deglutition when the patient swallows barium soaked cookies or bread. Not only will this examination identify and characterize disorders of oropharyngeal coordination, it will also help exclude structural lesions. If an inflammatory, neoplastic or other structural lesion is suspected, direct or indirect laryngoscopy is indicated. At present, manometric studies of the pharynx and UES add little to what can be learned from radiologic studies.

Ideally, treatment of oropharyngeal motor disorders should be directed at the underlying disease. Frequently this is not possible, and nonspecific treatment must be instituted. In some cases reassurance and education are all that is required. Many patients will be able to control their symptoms simply by eating slowly and carefully in a relaxed atmosphere. In patients in whom aspiration develops because of inadequate clearing of the hypopharynx after the initial swallow, it is beneficial to have the patient immediately follow a “bolus” swallow with a second, “dry” swallow. Correcting denture problems and avoiding foods of certain consistency may also help. Speech-language pathologists have special expertise as swallowing therapists and can be very helpful in the management of these patients.

A *normal* tracing is on the left and depicts sequential “peristaltic” contractions in the esophageal body with full LES relaxation. *Hypertensive peristalsis* or “*nutcracker*” *esophagus* is characterized by normal peristalsis and LES relaxation, but the amplitude of contraction in the distal esophagus is abnormally high (> 180 mmHg). In *diffuse esophageal spasm*, normal peristaltic waves are interspersed with high-pressure, nonpropulsive (simultaneous) contraction waves and are often repetitive. The resting LES pressure may be abnormally high, but swallow-induced LES relaxation is normal. In *achalasia* there is complete absence of normal peristalsis in the smooth-muscle esophagus (simultaneous contractions only) and swallow-induced LES relaxation is either absent or incomplete. Note also that resting intraesophageal pressures are elevated. *Scleroderma* is characterized by the presence of weak, nonperistaltic esophageal contractions and a markedly hypotensive LES that relaxes normally with swallowing.

For patients in whom these simple measures are not helpful and whose symptoms are such that respiratory and nutritional complications are developing, cricopharyngeal myotomy is sometimes performed. This helps patients with true cricopharyngeal achalasia or Zenker’s diverticulum (Section 13). Unfortunately, the response to myotomy is inconsistent in most other patients with oropharyngeal dysphagia, because inadequate opening of the UES is rarely due to dysfunction of the cricopharyngeal muscle alone. More often there is associated weakness of the suprahyoid muscles, which actually open the sphincter, and/or associated problems with pharyngeal peristalsis. Cricopharyngeal myotomy does little to improve such altered physiology. Once cricopharyngeal myotomy has been performed, the patient has lost an important defense mechanism against the aspiration of refluxed material. The patient should therefore be instructed to elevate the head of his or her bed on blocks in order to minimize this risk. For this same reason patients



with severe GERD should not undergo cricopharyngeal myotomy unless the reflux can be controlled.

Table 1. Classification of disorder causing oropharyngeal dysphagia

-
- Central nervous system disease
 - Cerebrovascular accident (brainstem, pseudobulbar palsy)
 - Wilson's disease
 - Amyotrophic lateral sclerosis
 - Brainstem neoplasm
 - Tabes dorsalis
 - Parkinson's disease
 - Peripheral nervous system disease
 - Bulbar poliomyelitis
 - Miscellaneous peripheral neuropathies
 - Head and neck neoplasms
 - Past-radical neck surgery
 - Muscle disease
 - Muscular dystrophy
 - Polymyositis and dermatomyositis
 - Metabolic myopathy (e.g., hypo- and hyperthyroidism)
 - Amyloidosis
 - Systemic lupus erythematosus
 - Myasthenia gravis
-
- Local disorders
 - Oropharyngeal inflammation
 - Oropharyngeal neoplasms
 - Zenker's diverticulum
 - Idiopathic conditions
 - Cricopharyngeal achalasia
 - Idiopathic oropharyngeal incoordination
-

When all other measures fail and nutritional and respiratory complications develop, a gastrostomy feeding tube should be placed.

10. Motor Disorders of the Esophagus and Lower Esophageal Sphincter

Esophageal motor disorders can be classified as either primary or secondary. Primary disorders refer to those that usually affect the esophagus alone and have no known etiology. Secondary disorders are motility derangements caused by some other systemic or local condition. Examples of secondary disorders include acid-reflux-induced dysmotility, dysmotility related to the neuropathy associated with diabetes and motor dysfunction secondary to esophageal involvement in scleroderma or other



connective tissue disorders. The well-defined primary motor disorders include the hypertensive peristaltic or “nutcracker” esophagus, diffuse esophageal spasm and achalasia (Figure 13).

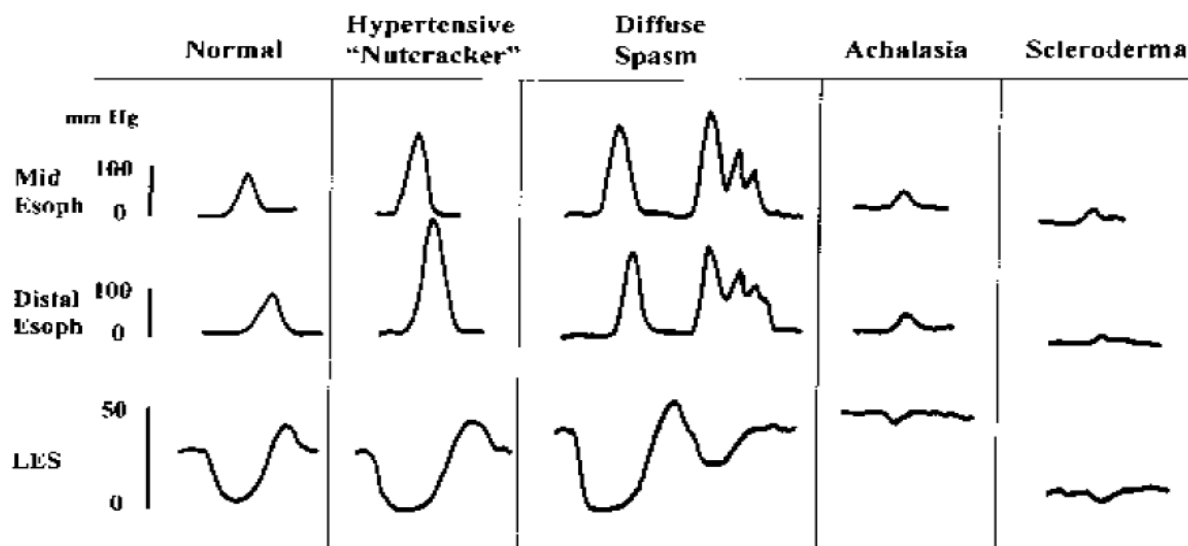


Figure 13. Schematic representation of manometric features of the major esophageal motor disorders.

Many cases of primary motility disorders are actually “nonspecific,” having a variety of abnormalities that do not fulfill criteria established for the well-defined esophageal motor disorders. Patients with primary motor disorders typically present with dysphagia and/ or chest pain. The pain is often qualitatively similar to angina pectoris and has been classically attributed to smooth-muscle spasm. However, recent studies have suggested that the pain may be secondary to a lowered sensory threshold to esophageal stimuli such as distention or acid. Some patients with motor disorders will have secondary GERD because of poor clearing or poor LES function. Here, heartburn and regurgitation may be prominent symptoms. The diagnosis of a motor disorder can be made on the basis of history and barium swallow x-ray and endoscopy. If there is dysphagia referred to the retrosternal area and no evidence of a structural lesion or inflammatory disease on x-ray or endoscopy, then by exclusion the patient’s dysphagia is likely related to a motor disorder. As mentioned previously, the quality of the dysphagia (e.g., sporadic, unpredictable dysphagia to both liquids and solids) is also helpful in differentiating motor disorders from structural causes of dysphagia. During fluoroscopy, the radiologist is usually able to detect abnormalities of motor function as the barium is swallowed. The use of a solid bolus, such as a piece of bread soaked in barium, may be helpful in diagnosing esophageal rings or webs. Endoscopy primarily rules out secondary causes of the disorder (i.e., reflux or eosinophilic esophagitis and neoplasm). In order to define specifically the type of motor disorder present, however, esophageal motility studies are required. The manometric features of the important esophageal motor disorders are depicted schematically in Figure 9.



10.1. “Nutcracker” Esophagus

This motility disorder is characterized by normally propagated but high amplitude peristaltic waves in the distal esophagus. The duration of the contraction wave is also often prolonged. LES relaxation is normal, although in many patients the resting LES pressure is elevated. Patients often present with angina-like chest pain and usually do not complain of dysphagia. Nutcracker esophagus is the most frequent abnormal manometric finding in patients referred for evaluation of noncardiac angina-like chest pain. The etiology is unknown. Rarely, this disorder progresses to diffuse esophageal spasm or even vigorous achalasia. Reassurance that the pain is not cardiac but is secondary to a benign esophageal condition is the most important part of treatment. Nitrates and calcium channel blockers (to relax smooth muscle) have been used extensively, but have no proven benefit. Tricyclic antidepressant drugs are effective in alleviating the pain in these patients, presumably because of their effect on visceral sensation. In some patients with nutcracker esophagus, pain is actually triggered by acid reflux; these patients often respond dramatically to appropriate antireflux therapy.

10.2. Diffuse Esophageal Spasm

This is characterized by normal peristalsis interspersed with frequent high pressure nonpropagated or “tertiary” waves and multi-peaked waves. Patients often present with dysphagia and chest pain. In advanced diffuse esophageal spasm, the x-ray will show a corkscrew pattern (Figure 14) as different segments of the esophagus vigorously and simultaneously contract. The etiology is obscure, but may relate to degenerative changes in the intrinsic and extrinsic esophageal nerves. Management involves reassurance and the use of nitrates or calcium channel blocking agents. Injection of Botulinum toxin into the muscle of the LES or distal esophagus also appears to be effective in alleviating dysphagia in this condition. Rarely, patients with severe disease unresponsive to medical measures may benefit from a long esophageal myotomy.



Figure 14. Barium contrast X-ray depicting a “Corkscrew” esophagus, typical of diffuse esophageal spasm. Simultaneous contractions at multiple sites along the esophagus create this pattern. A similar X-ray picture may be seen in vigorous achalasia, therefore manometry is required to firmly establish the diagnosis.



10.3. Achalasia

This uncommon primary motility disorder is characterized by aperistalsis in the body of the esophagus and absent or incomplete LES relaxation in response to swallowing. Resting LES pressures may also be elevated. Failure of LES relaxation leads to progressive proximal dilation of the esophagus with consequent elevated resting intraesophageal pressures. On x-ray the esophagus is dilated, and retained food and fluid may be present. The distal esophagus narrows in a beak-like fashion (Figure 15). This “beak” represents the hypertonic, nonrelaxing LES. In some patients there are associated high amplitude nonperistaltic contractions in the esophageal body, a condition called *vigorous achalasia*. Achalasia is caused by an inflammatory reaction directed against the inhibitory nitric oxide neurons within the esophageal and LES myenteric plexus. Nerve damage may also be found in the vagal nerve trunks and the dorsal motor nuclei, although these are likely secondary to the myenteric plexus damage. The parasite *Trypanosoma cruzi*, which is endemic in Brazil, can cause achalasia by destroying myenteric neurons (Chagas’ disease). Neoplastic disease can also interfere with esophageal and LES nerve function and cause secondary or “pseudo” achalasia. In most cases, however, the cause of the degeneration is unknown. The cardinal symptom of achalasia is dysphagia, although chest pain and even heartburn may be present. The heartburn is usually not due to gastroesophageal reflux. It may be caused by lactic acid formed by fermentation of stagnant esophageal contents. Another common symptom of achalasia is regurgitation of esophageal contents. Patients with achalasia secondary to cancer are typically older and present with rapidly progressive dysphagia and significant weight loss.



Figure 15. Typical barium x-ray in a patient with achalasia. Note that the esophagus is dilated and there is an air-barium meniscus indicative of stasis. At the gastroesophageal junction there is a beak-like narrowing, which is caused by the nonrelaxing LES. The mucosal contour at this narrow area appears normal, which helps distinguish this from a stricture caused by malignancy or reflux disease.

In mild cases of idiopathic achalasia treatment can begin with the use of calcium channel blockers or long-acting nitrates, which have been shown to decrease LES pressure. This is rarely successful in the long term, however. The treatment then usually performed is pneumatic balloon dilation of the LES. This consists of passing a balloon across the sphincter and inflating it rapidly so that the sphincter is forcefully dilated. Pneumatic dilation is successful in alleviating the dysphagia and improving esophageal transport in 60–90% of patients, although repeated dilations are often



required to achieve the highest success rate. Patients who do not respond to pneumatic dilation should be treated with Heller myotomy. This consists of a longitudinal incision through the muscle of the LES, which is now done via a laparoscopic approach. Increasingly, laparoscopic Heller myotomy is being offered as first-line therapy in patients with achalasia. Following either pneumatic dilation or Heller myotomy, the patient can develop GERD, because the pressure barrier preventing reflux has been destroyed. This tends to be worse after Heller myotomy and has led some surgeons to perform a modified antireflux procedure at the time of myotomy. Recent studies have found that injection of botulinum toxin into the muscle of the LES can alleviate dysphagia in approximately two-thirds of patients with achalasia. This therapy is limited because the response is not sustained (average duration is approximately one year), but it may be a useful treatment option in elderly patients who would not tolerate the complications of more invasive therapy. Achalasia patients have an increased risk of developing esophageal cancer and need to be carefully evaluated if new esophageal symptoms develop. Unlike Barrett's esophagus, regular endoscopic surveillance is not recommended in achalasia patients.

10.4. Scleroderma Esophagus

Patients with scleroderma frequently have esophageal involvement. This may occur even in the absence of obvious skin and joint involvement, although in such cases, Raynaud's phenomenon is almost always present. The initial event is damage to small blood vessels, which in turn leads to intramural neuronal dysfunction. With time, actual muscle damage and fibrosis occur. This results in a very hypotensive LES, as well as weak, nonpropulsive esophageal contractions. Scleroderma may also involve the stomach and cause delayed gastric emptying. As a result, patients develop gross GERD. They present with heartburn and regurgitation, as well as dysphagia. The dysphagia can be due to poor esophageal propulsion and/or reflux-induced stricture. These patients need very aggressive treatment for GERD, often requiring twice-daily PPI therapy. Because they have very poor peristaltic function, increasing the barrier at the LES with antireflux surgery may markedly worsen the dysphagia.

11. The Esophagus as a Cause of Angina-Like Chest Pain

At least one-third of the patients referred to a cardiologist or admitted to a coronary care unit because of angina-like chest pain will have cardiac causes excluded. Because in most of these patients an alternative etiology is not apparent, they are often labeled as having "noncardiac chest pain." Lack of a specific diagnosis may lead to ongoing anxiety, changes in lifestyle and frequent medical consultations if the patient continues to worry that serious heart disease may be present. In such patients esophageal disease or dysfunction should be considered. The pathophysiology of angina-like chest pain of esophageal origin is poorly understood. In some patients acid reflux is the cause: these patients experience angina-like chest pain under circumstances in which most people would experience heartburn. In others, the pain is caused by abnormal "spastic" contractions of the esophagus that either occur spontaneously or are secondary to acid reflux. These contractions may be confined to the longitudinal smooth muscle layer, therefore would not be detectable using conventional intraluminal manometry. Many of these patients appear to have an



abnormal esophageal pain threshold; pain episodes may be triggered by multiple different stimuli that in normal subjects would not be perceived as painful. The diagnostic approach to patients with noncardiac chest pain is controversial. In the past, full esophageal testing was usually recommended, including upper GI endoscopy, esophageal manometry with provocative testing (Figure 16) and/or 24-hour ambulatory esophageal pH monitoring (Figure 4). More recently the value of such testing has been called into question.

Endoscopy is performed primarily to look for evidence of reflux esophagitis, but the diagnostic yield in this setting is low, and a negative result does not rule out acid reflux as a cause of pain. Esophageal manometry with “provocative testing” (e.g., esophageal acid perfusion, balloon distention or administration of muscarinic agonist) may be used in an attempt to reproduce the patient’s chest pain and possibly relate it to induced esophageal muscle spasm.

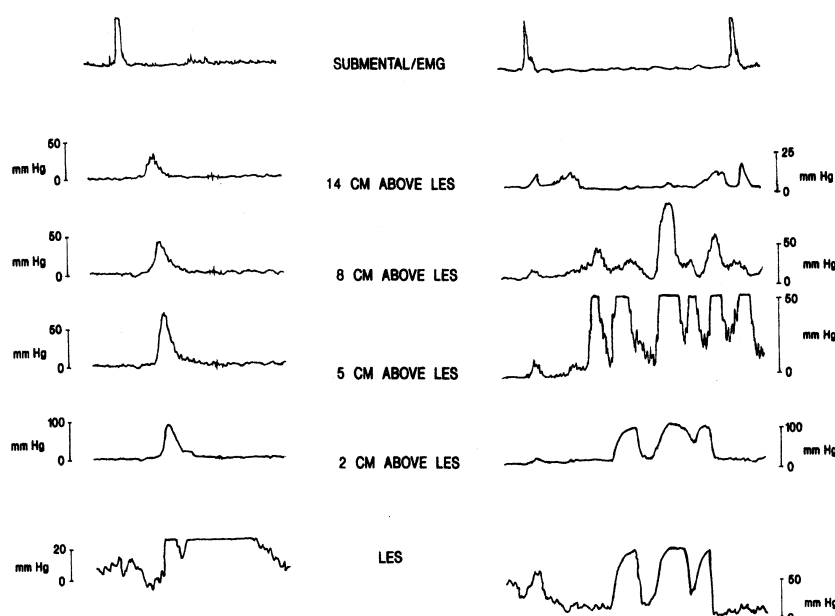


Figure 16. Example of esophageal manometry with provocative testing in a patient with angina-like chest pain and normal coronary angiography. The baseline tracing (left) is within normal limits. During acid perfusion (right) a pattern of diffuse esophageal spasm is induced, which coincided with the patient experiencing her typical angina-like pain. The patient also developed marked esophageal spasm with coincident pain following the injection of bethanechol (not shown). The top tracing is the submental electromyogram (EMG), which records the onset of deglutition. This is followed in sequence by intraluminal side hole pressure recordings from 14, 8, 5 and 2 cm above the lower esophageal sphincter (LES). The lowermost tracing is the pressure recorded by a pressure sensor straddling the LES.

Source: Paterson WG, Marciano-D'Amore DA, Beck IT, et al. Esophageal manometry with provocative testing in patients with non-cardiac angina-like chest pain. *Canadian Journal of Gastroenterology* 1991; 5(2):51–57. Reproduced with permission of the *Canadian Journal of Gastroenterology*.



However, this test appears to lack specificity, as the patient with a positive provocative test may experience seemingly identical spontaneous pain episodes that are unrelated to esophageal dysfunction. Ambulatory 24-hour pH monitoring can be extremely useful in correlating pain episodes with reflux events, but patients must have frequent (i.e., daily) pain attacks if one is likely to be captured during the monitoring period. Because GERD is probably the most common, specifically treatable cause of noncardiac chest pain, it has been recommended that these patients first receive intensive treatment for GERD (i.e., twice-daily proton pump inhibitor therapy). If symptom resolution occurs, then a diagnosis of reflux-induced pain can be presumed and the patient managed accordingly. More in-depth esophageal testing can then be reserved for those patients who fail this empiric therapy and have persisting troublesome pain, especially if associated with considerable anxiety surrounding the diagnosis. Management of angina-like chest pain of esophageal origin should be directed at the specific pathophysiological process. If the pain is triggered by gastroesophageal reflux, then antireflux treatment may be quite helpful. If the pain is due to esophageal spasm, smooth-muscle relaxants such as nitrates and calcium channel blockers may help, although few controlled clinical trials have demonstrated any significant benefit. Tricyclic antidepressants in relatively low dosage have been shown to be beneficial and should be tried in patients with frequent pain episodes that are not caused by reflux or severe esophageal spasm. These are most likely to be useful in patients with abnormal visceral nociception, or the so-called irritable esophagus. Simple reassurance and education are probably the most important part of treatment. Symptoms often improve once the patient is given a positive diagnosis and no longer fears that underlying heart disease is the cause.

12. Esophageal Neoplasms

A large number of different tumors can involve the esophagus (Table 2). The vast majority are extremely rare and often do not produce clinical disease.

Table 2. Classification of esophageal tumors

-
- Benign tumours
 - Epithelial origin
 - Squamous cell papilloma
 - Non-epithelial origin
 - Leiomyoma
 - Granular cell tumor
 - Hemangioma
 - Lymphangioma
 - Malignant tumors
 - Epithelial origin
 - Squamous cell carcinoma
 - Adenocarcinoma
 - Adenoid cystic carcinoma
 - Mucoepidermoid carcinoma
-



- Adenosquamous carcinoma
 - Undifferentiated carcinoma; small-cell carcinoma
 - Non-epithelial origin
 - Leiomyosarcoma
 - Carcinosarcoma
 - Malignant melanoma
 - Secondary tumors
 - Malignant melanoma
 - Breast carcinoma
- Tumor-like lesion
- Fibrovascular polyp
 - Heterotopia
 - Congenital cyst
 - Glycogen acanthosis

Carcinoma of the esophagus is a relatively uncommon malignancy in Canada, with only 3 to 4 new cases per 100,000 population per year in males and just over 1 new case per 100,000 population per year in females. Nevertheless, because of its poor prognosis, esophageal cancer ranks among the 10 leading causes of cancer death in Canadian men 45 years of age and older. Although several different types of primary and secondary malignancies can involve the esophagus (Table 2), squamous cell carcinoma and adenocarcinoma are by far the most common esophageal malignancies.

12.1. Adenocarcinoma

Adenocarcinoma used to make up approximately 10% of all esophageal cancers. However, its incidence has been increasing in recent decades such that now it comprises up to 40–60% of esophageal cancers in North America. Rarely, primary esophageal adenocarcinomas arise from embryonic remnants of columnar epithelium or from superficial or deep glandular epithelium. In most instances, adenocarcinoma arises from metaplastic Barrett's epithelium in the distal esophagus (Figure 17). Adenocarcinoma of the cardia of the stomach may also involve the distal esophagus and give the appearance that the cancer arises from the esophagus.

The true incidence of Barrett's-related cancer is uncertain, but most studies suggest that patients with Barrett's esophagus will develop adenocarcinoma at a rate of about 0.5% per year. This is a significant problem given the large number of reflux patients with Barrett's metaplasia. Because dysplasia develops prior to frank carcinoma in Barrett's epithelium, current guidelines recommend that these patients should undergo surveillance endoscopy with multiple biopsies every 2-3 years to identify those who are likely to progress to cancer (Section 7).

The clinical presentation and diagnostic evaluation of patients with adenocarcinoma of the esophagus are similar to those of squamous cell carcinoma (Section 12.2.2). Neoadjuvant therapy with concomitant radiation and chemotherapy followed by surgical resection of the esophagus has a 13% absolute benefit in survival at 2 years versus surgery alone. Surgical resection may be performed with curative intent. However, surgical resection for palliation, or palliation with laser, photodynamic therapy, peroral



dilation and/or stent placement are more often required, since curative surgery is feasible in only 20% of patients. The prognosis is similar to that for gastric adenocarcinoma – i.e., an overall five-year survival rate of < 10%.

Table 3. Esophageal squamous cell carcinoma: possible factors

-
- Alcohol
 - Tobacco
 - Nutritional exposure
 - Nitrosamines: “bush teas” containing tannin and/or diterpene phorbol esters
 - Nutritional deficiencies (riboflavin, niacin, iron)
 - Chronic esophagitis
 - Achalasia
 - Previous lye-induced injury
 - Tylosis
 - Plummer Vinson (Paterson-Kelly) syndrome
-

12.2. Squamous Cell Carcinoma

The occurrence of squamous cell carcinoma of the esophagus shows striking geographic variability, with high frequencies in certain regions of Iran, Africa, China and the former USSR. This has led to several theories concerning certain environmental agents that may be important etiologically (Table 3). In North America, squamous cell carcinoma is associated with alcohol ingestion, tobacco use and lower socioeconomic status. It is also significantly more common in blacks and in males.

Characteristically these cancers, similarly to adenocarcinoma, extend microscopically in the submucosa for substantial distances above and below the area of the gross involvement. They also have a propensity to extend through the esophageal wall and to regional lymphatics quite early. Furthermore, they usually produce symptoms only when they have become locally quite advanced. For these reasons approximately 95% of these cancers are diagnosed at a time when surgical cure is impossible.

In most studies, the mid-esophagus is the most common site of origin; however, others have reported distal cancers to be most common. The lungs, liver and bones are the most common sites of distant metastases.

Most patients present with progressive, predictable dysphagia and weight loss. Other symptoms include odynophagia, chest pain (which may radiate to the mid-scapular region), hoarseness (due to recurrent laryngeal nerve involvement) and blood loss. Pulmonary complications due to either direct aspiration or esophagorespiratory fistulas are also quite common during the course of the disease. Physical examination is usually negative aside from signs of weight loss. Hepatomegaly or enlarged cervical or supraclavicular lymph nodes may be detected in cases of disseminated metastases.

Barium swallow is usually diagnostic, although small cancers can be missed in up to 30% of cases. Endoscopy with multiple directed biopsies combined with brush cytology is required to confirm the diagnosis. This should be followed by careful attempts to stage the disease prior to deciding on therapeutic intervention. CT scan of the thorax and upper abdomen is required to look for local spread and metastasis.



Unfortunately the CT scan lacks sensitivity in this regard. Endoscopic ultrasound appears promising in accurately assessing depth of tumor involvement and presence or absence of enlarged mediastinal lymph nodes. PET scanning is useful to delineate lymph nodes positive for metastatic malignancy.

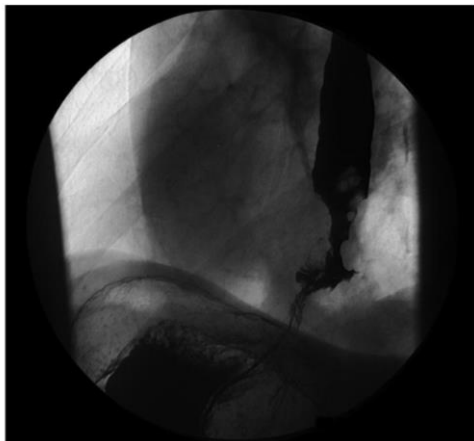


Figure 17. Barium swallow radiograph in a patient with adenocarcinoma of the distal esophagus. Note narrowing of the esophageal lumen with irregular mucosal contour. When similar lesions are in mid or proximal esophagus, they usually are squamous cell cancers. Endoscopic biopsies are required to establish the diagnosis.

Treatment results of squamous cell carcinoma of the esophagus are discouraging. These tumors are quite radiosensitive; however, most centers give radiotherapy to patients who have advanced unresectable tumors or other health problems that make them poor surgical candidates. This understandably leads to very poor overall survival following radiotherapy. In the few reports where radiotherapy is used as the primary mode of therapy in patients who might otherwise be considered surgical candidates, the five-year survival rate is as high as 17%, which compares quite favorably to surgical results. Both forms of treatment have significant morbidity, but the surgical mortality following esophageal resection is 5–10%. Controlled trials are needed, but in only a small proportion of the total population of esophageal cancer patients is cure a realistic goal. In the majority the disease is too far advanced. New regimens that combine radiotherapy and chemotherapy, with or without surgery, are currently being evaluated and show promise in improving cure rates and disease-free survival. However, the toxicity and morbidity from combined treatment can be substantial.

The goal of treatment has to be palliation in most patients. Both radiotherapy and palliative surgery can be used in this setting; however, other modalities are often necessary. The dysphagia can be relieved with peroral dilation, but in many patients this becomes exceedingly difficult as the disease progresses. If this is the case, a prosthetic device can sometimes be placed across the tumor to maintain luminal patency. These stents can work quite well, although tube blockage, tube migration, erosion through the esophageal wall and sudden massive aspiration are important complications. These prosthetic devices are the best treatment for an esophagorespiratory fistula. Photodynamic therapy and radiofrequency ablation are two relatively new minimally invasive treatment modalities for palliating esophageal cancer. The former involves using a photosensitizing compound that accumulates in cancer cells, which leads to their destruction when they are exposed to light of a certain wavelength. The caring physician must also provide emotional support, nutritional support and adequate pain therapy for these unfortunate patients.



13. Miscellaneous Disorders of the Esophagus

13.1. Webs and Rings

Webs are thin, membrane-like structures that project into the esophageal lumen. They are covered on both sides with squamous epithelium and are most commonly found in the cervical esophagus. Webs are usually detected incidentally during barium x-rays and rarely occlude enough of the esophageal lumen to cause dysphagia. The etiology of these webs is unclear. Most are probably congenital in origin. In some instances postcricoid esophageal webs are associated with iron deficiency and dysphagia – the so-called *Plummer-Vinson* or *Paterson-Kelly* syndrome. This syndrome is associated with increased risk of hypopharyngeal cancer and should be managed with bougienage, iron replacement and careful follow-up. Esophageal webs may also form after esophageal injury, such as that induced by pills or lye ingestion, and have also been reported in association with graft-versus-host disease. The lower esophageal or *Schatzki's ring* is also a membrane-like structure, but unlike webs is lined by squamous epithelium on its superior aspect and columnar epithelium inferiorly. Such a ring is quite common, being detected in up to 10% of all upper GI barium x-rays. Few produce sufficient luminal obstruction to cause dysphagia (yet a lower esophageal ring is a common cause of dysphagia). When the lumen is narrowed to a diameter of 13 mm or less, the patient will experience intermittent solid-food dysphagia or even episodic food-bolus obstruction. Treatment of a symptomatic Schatzki's ring involves shattering the ring with a large-diameter bougie or a balloon dilator. Subsequent treatment with a proton pump inhibitor has been shown to decrease the recurrence of symptomatic Schatzki's rings.

13.2. Diverticula

Pharyngoesophageal diverticula are outpouchings of one or more layers of the pharyngeal or esophageal wall and are classified according to their location.

13.2.1. Zenker's Diverticulum (Figure 18)

This diverticulum arises posteriorly in the midline between the oblique and transverse (cricopharyngeal) fibers of the inferior pharyngeal constrictor muscles. As this diverticulum enlarges, it usually shifts to the left of the midline. Zenker's diverticulum forms because of decreased compliance of the cricopharyngeal muscle, which results in abnormally high pressures in the hypopharynx during deglutition. In addition to pharyngeal-type dysphagia, Zenker's diverticulum may be associated with effortless regurgitation of stagnant, foul-tasting food, as well as aspiration. A very large diverticulum can produce a neck mass, usually on the left side.

Treatment of a symptomatic Zenker's diverticulum is surgical. Most surgeons will either resect the diverticulum or suspend it (diverticulopexy) so that it cannot fill. This is combined with cricopharyngeal myotomy. In many cases, particularly if the diverticulum is small, cricopharyngeal myotomy alone will alleviate symptoms. This procedure can now be performed endoscopically in selected cases. Once the cricopharyngeal myotomy has been performed, the patient has lost an important defense mechanism to prevent the aspiration of refluxed material.





Figure 18. Lateral barium x-ray of a Zenker's diverticulum (white arrow). These diverticuli form just above the poorly relaxing cricopharyngeus muscle, which appears as a cricopharyngeal "bar" (black arrow). These diverticuli extend posteriorly and most tend to shift to the left of the midline as they enlarge.

The patient should therefore be instructed to elevate the head of the bed in order to minimize this risk. For the same reason patients with severe GERD should not undergo cricopharyngeal myotomy unless the reflux can be controlled either medically or surgically.

13.2.2. Midesophageal Diverticula

Traditionally, midesophageal diverticula have been called "traction" diverticula because of their supposed etiology. They were believed to arise secondary to old mediastinal inflammation, such as tuberculosis, that caused adherence of mediastinal structures to the outer esophageal wall so that outward traction occurred during peristalsis. It now appears likely that very few midesophageal diverticula arise this way. In most there is an associated motility disorder and it is likely that this is actually a "pulsion" diverticulum formed when a peristaltic wave deteriorates into a simultaneous or spastic contraction in the smooth-muscle esophagus. Midesophageal diverticula rarely require specific therapy. Rather, the associated motor disorder requires treatment if symptomatic.

13.2.3. Lower Esophageal or Epiphrenic Diverticula

These "pulsion" diverticula form just above the LES and are invariably associated with an esophageal motor disorder – usually diffuse esophageal spasm, with or without abnormal relaxation of the LES. Patients with these diverticula usually present with dysphagia and/or angina-like chest pain. In addition, they may complain of nocturnal regurgitation of large quantities of stagnant fluid. If symptoms are present, treatment with nitrates or calcium channel blockers may be helpful. If this is not successful, surgery is indicated. Any surgical attack on these diverticula should involve a myotomy of the spastic distal esophagus and/or LES. Resection of the diverticula alone seldom affords long-term benefit.

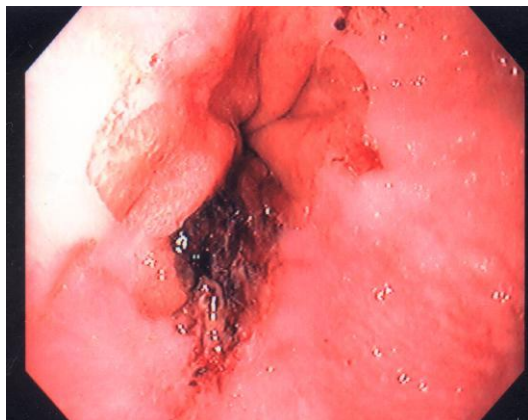
13.2.4. Intramural Diverticulosis

This disorder has a characteristic radiologic appearance consisting of numerous tiny, flask-shaped outpouchings from the esophageal lumen. There is usually an associated smooth stricture in the proximal esophagus. Patients typically present with dysphagia that responds to peroral dilation. The outpouchings are actually dilated ducts coming from submucosal glands and thus are not true diverticula. The etiology is obscure. Some cases are associated with esophageal candidiasis, but this organism does not appear to be of etiological importance.



13.3. Esophageal Trauma

Blunt or penetrating trauma to the chest can cause esophageal injury. In addition, esophageal instrumentation such as that used in bougienage, endoscopy or stent insertion may cause perforation or mucosal laceration. Severe retching or vomiting can also cause esophageal perforation (*Boerhaave's syndrome*) or mucosal laceration (*Mallory-Weiss tear*). Boerhaave's syndrome is a life-threatening condition that requires immediate surgery to drain the mediastinum and repair the defect in the esophageal wall. Patients, typically alcoholics, present with sudden epigastric and/or chest pain following a bout of vomiting and usually have fever and signs of hypovolemia or shock. The diagnosis is established by having the patient swallow a small amount of water-soluble contrast material (e.g., Gastrografin®), which is seen to leak into the mediastinum or pleural cavity through the esophageal perforation. CT of the chest may also reveal an esophageal perforation. If the perforation is large, a chest x-ray may be diagnostic.



The mucosal laceration of the 'Mallory-Weiss' tear (Figure 19) is probably better classified as a disorder of the stomach, because in most cases the laceration starts at the GE junction and extends down into the stomach. These patients present with hematemesis or melena following a bout of retching or vomiting. The bleeding usually stops spontaneously and only supportive therapy is required. If bleeding persists, endoscopically applied hemostasis or surgical intervention may be necessary.

Figure 19. Endoscopic view of a Mallory-Weiss tear. Note the mucosal laceration with blood clot at its base at the gastroesophageal junction. Patients with this lesion typically have vigorous retching or vomiting before vomiting up fresh blood and/or passing melena.

13.4. Food-Bolus Obstruction and Foreign Bodies

A surprising variety of foreign bodies can lodge in the esophagus after being swallowed either inadvertently or deliberately. The three most common sites where foreign bodies become stuck are the piriform sinuses, at the aortic arch and just above the LES. The patient can usually localize the site of the obstruction quite accurately, and this can be confirmed using routine x-rays if the object is radiopaque. Most foreign bodies can be removed by an expert endoscopist. Surgery is rarely required, except when perforation has occurred. A more common clinical problem is esophageal food-bolus obstruction. This typically occurs when a patient with a motility disorder, esophagitis, stricture or Schatzki's (lower esophageal) ring swallows a large solid-food bolus. The patient notices immediate pain, usually well localized to the site of obstruction in the chest, but sometimes referred to the suprasternal notch. Attempts to swallow anything further are unsuccessful and usually lead to prompt regurgitation.



Many physicians will initially treat these patients with smooth-muscle relaxants such as intravenous glucagon or sublingual nitroglycerin; however, there is little evidence that this approach is efficacious. Drinking carbonated beverages may also help the bolus pass, presumably by distending the esophageal lumen with gas. If the food bolus does not pass on spontaneously within a few hours, endoscopy should be performed, at which time the bolus can either be removed per os or pushed through into the stomach. A persistent food bolus impaction, if left untreated for a long period (> 12-24 hours), may lead to mucosal ulceration and even a localized perforation.



Chapter 3: Scientific Basis of Gastric Disorders

A.B.R. Thomson and R.H. Hunt



1. Introduction

Diseases of the GI tract are common, accounting for about one out of seven persons presenting to their primary care physician. Disorders of the stomach and duodenum make up a large part of these.

It has been known for many centuries that the gastric juice is acidic in nature, but it was not until 1824 that William Prout established that the acid in the stomach is hydrochloric acid. Since then physicians have been fascinated by the ability of the healthy stomach and duodenum to withstand hydrochloric acid and pepsin. In particular, the mechanisms controlling gastric secretion have been extensively studied in the hope of finding a satisfactory way to explain and treat peptic ulcer disease. Further studies turned to the role of mucus, bicarbonate and prostaglandins in the maintenance and defence of the gastric mucosa against acid injury. In 1983 Marshall and Warren isolated the bacteria now known as *Helicobacter pylori* (Figure 1) from gastric biopsies in duodenal ulcer patients. They won the Nobel Prize in Medicine, and a new era in the understanding and treatment of gastroduodenal disease was born. This chapter will review the anatomy, clinical physiology and related common disorders of the stomach and duodenum.

2. Anatomy

The stomach is the most capacious part of the GI tract and lies between the distal esophagus and the duodenum. It is situated entirely within the abdomen below the diaphragm (Figure 2). The body of the stomach lies slightly to the left of the midline; the antrum crosses the spinal vertebrae at the level of T10-L1, and the pylorus lies to the right of the vertebral column. The duodenum is predominately retroperitoneal and comprises the cap, the descending and the distal portions.

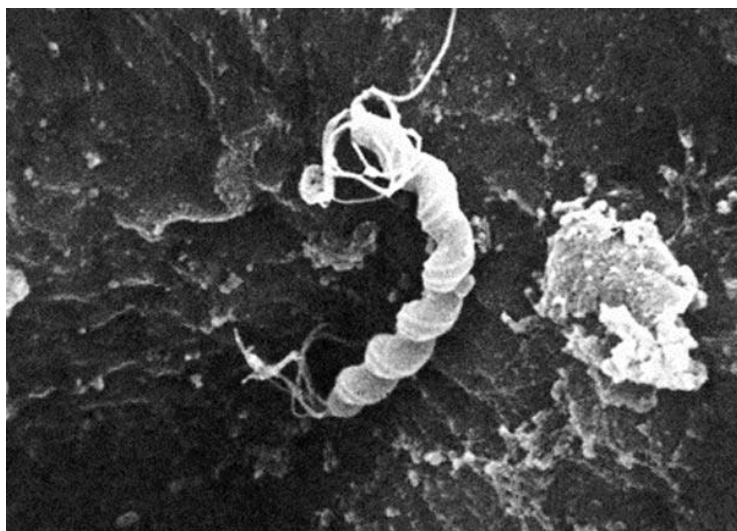


Figure 1. *Helicobacter pylori*.
(Courtesy of McMaster University
Medical Centre Electron
Microscopy Lab.)

The greater curvature is some three or four times the length of the lesser curvature. A point known as the angulus or incisura may be defined on the lesser curvature. This point is relatively constant and marks a change from the prominent rugal folds of the gastric body to the smoother, less-prominent folds of the antrum.

The stomach and duodenum lie in close proximity to a number of important anatomic structures. Anterosuperiorly are the left diaphragm and left lobe of the liver, while the body and tail of the pancreas lie posteriorly. Laterally to the left are: the hilum of the left kidney, the left adrenal gland and, above that, the spleen. These organs form the stomach bed and are separated from it by the lesser omentum and the lesser sac.



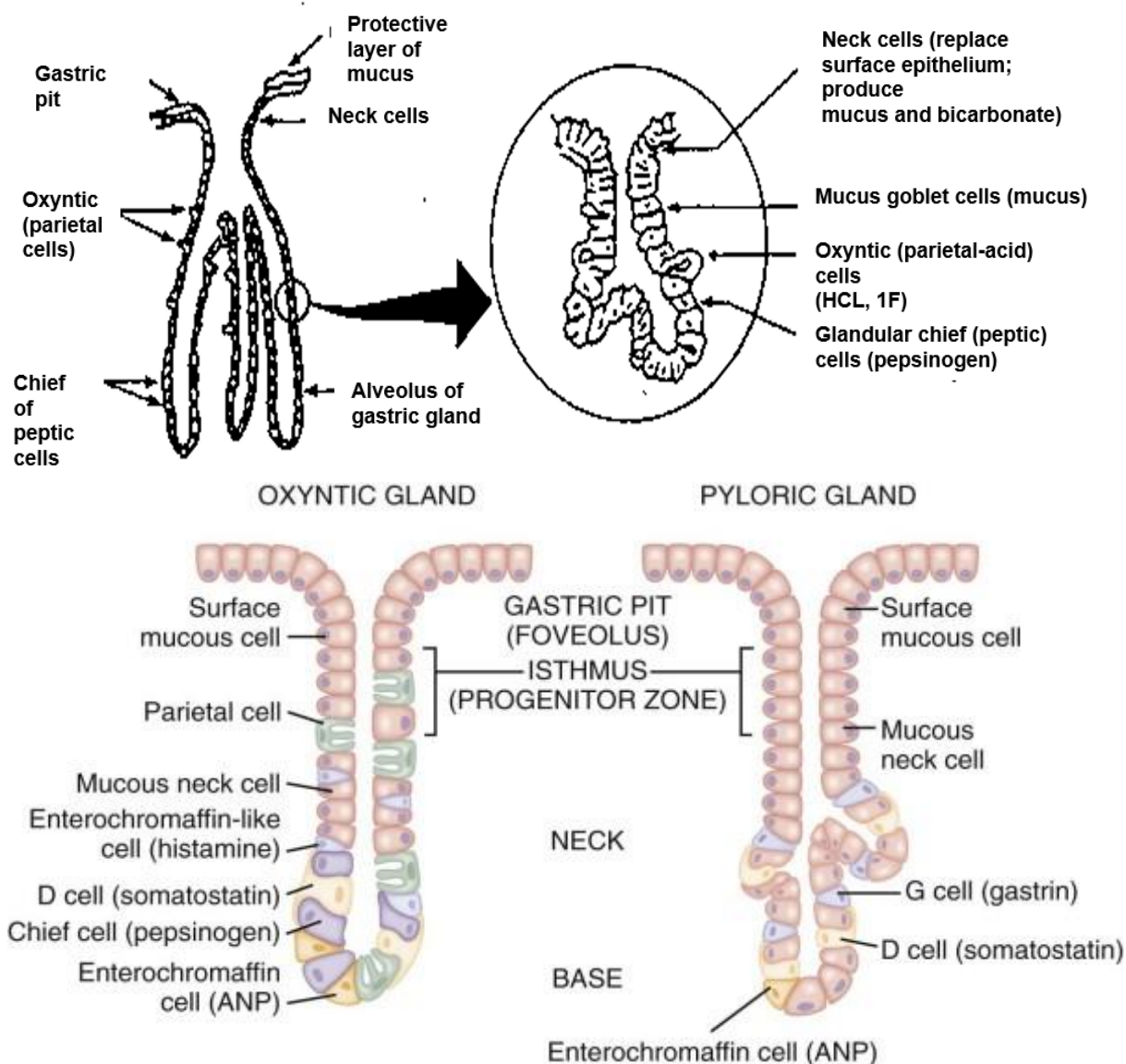


Figure 2. Microscopic appearances of gastric pit and glands.

- Somatostatin-containing D cells contain cytoplasmic processes that terminate in the vicinity of acid-secreting parietal and histamine-secreting enterochromaffin-like cells in the oxyntic gland area (fundus and corpus) and gastrin-secreting G cells in the pyloric gland area (antrum).
- The functional correlate of this anatomic coupling is a tonic paracrine restraint on acid secretion by somatostatin that is exerted directly on the parietal cell as well as indirectly by inhibiting histamine and gastrin secretion. ANP, atrial natriuretic peptide.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-4, pg 819, Ninth Edition, 2010

Vagal reflexes initiated during the initial phase of eating, the lower luminal



acidity and distention caused by the entrance of food into the stomach stimulate release of hormones by the enteroendocrine cells of the stomach. Gastrin (from G cells) is released into the bloodstream and is carried by the blood to the mucosa of the stomach where it stimulates HCl production. Enterochromaffin-like (ECL) cells are stimulated by gastrin to release histamine, and it is thought that the stimulation of parietal cells is mainly due to histamine binding secondary to gastrin's effects on histamine release. Protein in food is also a potent stimulator of gastrin release.

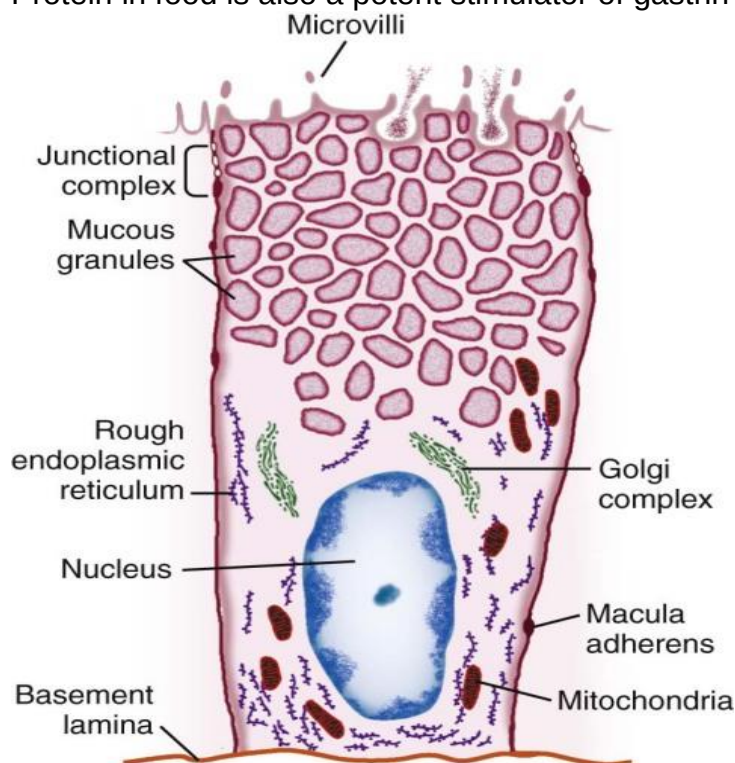


Figure 3. Schematic representation of a surface mucous cell.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 47-4, pg 776, Ninth Edition, 2010

The sympathetic nerve supply arises from the spinal cord between T6 and T10 and passes to the sympathetic ganglia. The parasympathetic supply contracts the stomach, relaxes the pylorus and stimulates acid, pepsin and mucus secretion, whereas sympathetic stimulation constricts the blood supply and reduces gastric motor activity and secretion while the pylorus is contracted.

3. Functions of the Stomach

The food bolus exits the lower esophageal sphincter through the cardiac orifice, the opening that connects the cardia region of the stomach to the esophagus. Vagal reflexes initiated by the cephalic phase of eating inhibit contractile activity in the proximal stomach and the entry of food into the stomach promotes relaxation of the cardia of the stomach. Upon entry of food into the stomach, the stomach muscles relax. When relaxed and empty, the adult human stomach has a near empty volume, but it normally expands to hold about 1 L of food and liquid. The stomach temporarily stores the swallowed food and liquid until it is passed to the intestines. The stomach secretes HCl and for initiating digestion, intrinsic factor which is essential for vitamin B₁₂ absorption in the small intestine, and also secretes endocrine hormones. Ghrelin is another hormone released by the stomach. The release of ghrelin is stimulated by fasting and is suppressed by the ingestion of food. Ghrelin stimulates gastric emptying and acts via the central nervous system to stimulate appetite. The stomach mixes up food and digestive juice and macerates the mixture into a semiliquid state, called chyme. Gastric inflammatory mediators can modulate gastric secretion and motility. Finally, the stomach regulates the rate of entry of chyme into the duodenum.



Table 1. Functions of the Stomach

-
- Storage reservoir
 - Secretion of HCl, digestive enzymes and peptides
 - Mixing of food with gastric juice
 - Controlled release of food/fluid into duodenum
 - Contributes to regulation of food intake
 - Immune modulation.
-

3.1. Acid Secretion

The thick layers of gastric mucosa secrete gastric juice, which contains two key substances involved in digestion: hydrochloric acid and pepsin. Gastric juice also contains mucus, bicarbonate, water, and minerals- all involved in protecting the gastric mucosa from the destructive forces of acid and pepsin and also intrinsic factor, required for the absorption of vitamin B₁₂.

Parietal cells contain secretory channels called canaliculi from which the gastric acid is secreted into the lumen of the stomach. Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi. H⁺ ions are generated within the parietal cell from dissociation of H₂O. The OH⁻ ions formed in this process combine with CO₂, in a reaction catalyzed by carbonic anhydrase, to form HCO₃⁻. The HCO₃⁻ is transported out of the cell in exchange for Cl⁻ ions. Thus the parietal cell now has a supply of both H⁺ and Cl⁻ ions for secretion. Cl⁻ and K⁺ ions are transported into the lumen of the canaliculus by conductance channels.

- In the resting state, H⁺,K⁺-ATPase is sequestered within cytoplasmic tubulovesicles and is inactive.
- On stimulation, the tubulovesicles move to and fuse with the apical membrane, forming an extensive canalicular system.
- Translocation of H⁺,K⁺-ATPase into the canalicular membrane together with the presence of luminal K⁺ activates the enzyme.



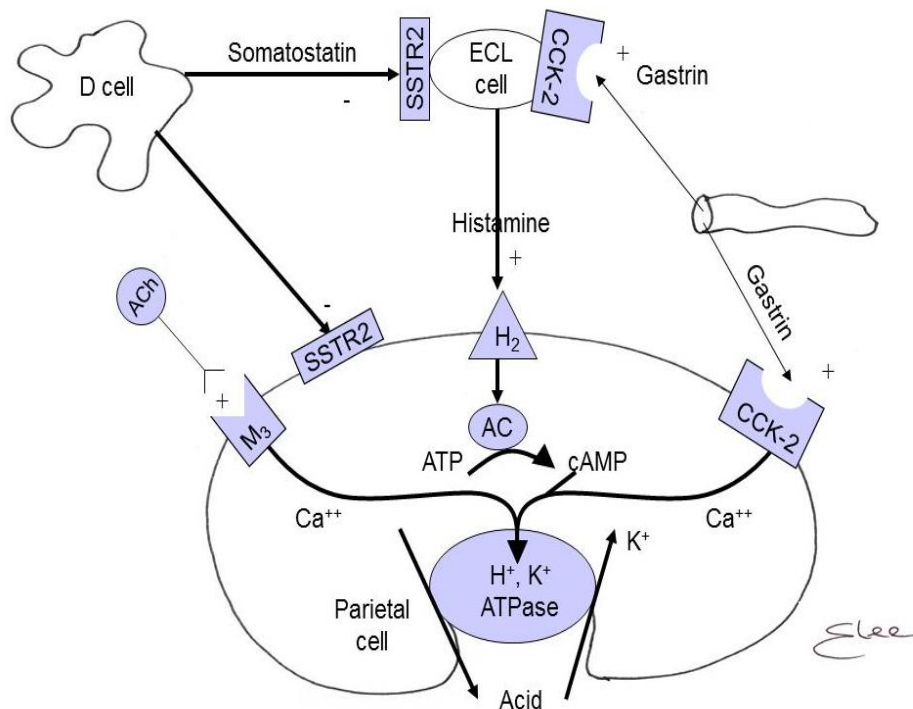


Figure 4. Model illustrating parietal cell receptors and transduction pathways.

- The principal stimulants of acid secretion at the level of the parietal cell are histamine (paracrine), gastrin (hormonal), and acetylcholine (ACh; neurocrine).
- Histamine, released from enterochromaffin-like (ECL) cells, binds to H_2 receptors that activate adenylate cyclase (AC) and generate adenosine 3',5'-cyclic monophosphate (cAMP).
- Gastrin, released from G cells, binds to cholecystinin-2 (CCK-2) receptors that activate phospholipase C (not shown) to induce release of cytosolic calcium (Ca^{++}).
- Gastrin stimulates the parietal cell directly and, more importantly, indirectly by releasing histamine from ECL cells.
- ACh, released from intramural neurons, binds to M_3 receptors that are coupled to an increase in intracellular calcium.
- The intracellular cAMP- and calcium-dependent signaling systems activate downstream protein kinases, ultimately leading to fusion and activation of H^+, K^+ -ATPase, the proton pump.
- Somatostatin, released from oxyntic D cells, is the principal inhibitor of acid secretion.
- Somatostatin, acting via the SSTR2 receptor, inhibits the parietal cell directly as well as indirectly by inhibiting histamine release from ECL cells. +, stimulatory; –, inhibitory.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-10, pg 777 and 821, Ninth Edition, 2010.



- Efferent vagal fibers synapse with intramural gastric cholinergic (ACh) and peptidergic (gastrin-releasing peptide [GRP] and vasoactive intestinal peptide [VIP]) neurons. In the fundus (oxyntic mucosa), ACh neurons stimulate acid secretion directly as well as indirectly by inhibiting somatostatin (SST) secretion, thus eliminating its restraint on parietal cells and histamine-containing enterochromaffin-like (ECL) cells.
- In the antrum (pyloric mucosa), ACh neurons stimulate gastrin secretion directly as well as indirectly by inhibiting SST secretion, thus eliminating its restraint on gastrin-containing G cells. GRP neurons, activated by luminal protein, also stimulate gastrin secretion.
- VIP neurons, activated by low-grade gastric distention, stimulate SST and thus inhibit gastrin secretion.
- Dual paracrine pathways link SST-containing D cells to parietal cells and to ECL cells in the fundus.
- Histamine released from ECL cells acts via H_2 receptors to inhibit SST secretion.
- This serves to accentuate the decrease in SST secretion induced by cholinergic stimuli and thus augments acid secretion. In the antrum, dual paracrine pathways link SST-containing D cells to gastrin cells.
- Release of acid into the lumen of the stomach restores SST secretion in both the fundus and antrum; the latter is mediated via release of calcitonin gene-related peptide (CGRP) from extrinsic sensory neurons.
- Acute infection with *Helicobacter pylori* (HP) also activates CGRP neurons to stimulate SST and thus inhibit gastrin secretion.
- In duodenal ulcer patients who are chronically infected with HP, the organism or cytokines released from the inflammatory infiltrate inhibit SST and thus stimulate gastrin (and acid) secretion.
- Acid secretion requires a functional H^+, K^+ -ATPase as well as apical K^+ and Cl^- channels and basolateral transporters and/or channels for K^+ , Cl^- , and HCO_3^- .
- Acid is produced from the hydration of CO_2 to form H^+ and HCO_3^- , a reaction catalyzed by cytoplasmic carbonic anhydrase (CA).
- In the presence of luminal K^+ , H^+, K^+ -ATPase pumps H^+ into the lumen in exchange for K^+ .
- Luminal K^+ channels (KCNE2/KCNQ1 and ROMK [not shown]) recycle K^+ across the luminal membrane.
- The source of intracellular K^+ is the basolateral Na^+, K^+ -ATPase and the sodium-2 chloride potassium-cotransporter-1 (NKCC1).
- For each H^+ secreted, a HCO_3^- exits the cell across the basolateral membrane via the anion exchanger (AE2, or Slc4a2).
- Concurrently with H^+ , Cl^- is extruded across the luminal membrane via an apical chloride channel. The sources of intracellular Cl^- are AE2, NKCC1, and the SLC26A7 channel.
- SST-containing D cells are structurally and functionally coupled to their target cells: parietal, enterochromaffin-like (ECL), and gastrin cells.
- SST, acting via SSTR2 receptors, tonically restrains acid secretion.



- This restraint is exerted directly on the parietal cell as well as indirectly by inhibiting histamine secretion from ECL cells and gastrin secretion from G cells.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-5, pg 820 and 824, Ninth Edition, 2010

3.2 Motility

- Slow waves originate in the pacemaker region located at the juncture of the fundus and the corpus on the greater curvature.
- Note the fundus does not have slow wave activity (electrode A).
- Slow waves propagate circumferentially and migrate distally to the pylorus approximately every 20 seconds, or 3 cycles per minute (cpm) (*dotted lines with arrowheads*).
- The myoelectrical activity of the slow wave can be recorded with cutaneous electrodes.
- The summed gastric myoelectrical activity recorded from electrodes positioned on the abdominal surface in the epigastrium is termed an electrogastrogram (EGG), and the normal rhythm is 3cpm.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 48-1, pg 790 and 791, Ninth Edition, 2010

- The plateau and action potentials occur during circular muscle contractions. Peristaltic waves originate in the pacemaker area. The frequency (3 cycles per minute [cpm]) and propagation velocity (approximately 14 mm/second) of the gastric peristaltic waves are controlled by the slow wave, which leads the contraction from the proximal corpus to the distal antrum, as shown at electrodes A through D.
- The *solid black lines* and *arrows* indicate the circumferential and distal propagation of the peristaltic wave, which forms a ring contraction (*small arrow*), indicating a moving peristaltic contraction. Peristaltic contractions occur three times per minute, the frequency of the gastric slow wave.
- The increased myoelectrical activity of the plateau potentials and action potentials linked with the slow wave results in increased amplitude of the EGG signal (*thick black lines*).
- The fundus does not participate in the gastric peristaltic contractions.



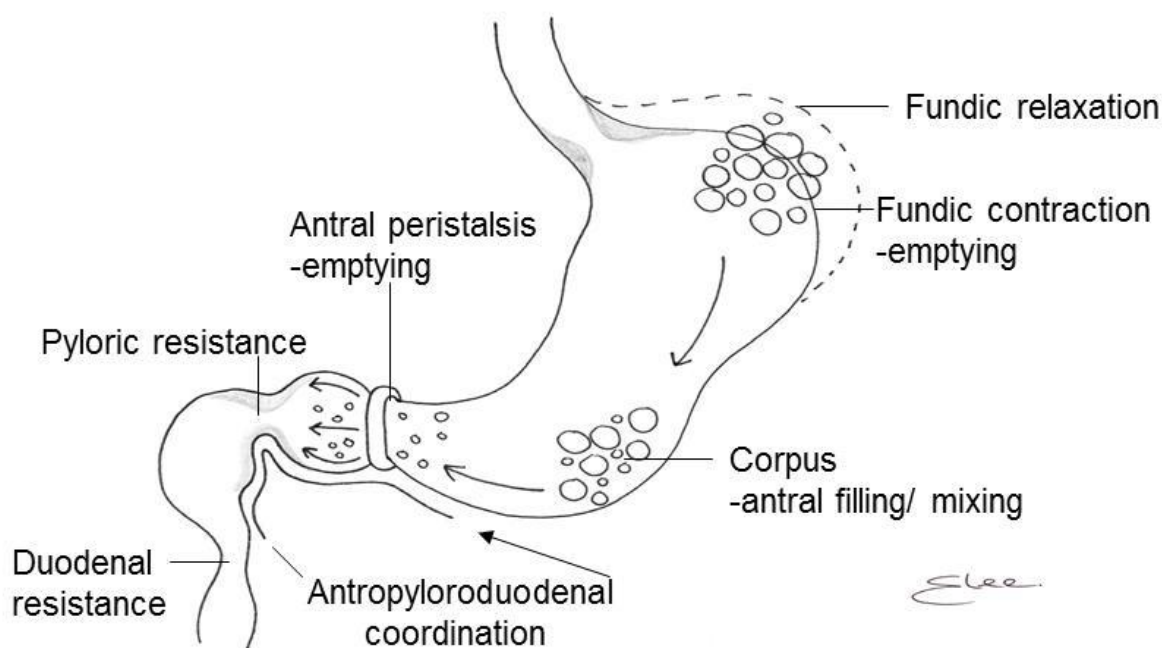


Figure 5. Gastric Emptying

- The fundus then contracts to empty the ingested food into the corpus and antrum for trituration and emptying.
- Recurrent corpus-antral peristaltic waves mill the solids into chyme, which is composed of 1- to 2-mm solid particles suspended in gastric juice.
- Antral peristaltic waves, indicated by the ring-like indentation in the antrum, empty 2 to 4 mL of the chyme through the pylorus and into the duodenal bulb at the slow wave frequency of three peristaltic contractions per minute.
- Antropyloroduodenal coordination indicates efficient emptying of chyme through the pylorus, which modulates flow of the chyme by varying sphincter resistance. Contractions in the duodenum also provide resistance to emptying.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 48-8, pg 795, Ninth Edition, 2010



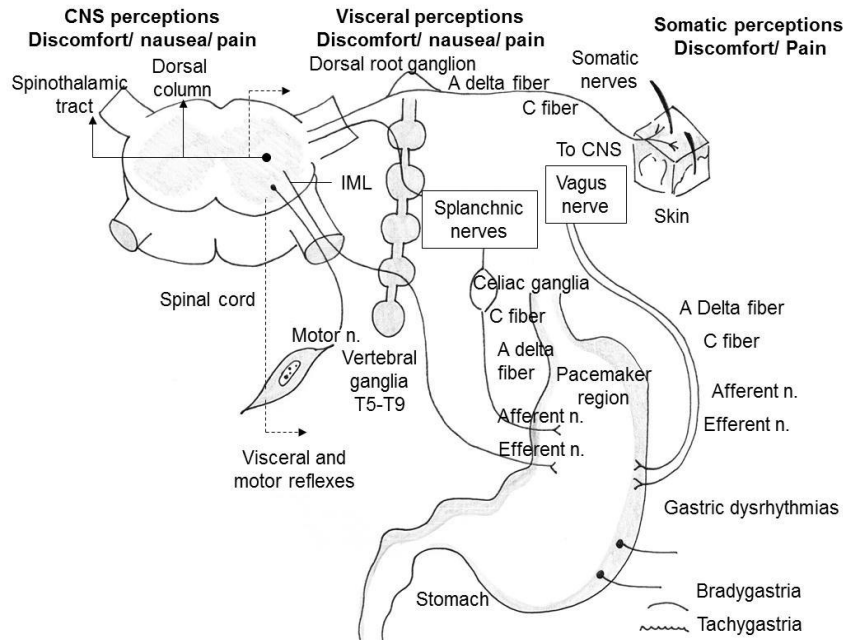


Figure 6. Neural connections between the stomach and CNS

- The vagus nerve contains afferent nerves with A-delta and C pain fibers with cell bodies in the nodose ganglia with connections to the nucleus tractus solitarius (not shown).
- Low threshold mechano- and chemoreceptors stimulate visceral sensations such as stomach emptiness or fullness and symptoms such as nausea and discomfort.
- These stimuli are mediated through vagal pathways and become conscious perceptions of visceral sensations if sensory inputs reach the cortex.
- The splanchnic nerves also contain afferent nerves with A-delta and C fibers that synapse in the celiac ganglia with some cell bodies in the vertebral ganglia (T5-T9)
- Interneurons in the white rami in the dorsal horn of the spinal cord cross to the dorsal columns and spinothalamic tracts and ascend to sensory areas of the medulla oblongata..
- These splanchnic afferent fibers are thought to mediate high-threshold stimuli for visceral pain. In contrast to visceral sensations, somatic nerves such as from the skin carry sensory information via A-delta and C fibers through the dorsal root ganglia and into the dorsal horn and then through dorsal columns and spinothalamic tracts to cortical areas of somatic representation.
- Changes in gastric electrical rhythm, excess amplitude contractions, or stretch on the gastric wall are peripheral mechanisms that elicit changes in afferent neural activity (via vagal and/or splanchnic nerves) that may reach consciousness to be perceived as visceral perceptions (symptoms) emanating from the stomach. IML, intermediolateral nucleus; n., nerve.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 48-17, pg 801, Ninth Edition, 2010.



Table 2. Mechanism of action of prokinetic drugs used for the treatment of symptoms of gastroparesis, as well as nausea and vomiting arising from dysmotility of the GI tract. The FDA pregnancy category is shown in brackets

Drug	Receptor
➤ Metoclopramide (B)	○ Central/peripheral dopamine receptor antagonist (D₂) ○ 5-HT₃ receptor antagonist ○ 5-HT₄ receptor agonist
➤ Domperidone (C)	○ peripheral D₂ antagonist
➤ - Cisapride (C)	○ muscarinic (acetylcholine) receptor agonist ○ 5-HT₃ receptor antagonist ○ 5-HT₄ receptor agonist
➤ - Ondansatrom (B)	○ 5-HT₃ receptor antagonist
➤ - Erythromycin (B)	○ motilin receptor agonist
➤ - Tegaserod	○ Cholinergic 5-HT₄ partial agonist
➤ - Bethanechol	○ muscarinic receptor agonist
➤ Anticholinergic (buscopan, for tachygastria)	
➤ - α -adrenergic antagonists	○ α-adrenergic antagonist
➤ - Botulism toxin injection	○ phosphodiesterase inhibitors (Viagra®)
➤ - Octreotide injection	○ somatostatin receptor agonist

Adapted from: Quigley EMM. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 1007.

Dumping syndrome is a frequent complication of esophageal, gastric or bariatric surgery. The early postprandial phase results from the rapid emptying of the stomach including larger than normal food particles, with the osmotic shift of fluid into the duodenal lumen plus the distention of the human releasing gastrointestinal and pancreatic hormones. These hormones cause the gastrointestinal and vascular symptoms of the early dumping syndrome. The rapid and early absorption of nutrients causes prompt secretion of insulin, and the late dumping syndrome characterized by reactive hypoglycaemia (Tack et al. 2009). A modified oral glucose tolerance test may be used to establish the reactive hypoglycaemia. The dumping syndrome does not always respond to dietary maneuvers, and pectin or guar gum may be needed to slow gastric emptying, a carbose to slow starch digestion and reduce pos-prandial reactive hypoglycaemia, or in extreme cases somatostatin injections may be given to slow gastric emptying and to slow sugar absorption.



There are many causes of nausea and vomiting, some due to disorders of the GI tract and some due to disorders affecting the central vomiting centre. The vomiting centre is on the blood side of the blood-brain barrier. There are numerous centrally acting drugs used for the treatment of the symptoms of nausea and vomiting (Table 3). Some persons with severe, intractable gastroparesis, such as may occur with severe type I diabetes, may improve with near-total gastrectomy and Roux-en-Y anastomosis. Slowed gastric emptying and delayed small intestinal transit occur in persons with cirrhosis. If these symptoms are due to disorders of the upper GI tract, then stimulating smooth muscle activity is useful, as outlined in Table 2. If intractable symptoms persist, acupuncture (P6 point) or gastric electrical stimulation may be of limited benefit. Unfortunately, nausea and vomiting is common during pregnancy, particularly during the first trimester. Curiously, vitamin b6 (thiamine), soda crackers, and ginger are often helpful (Table 4). If symptoms persist, there are a number of medications which can safely be used during pregnancy, especially FDA category A and B (Table 5).

Table 3. Mechanisms of centrally acting drugs used for the treatment of symptoms of nausea and vomiting

H-1 receptor antagonists – diphenhydramine, promethazine
Cannabinoids – dronabinol, nabilone
Neurokinin (NK)-1-antagonist – aprepitant, talnetant, osanetant
Neuroleptic – chlorpromazine, haloperidol
Benzodiazepines
5 HT3 antagonist - Ondansatron
Tricyclic antidepressants
Steroids (e.g. dexamethasone) (Mannitol (nausea and vomiting due to increased intracranial pressure)



Table 4. Non-pharmaceutical options (Dietary and lifestyle modifications) for the treatment of nausea and vomiting during pregnancy

Avoidance of precipitating factors
Frequent, small meals high in carbohydrate and low in fat
Vitamin B6 (thiamine)
Ginger
Stimulation of P6 acupuncture point
Treat dehydration, electrolyte disturbances
Correct malnutrition
Soda crackers (unproven benefit)
Avoid offending foods/beverages

Modified from: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): page 433.

Table 5. Drugs that may be used for nausea and vomiting in pregnancy and their FDA pregnancy use category

Drug	FDA category	Usual dosage
Vitamin B ₆	A	10-25 mg three times daily
Doxylamine	B	12.5 mg twice daily
Erythromycin	Erythromycin (FDA category B; used rarely to treat hyperemesis)	Erythromycin (FDA category B; used rarely to treat hyperemesis)
Prochlorperazine	C	5-10 mg three times daily
Metoclopramide	B	10-20 mg four times daily
Ondansetron	B	4-8 mg three times daily
Promethazine	C	12.5-25.0 mg four times daily
Domperidone	C	20 mg three to four times daily

Adapted from: Thukral C, and Wolf JL. *Nature Clinical Practice Gastroenterology & Hepatology* 2006; 3(5): page 258; and printed with permission: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): page 433.



Table 6. Smooth muscle as well as the CNS receptors responsible for the mechanism (s) of action for drugs used in the treatment of refractory nausea and vomiting

-
- GI receptors
 - Central
 - H-1 receptor antagonists – diphenohydramine, promethazine
 - Cannabinoids – dronabinol, nabilone
 - Neurokinin (NK)-1-antagonist – aprepitant, talnetant, osanetant
 - Neuroleptic – chlorpromazine, haloperidol
 - Benzodiazepines
 - Ondansatrom – 5 HT₃ antagonist
 - Tricyclic antidepressants
 - Steroids (e.g. dexamethasone), mannitol (nausea and vomiting due to increased intracranial pressure)
-

Table 7. Factors that slow the rate of gastric emptying rate

-
- Gastric Neuromuscular
 - Tachygastria
 - Decreased fundic accommodation
 - Increased fundic accommodation
 - Antral hypomotility
 - Pylorospasm
 - Antroduodenal dyscoordination
 - Meal-related factors
 - Increased acidity
 - Increased osmolarity
 - Nutrient density: fat > protein > CHO
 - Tryptophan
 - Undigestible fibers
 - Small intestinal factors
 - Fatty acids in duodenum
 - Fatty acids in ileum
 - Colonic factors
 - Constipation, IBS
-



- Other factors
 - Hyperglycemia
 - Hypoglycemia
 - Illusory self-motion (vection)

Abbreviations : CHO, carbohydrate; IBS, irritable bowel syndrome.

Only ↓ fundic accommodation and hypoglycemia accelerate gastric emptying. The volume of the meal alters the rate of gastric emptying in proportion to the volume of the meal.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 48-1, pg , Ninth Edition, 2010

4. Hypergastrinemia

From our appreciation of the numerous ways in which acid secretion may be turned on or off, it is straight-forward to work out the causes of hypergastrinemia, and those mechanisms of hypergastrinemia which would be associated with increased gastric acid secretion, and might lead to severe peptic ulcer disease (Table 8 and 9)

Table 8. Causes of hypergastrinemia

With acid hypersecretion	With variable acid secretion	With acid hyposecretion
Gastrinoma	Hyperthyroidism	Atrophic gastritis
Isolated retained gastric antrum	Chronic renal failure	Pernicious anemia
Antral G-cell hyperplasia	Pheochromocytoma	Gastric cancer
Massive small bowel resection		Postvagotomy and pyloroplasty
Pyloric outlet obstruction		
Hyperparathyroidism		



Table 9. Mechanisms of hypergastrinemia associated with gastric acid (HCl), hypersecretion and with HCl hyposecretion or achlorhydria.

➤ ↑ Stimulation	➤ ↓ Feedback inhibition
○ Non-fasting	○ Atrophic gastritis (pernicious anemia, Hp infection, gastric cancer)
○ Gastric outlet obstruction	○ Reduced acid – PPI, H ₂ RA, antacids
○ Hyperthyroidism	○ Retained antrum
○ Pheochromocytoma	
○ Hypercalcemia	➤ ↑ Secretion
○ Mastocytosis	○ ZES, MEN-1°, G-cell
	○ Hypertrophy/hyperplasia
➤ ↓ Metabolism	○ Retained gastric antrum
○ Chronic renal failure	

Adapted from: Metz DC, and Jensen RT. *Gastroenterology* 2008;135: page 1469-1492.

While peptic ulcer disease (PUD) is usually caused by *H. pylori* infection or NSAIDs, in many non-explanation is found (idiopathic). A very uncommon cause of PUD is hypergastrinemia, associated with a gastrin producing tumor. The normal control of gastrin secretion is lost, and the hypergastrinemia may cause numerous symptoms (Table 10) as part of the Zollinger-Ellison syndrome (ZES). For persons with PUD as part of their ZES, they often have a history of multiple ulcers, ulcers at unusual sites, ulcers which are slow to heal, or are complicated.

Table 10. Presenting features of ZES, and their approximate frequency

○ Abdominal pain (75%-100%)	○ Multiple ulcers in unusual places
○ Diarrhea (35%--73%) (isolated presentation in up to 35%)	○ Stomal ulcers
○ Pain and diarrhea (55%-60%)	○ PUD refractory to treatment
○ Heartburn (44%-64%)	○ Ulcer complications (bleeding, 1%-17%; perforation, 0%-5%, or obstruction, 0%-5%)
○ Duodenal and prepyloric ulcers (71%-91%)	○ Associated with MEN1 (22%-24%)

Abbreviations: MEN, multiple endocrine neoplasia; PUD, peptic ulcer disease; ZES, Zollinger-Ellison syndrome

Adapted from: Metz DC, and Jensen RT. *Gastroenterology* 2008;135: page 1469.

In the person suspected as having ZES (Table 10), a fasting gastrin measurement is obtained. There are many possible explanations for an elevated serum gastrin concentration (Table 9). After these have been considered and excluded, if there is a high pretest probability of ZES, then proceed with diagnostic investigations (Table 11). There are mostly parathyroid, pancreatic and pituitary tumours associated with MEN-1 (Table 12). For MEN-1 associated with a gastrinoma and ZES, management is



usually PPI acid inhibition, and resection or chemotherapy if the tumour is suspect of being malignant. Treatment is complex and requires specialist consultation.

Table 11. Investigation of the patient with confirmed fasting hypergastrinemia, performed after a detailed history and physical examination

- Laboratory tests
 - Confirm fasting state for gastrin measurement
 - Creatinine, calcium, PTH
 - Chromogranin A (exclude renal failure)
 - Schillings test, serum B₁₂
 - Provocative tests
 - Secretin infusion (increases gastrin paradoxically in ZES)
 - TSH
 - Urinary metanephins
 - Ca⁺² infusion (marked increase in serum gastrin)
 - Basal and pentagastrin stimulated acid secretion (↑↑ BAO), BAO/MAO>60% (ZES)
 - Food-stimulated acid secretin (G-cell hyperplasia/ hyperfunction)
 - Endoscopy
 - EGD
 - Multiple ulcers in unusual sites
 - Biopsy antrum for G-cell number (to distinguish between G-cell hyperplasia [↑G-cell number] vs G-cell hyperfunction (normal G-cell number); *H. pylori*)
 - Thick gastric folds
 - EUS for possible tumor localization
 - Diagnostic imaging
 - Abdominal ultrasound
 - CT/ MRI, head (pituitary fossa, tumor in MEN I)
 - Osteotide scan
 - MBIG scan
 - CT scan of abdomen
 - MRI of abdomen
 - Parathyroid scan
-

Abbreviations: EUS, endoscopic ultrasound; ZES, Zollinger-Ellison syndrome



Table 12. Tumors found in patients with multiple endocrine neoplasia-type I (MEN-1) (their approximate frequency % is shown for interest.)

Tumors

- Parathyroid (90)
 - Pancreas (80)
 - Gastrinoma (50)
 - Insulinoma (20)
 - Glucagonoma
 - VIPoma
 - Pituitary (40)
 - Prolactin-secreting (30)
 - Growth-hormone secreting (15)
 - Cushing's syndrome (15)
 - Adrenal cortical adenoma (20)
 - Thyroid adenoma (20)
-



Chapter 4: Dyspepsia, Peptic Ulcer Disease and Upper GI Bleeding

A.B.R. Thomson and R.H. Hunt

1. Dyspepsia

“Dyspepsia” is defined as pain or discomfort in the upper abdomen. It is one of the most common complaints bringing patients to consult their family physician. These patients may also complain of nausea, fullness, early satiety, bloating, or regurgitation. Dyspepsia is a symptom or symptoms, and when the person presents, their symptom is not diagnosed, so this is called uninvestigated dyspepsia.

Each year, dyspepsia occurs in about 25% of the North American population. 25% of patients with chronic dyspepsia have esophagitis due to gastroesophageal reflux disease (GERD), 5-10% have peptic ulcer disease (PUD), < 2% have gastric or esophageal cancer, and the rest have a normal endoscopy (functional or idiopathic dyspepsia).

Lifestyle factors such as smoking, excess alcohol intake, stress and a high fat diet could precipitate dyspeptic symptoms. Non-ulcer dyspepsia (NUD) and non-erosive reflux disease (NERD) are types of functional dyspepsia with PUD-like and GERD-like symptoms respectively (Figure 1). Unlike PUD and GERD, NUD and NERD are not associated with erosive mucosal findings when investigated by esophagogastroduodenoscopy (EGD). The severity of dyspeptic symptoms is not useful in predicting what the result of the EGD might be, and there is no relationship between the severity of symptoms and the severity of underlying pathology of esophagitis or PUD.

Table 1. Commonly Used Terms to be Distinguished

➤ Dyspepsia	- A symptoms or symptoms, with no known diagnosis because the symptom has not be investigated. (aka undiagnosed dyspepsia)
➤ FD	- Functional dyspepsia: dyspepsia in which EGD and possibly other tests as well are normal
➤ NERD	- Normal endoscopy reflux disease: because GERD is a cause of dyspepsia, and GERD symptoms are included in the definition, this term may be used in the person with dyspepsia and a normal EGD
➤ NUD	- Non-ulcer dyspepsia: dyspeptic symptoms, patient investigated with a normal EGD; this term is used interchangeably with BERD and FD
➤ UD	- Uninvestigated dyspepsia: dyspepsia occurring in a person who has had no investigations

The lifetime prevalence of PUD is about 10% in North Americans. Chronic PUD is most commonly caused by *Helicobacter pylori* (*H. pylori*) infections and use of nonsteroidal anti-inflammatory drugs (NSAIDs) or ASA. Between 5 and 20% of patients with GU/DU have no evidence of either *H. pylori* or ASA/NSAID use, and may be due to rare conditions such as Zollinger Ellison syndrome (ZES)-associated gastrin-producing tumor, rarely DU or GU may be from Crohn disease or lymphoma, but about 25% have no known explanation (idiopathic). PUD may present with epigastric tenderness upon examination with other typical

symptoms including nausea, vomiting, dyspepsia, bloating or burning epigastric pain which may be relieved by food or antacids.

When the patient presents with (uninvestigated) dyspepsia, there are several approaches which may be taken (Table 2).

Table 2 Benefits and limitations associated with 5 interventional/ diagnostic approaches to the patient with dyspepsia who is under 50 years of age and who has no alarm symptoms

Diagnostic approach	Benefits	Limitations
○ “Watchful waiting” only	-Patients with mild and transient symptoms are not prescribed medication or investigated	-No clinical studies
○ Empirical Antisecretory therapy (PPI or H2RA)	-Addresses symptoms immediately	-Recurrence after therapy is the rule
○ Treat based on clinical diagnosis	-Documented effect on reflux and ulcer-related symptoms	-EGD is often only postponed, and may be falsely negative
○ Treat based on subgrouping and computer-based algorithms	-Clinically meaningful	-Unreliable
○ <i>H.pylori</i> test-and-treat	-Low costs	-Does not reliably predict EGD diagnosis or response to therapy
	-Clinically attractive	
	-Low costs	
	-Infected patients with ulcer disease will have symptomatic benefits	-Low benefit in those without peptic ulcer disease will not benefit
	-Reduces endoscopy rates. Safe and cost-effective compared with endoscopy	-Continuing or recurrent symptoms may frustrate patients and clinician
	-Possible reduced risk of later ulcer development	
○ <i>H.pylori</i> test-and-scope	-Potential to reduce upper EGD rates in <i>H. pylori</i> low-prevalence areas	Only meaningful if a decision about eradication therapy in infected patients is influenced by endoscopy result
		-Increases endoscopy demands
		-Not applicable in <i>H. pylori</i> -high prevalence areas



○ Early endoscopy	-Diagnostic “gold standard” -Might lead to reduced medication in patients with normal findings -Increased patient satisfaction in some trials	-Invasive. Costly -Low yield: About half of EGDs will be normal. -Long waiting lists may lead to false negative results because of previous therapy -Not the preferred option for many patients. -Does not diagnose non-erosive reflux disease (NERD)

Abbreviations: EGD, esophagogastroduodenoscopy; H2RA, H2 receptor antagonist; NERD, non-erosive reflux disease; PPI, proton pump inhibitor.

Adapted from: Bytzer P. *Best Practice & Research Clinical Gastroenterology* 2004; 18(4): pp.683.

In Canada, the recommended approach to the patient with undiagnosed dyspepsia is “The Hand.” The physical may quickly determine the best approach to the patient with dyspepsia, based upon the response to five questions, representing the five fingers on the hand.

Table 3. Five questions to triage the patient with chronic uninvestigated dyspepsia

- Symptoms due to non-upper GI conditions
 - Age >50, or alarm symptoms at any age
 - Use of NSAIDs/ASA
 - GERD—predominant symptoms
 - Possible *H. pylori* associated GI condition
-



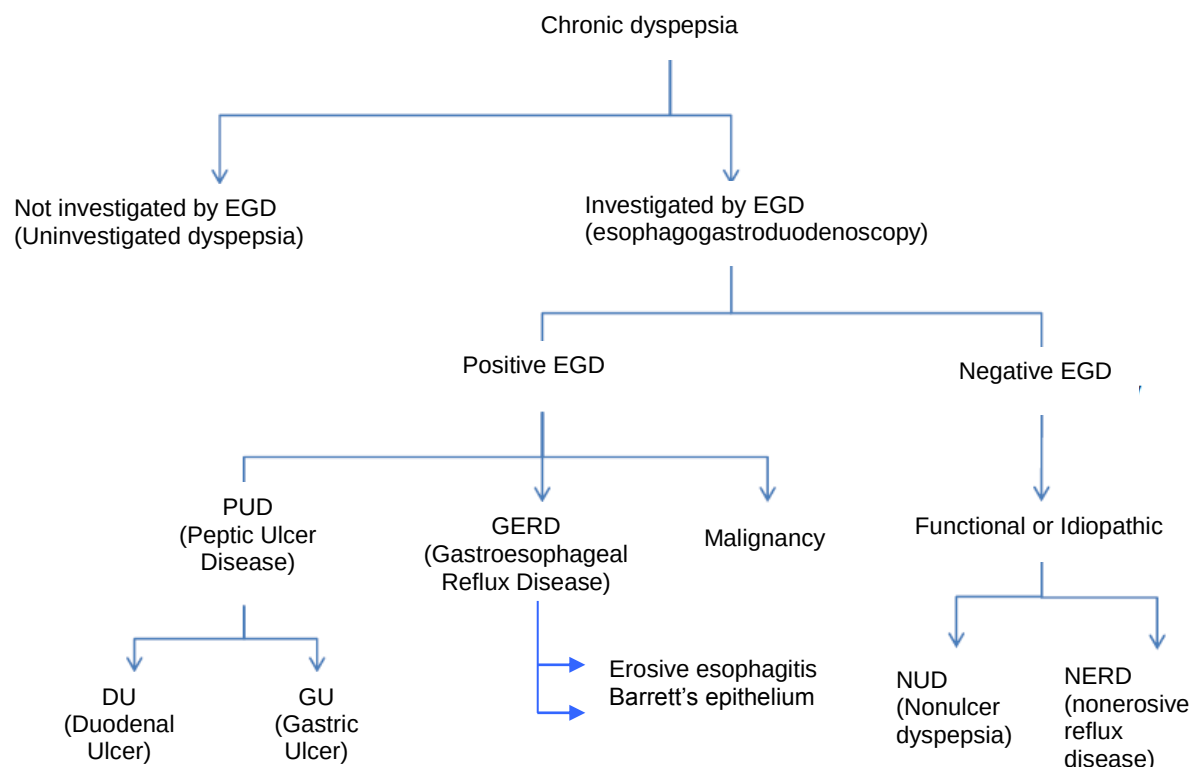


Figure 1. Terms used to describe Dyspepsia

History and physical examination

First exclude non-gastrointestinal sources of pain or discomfort in the upper abdomen, e.g., ischemic heart disease. If a non-GI condition is possible, stop and investigate. Determine if there are any “red flags” such as age more than 50 years, or at any age, abdominal mass, vomiting, bleeding, dysphagia, anemia or weight loss may be associated with rare but serious causes such as esophageal or gastric cancer (unfortunately, the stage of these malignancies is usually so far advanced when the patient presents that empirical treatment of dyspepsia for 4-8 weeks does not make the bad prognosis worse). If a patient is >50 years, if there are alarm symptoms, or if there is a history of esophagogastric malignancy—arrange for EGD.

Next, inquire if the patient is taking dyspepsia-causing medications, such as NSAIDs, ASA, antiplatelet drugs, or biphosphonates. If the answer is “yes,” attempt to stop the possibly offending medication, and treat with PPI od for 4-8 weeks. If symptoms persist, arrange EGD. If the answer is “no,” identify those with predominant reflux-like symptoms because they are more likely to respond to empiric PPI therapy for 4-8 weeks. For the person with uninvestigated dyspepsia (UD) who does not respond to lifestyle changes, avoidance of gastric irritant drugs (e.g. NSAIDs), and who does not respond to a 4-8 week course of PPI, the next step is to arrange for an urea breath test (UBT) to determine the possible presence of an *H. pylori* infection. The test-and-treat (for *H. pylori*) approach assumes that a DU/GU (if present) is responsible for the dyspeptic



symptoms and is caused by *H. pylori*. A diagnostic test is performed for *H. pylori* and patients with positive test results are treated with triple therapy (PPI plus 2 antibiotics; see later section). About 90% of patients with DU and 70% of those with GU may be *H. pylori*-positive, although the association may be less striking in community practice, or in patients with a past history of an ulcer complicated by bleeding. The advantage of this strategy is that the investigations needed to diagnose *H. pylori* produce rapid results and can be readily used by the family physician, when available in the community. The disadvantage is that serology is not reliable unless it is negative, and UBT is not universally available in Canada, and the cost of these tests may not be covered by provincial health care plans. Note that in patients with *H. pylori* infection or normal EGD the benefit of eradication is small (7% to 15% symptom resolution).

If PPI therapy is ineffective then the clinician may consider a UBT, endoscopy or referral. Long-term healthcare costs are estimated to be approximately the same regardless of which investigative approach is followed.

The nonradioactive ^{13}C UBT (rather than the radioactive ^{14}C UBT) is recommended for use in children and women of child-bearing age.¹ Patients should be off antibiotics and bismuth for 1 month and proton pump inhibitor (PPI) or histamine H₂-receptor antagonist (H₂RA) for at least one week prior to the breath test. These drugs may suppress growth of the *H. pylori* sufficiently to produce a false negative result. IgG serology is appropriate if there is no access to UBT or endoscopy. If the serology is negative, the patient is truly *H. pylori* negative. A 20% decline in IgG serology titer over 6 months correlates with successful eradication of *H. pylori*. The necessary wait of 6 months duration prior to repeat testing and the need to save and compare the sera has taken the utility of serology testing out of favour. Although prompt endoscopy is the most sensitive and specific means to diagnose the cause of dyspepsia, it would be most appropriate in dyspeptic patients with one or more of the following characteristics: age >50 years, alarm symptoms (vomiting, bleeding, anemia, weight loss, dysphagia), GU detected on an upper GI series (i.e., to obtain biopsies to exclude gastric cancer).

The use of EGD to confirm healing of GU has fallen out of favour and can likely be skipped unless there is a strong suspicion that an ulcer is malignant (large size, or ongoing symptoms despite *H. pylori* eradication or PPI therapy). Upper GI barium study has an approximately 20% false-positive and false-negative rate for detection of ulcer disease and is generally not recommended, especially in those aged >50 years and in those with alarm features (see above).² However, barium studies are often more readily available than UBT or endoscopy and are still used to reassure the physician, but this negative upper GI barium study may be falsely negative and falsely reassuring. Of course, if the x-ray study shows an abnormality, this may help to facilitate the booking of a prompt EGD.

About a third of persons with dyspepsia may have lower abdominal complaints suggestive of the irritable bowel syndrome (IBS). Treatment of IBS may reduce the severity of the reflux symptoms, and enhance the person's quality of life.



Although empiric antisecretory therapy is relatively simple and non-invasive, endoscopy would permit the diagnosis of dyspepsia causes such as erosive esophagitis, Barrett's epithelium, GU or DU, gastric or duodenal erosions, *H. pylori* infection and gastric or esophageal cancer. Normal EGD results would be reassuring to both patient and physician. From a practical point of view, these advantages must be balanced against the disadvantages of EGD in the patient chronic dyspepsia.

Table 4. The disadvantages of EGD in the patient with chronic dyspepsia

-
- Scarcity of gastroenterologists to perform the procedure (the average waiting time to arrange for an EGD is 2 to 6 months),
 - Cost (total cost approximately \$500),
 - Patient time lost from work
 - Risk of complications such as aspiration or perforation (about 1 per 5000 procedures).
-

For empirical therapy, or for erosive esophagitis or NERD/NUD, start with od PPI. For patients who respond to initial PPI therapy, subsequent “on-demand” PPI therapy is more efficacious than continuous standard dose H₂RAs but is not superior to on-demand H₂RAs in *H. pylori* negative patients. In patients who have completed their initial course of PPIs, continued PPI therapy is more efficacious than step-down to H₂RAs for providing symptom relief. Standard dose PPIs are more efficacious than continued H₂RAs in patients with uninvestigated GERD who have incomplete response to a previous trial of H₂RAs. Approximately 20% of patients with UD will remain asymptomatic for up to 6 months after a successful course of initial therapy with PPI or H₂RA. If dyspepsia symptoms persist, or if there are frequent recurrences, investigate with a UBT for *H. pylori* infection, or with prompt endoscopy. UBT for *H. pylori* is safe, effective, more comfortable and less distressing than endoscopy for the patient.⁶

Use of over-the-counter (OTC) therapy with antacids or H₂RAs is common before patients seek medical advice. These drugs provide moderate benefit for mild symptoms of pain. Prescription doses of H₂RAs relieve symptoms, but are much less effective for pain relief and ulcer healing than PPIs, and must be used twice daily and for longer periods (4 to 8 weeks for DU and 8 to 12 weeks for GU). Also, tachyphylaxis (loss of effectiveness over time) to H₂RAs may develop quickly.



2. Peptic Ulcer Disease

Table 5. The secretory cells of the stomach, and chemical/peptide/hormone the cell secretes

-
- Goblet cell – mucus
 - Parietal cell – HCl, intrinsic factor
 - Chief cells - pepsinogen
 - D cells – somatostatin
 - G cells – gastrin
 - Mast cells – histamine
 - Enterochromaffin-like cells – histamine
-

Table 6. Clinical situations/syndromes which can be associated with fundic gland polyps

-
- *H. pylori* infection
 - PPI use
 - Hypergastrinemia
 - Familial adenomatous polyposis (FAP; Attenuated FAP, 0.5-1.0% lifetime risk of gastric cancer)
 - Cowden's syndrome
 - Idiopathic
-

Table 7. Factors to consider when performing endoscopy in pregnant women

-
- A strong indication is always needed, particularly in high-risk pregnancies
 - Whenever possible, endoscopy should be deferred until the second trimester
 - The lowest possible dose of sedative medication should be used (wherever possible FDA category A or B drugs)
 - Procedure time should be short
 - To avoid inferior vena cava or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position
 - Presence of fetal heart sounds should be confirmed before sedation and after the procedure
 - Obstetric support should be immediately available
 - No endoscopy should be performed in patients with obstetric complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)
-

Printed with permission: Keller J, et al. *Nature Clinical Practice Gastroenterology & Hepatology* 2008; 5(8): page 435.



An ulcer is defined as a break in the mucosa, which extends through the muscularis mucosae, and is surrounded by acute and chronic inflammation. The lesion of peptic ulcer disease (PUD) is a disruption in the mucosal layer of the stomach or duodenum. An ulcer is distinguished from an erosion by its penetration of the muscularis mucosa or the muscular coating of the gastric or duodenal wall. Peptic ulcer diseases result from an imbalance between protective (defensive) mechanisms of the mucosa and harmful (aggressive) factors (Table 8).

Table 8. Pathophysiological Factors Speculated to Contribute to Peptic Ulcer

ProtectiveMucosal defence	Harmful Aggressive factors
○ Mucus secretion ○ Bicarbonate production ○ Mucosal blood flow ○ Cellular repair mechanisms ○ Prostaglandin E's ○ Growth factors	○ Acid/pepsin ○ Bile acids ○ NSAIDs ○ <i>H. pylori</i> infection ○ Cigarette smoking ○ EtOH, stresses, coffee

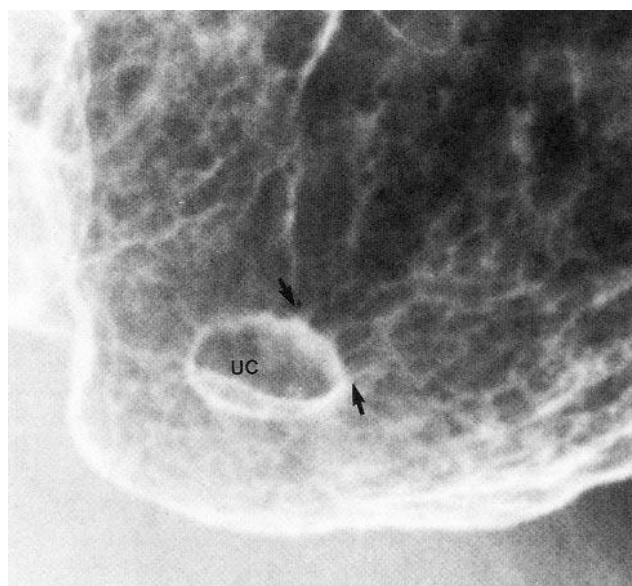


Figure 2. Benign gastric ulcer. Barium meal showing an ulcer crater (UC) situated on the greater curvature of the stomach, in the gastric antrum. The ulcer is visualized en face with a slightly oblique projection. Smooth mucosal folds radiating from the edge of the crater (arrows) in a regular fashion are a pathognomonic sign of a benign gastric ulcer. (Courtesy of Dr. J. Rawlinson.)





Figure 3. Penetrating gastric body ulcer (benign) in an asymptomatic elderly patient on NSAIDs.

2.1. Pathophysiological Factors

Given the multiple processes that control acid and pepsin secretion and defence and repair of the gastroduodenal mucosa, it is likely that the cause of ulceration differs between individuals. Acid and pepsin appear to be necessary but not sufficient ingredients in the ulcerative process. It is clear that the majority of gastric ulcers (Figures 1, 3) and a substantial number of duodenal ulcers (Figures 4, 5, 6) do not have increased gastric acid secretion.

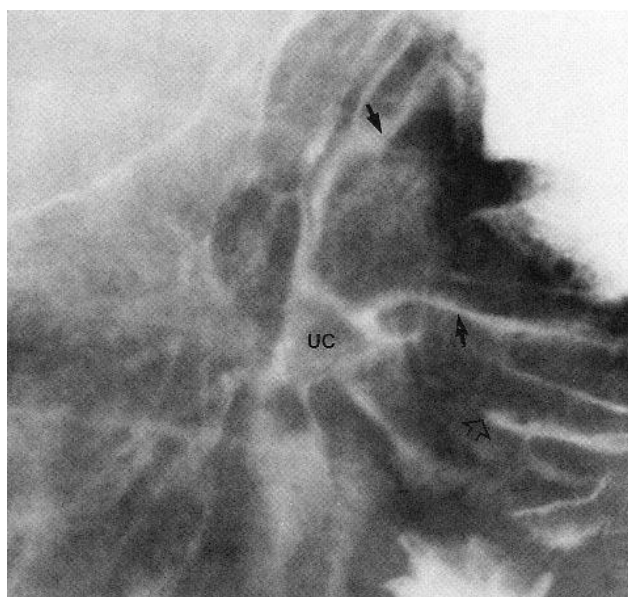


Figure 4. Malignant gastric ulcer. Barium meal demonstrating an ulcer crater (UC) on the lesser curvature of the stomach, also visualized en face. In this case the radiating mucosal folds are irregularly thickened (e.g., between closed arrows) and do not extend to the edge of the crater (open arrow) – features indicating a local infiltrative, malignant process. (Courtesy of Dr. J. Rawlinson.)

Peptic ulcers usually occur at or near mucosal transitional zones, areas that are particularly vulnerable to the deleterious effects of acid, pepsin, bile and pancreatic enzymes. Gastric ulcers are most commonly found on the lesser curvature, near the junction of acid-producing parietal cells and the antral mucosa, extending to an area 2–3 cm above the pylorus. Duodenal ulcers are usually found in the duodenal bulb, the pyloric channel or prepyloric area. Other peptic ulcers may occur in the esophagus, gallbladder (rarely, with ectopic gastric mucosa), and Meckel's diverticulum. Only one-third of DU patients have acid hypersecretion. Gastric acid production is usually normal in persons with gastric ulcers.



Table 9. Pathophysiologic defects in some patients with:

-
- Gastric ulcer disease
 - Decreased acid secretion, decreased parietal cell mass (PCM), back-diffusion of acid
 - Chronic superficial and atrophic gastritis
 - Increased concentration of bile acids and pancreatic juice in stomach (duodenogastric reflux) Delayed gastric emptying
 - Inappropriately decreased pyloric sphincter pressure under basal conditions and in response to acid (secretin) or fat (cholecystokinin) in the duodenum

 - Duodenal ulcer disease
 - Increased parietal cell mass
 - Increased sensitivity of parietal cells to gastrin and secretagogues
 - Increased secretory drive
 - Decreased acid-induced inhibition of meal-stimulated gastrin release
 - Increased gastric emptying
 - Increased duodenal acid/pepsin loads
 - Chronic active gastritis
-

The most important contributing factors are *H. pylori* infection and NSAIDs, with each of these causing a disturbance in the balance between the protective and harmful factors (Table 8). The important topics of NSAIDs and *H. pylori* will be covered in later sections. In the person with PUD who is not on NSAIDs and who does not have an *H. pylori* infection, the cause of their ulcer disease is usually unknown (idiopathic). Although hypergastrinemia leading to acid hypersecretion, ZES, and possibly associated MEN-I is rare, this condition must be suspected in the person with severe/intractable PUD, multiple ulcers or ulcers at unusual sites, diarrhea, or adenomas of the pituitary or parathyroid (see previous chapter).

Duodenal ulcer is also associated with other illnesses such as hyperpepsinogenemia I, systemic mastocytosis, MEN I, G-cell hyperfunction, rapid gastric emptying, childhood duodenal ulcer and immunological forms of peptic ulcer disease, glucocorticoid, chronic renal failure, renal transplantation, cirrhosis, chronic obstructive lung disease, and neurological trauma and burns (Curling's ulcer).

Heredity plays some role in peptic ulcer diseases, especially in DU. Twenty to 50% of patients with DU have a positive family history for PUD. Inheritance patterns of DU and GU appear distinct (i.e., DU→DU and GU→GU). Studies of twins show greater concordance among identical than among fraternal twins. In addition, individuals with blood group O have about a 30% increased risk of DU, compared with those of other blood groups



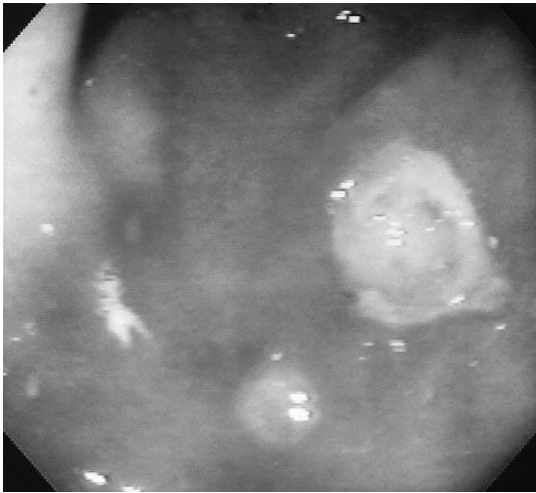


Figure 5. Duodenal ulcer, posterior wall.

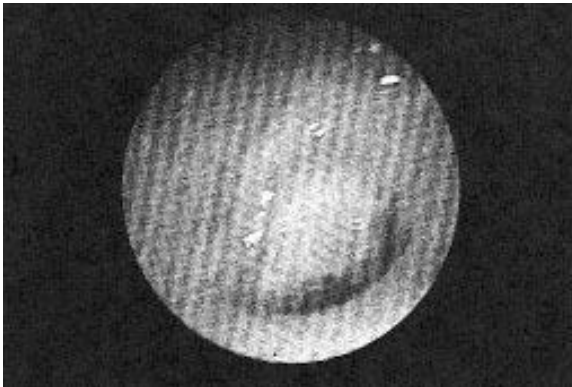


Figure 6. Duodenal ulcer. Endoscopic view of the duodenal cap ulcer.



Figure 7. Duodenal ulcer situated at the base of the duodenal cap. The ulcer crater is filled with barium (arrow). The surrounding inflammatory process has considerably distorted the normal bulbar configuration of the proximal duodenum. (Courtesy of Dr. J. Rawlinson.)



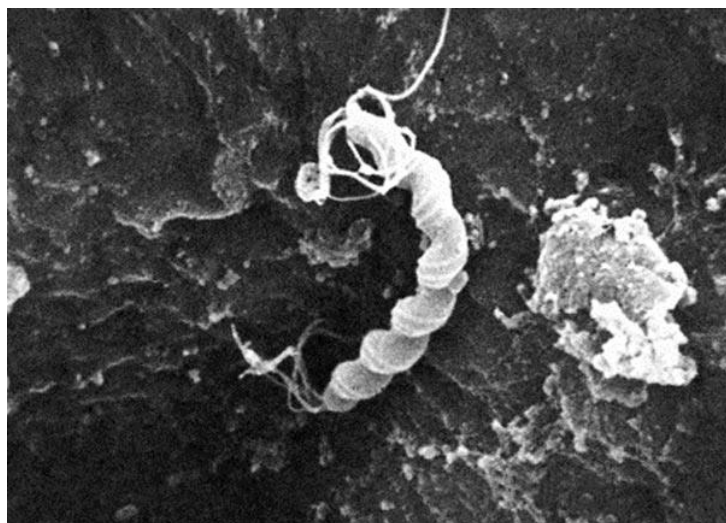


Figure 8. *Helicobacter pylori*.
(Courtesy of McMaster University
Medical Centre Electron
Microscopy Lab.)

2.2. *Helicobacter pylori* and Peptic Ulcer Disease

2.2.1. Introduction

The discovery that *H. pylori* infection is the main cause of peptic ulcer caused a paradigm shift in our understanding of the disease pathogenesis. This was

the first example of a common chronic bacterial infection usually acquired in childhood causing disease much later in life. In the future, many other diseases are likely to be linked to chronic infections but for now *H. pylori* studies provide fascinating insights into long term bacterial-host interactions.

2.2.2. Epidemiology

Studies around the world suggest the prevalence of *H. pylori* infection is 90–95% in patients with duodenal ulcer, 80–85% in patients with gastric ulcer and approximately 50% in the general population and 30% in Canada. Randomized controlled trial data proves that this association is causal but this does not mean that 90–95% of all duodenal ulcers are due to *H. pylori*. As the prevalence in the general population is also high, a few ulcers that are not due to *H. pylori* infection will still have the infection by chance. It is estimated that about 75% of all peptic ulcers are attributable to *H. pylori* infection with most of the rest being due to nonsteroidal anti-inflammatory drugs. The lifetime risk of having an ulcer in individuals infected with *H. pylori* is difficult to calculate, but is probably between 10 and 15%. *H. pylori* represents 60% of the causative factors for gastric cancer, and approximately 1% of persons infected with *H. pylori* will develop gastric cancer (see next chapter).

2.2.3. Pathophysiology

H. pylori infection may cause or increase dyspepsia and its complications. It is important to stress that about 25% of Canadians have an *H. pylori* infection in their stomach, but in less than a quarter of this quarter is the infection associated with a symptomatic condition that responds to eradication therapy of the *H. pylori*. To rephrase, if the patient with an *H. pylori* infection has dyspepsia but non RU/GU, there is only a small likelihood that their dyspepsia will respond to eradication of the *H. pylori*. In sharp contrast, if the dyspeptic person has a peptic ulcer plus an *H. pylori* infection, eradicating the infection cures the ulcer disease and resolves symptoms in over 80% of sufferers. Furthermore, in



persons with an *H. pylori* infection plus dyspepsia, *H. pylori* eradication decreases their dyspepsia score, but has no effect on the person's quality of life (Bektas et al, 2009).

H. pylori infection is the most common chronic bacterial infection worldwide yet only a small proportion of cases develop disease. The reasons for this are not fully understood but relate to a combination of environmental, host and bacterial factors. Certain strains of *H. pylori* are more likely to cause peptic ulcer disease. The most well characterized is the cytotoxin associated gene (*cagA*) and the vacuolating cytotoxin (*vacA*) gene. The *cagA* gene encodes for a *cagA* protein that is injected into the host epithelial cells to induce changes in the gastric cytoskeleton. All strains possess the *vacA* gene but the s1m1 variant has the most potent cytotoxic activity and highest risk of causing peptic ulceration. Contact with epithelial (*iceA*) gene is another virulence factor with the *iceA1* genotype, and is associated with increased gastric inflammation and higher likelihood of disease. Peptic ulceration is not universally present even with the most pathogenic strains of *H. pylori* and other factors such as male gender, host genetic factors (such as those that predict gastric acid output) and smoking will influence whether the infection causes disease.

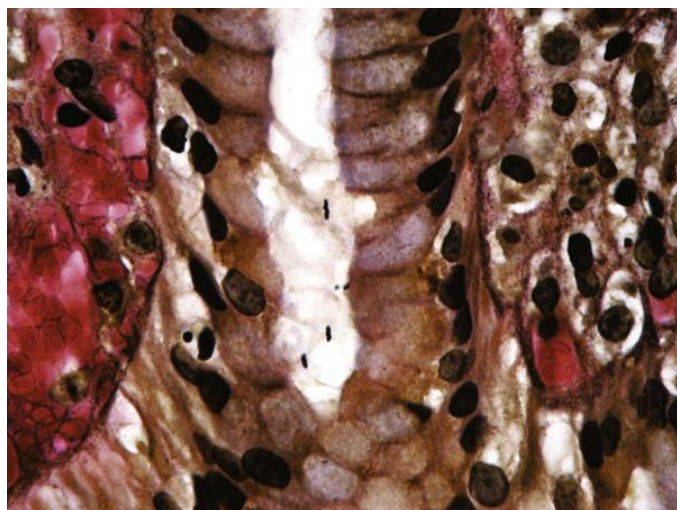


Figure 9. Photomicrograph of a gastric mucosal biopsy specimen, stained with the Genta stain, from a patient with *Helicobacter pylori* gastritis. The bacteria are well seen.

Another epidemiological paradox is how an infection can cause both gastric and duodenal ulcer disease yet both types of ulcer rarely exist in the same patient. The distribution of infection in the stomach appears to be the most important

determinant of disease phenotype. Duodenal ulceration most likely occurs when there is an antral predominant *H. pylori* infection that decreases antral somatostatin production. This reduces the negative inhibitory effect on gastrin production by antral G cells. The increased gastrin production increases parietal cell mass and acid output. The excess acid entering the duodenum causes the mucosa to undergo gastric metaplasia that can in turn be infected with *H. pylori*. The organism then causes inflammation, epithelial injury, and reduces duodenal bicarbonate secretion. This compromise to duodenal mucosal defence predisposes to ulcer formation.

In contrast, *H. pylori* infection is more likely to cause gastric ulceration if the infection is more evenly spread throughout the stomach. The pangastritis that results will cause inflammation of parietal cells and overall gastric acid secretion will be reduced. The inflammation will also impair mucosal defence and this can result in



gastric ulceration even in a relatively hypochlorhydric environment.

The distribution of *H. pylori* is predicted by environmental factors. Acid output has yet to reach full capacity in the neonatal period so if *H. pylori* is acquired soon after birth it will be able to infect the whole stomach causing a pan-gastritis. This is probably exacerbated by the poor nutrition seen in many developing countries. If the infection is acquired later in childhood when acid secretion is higher, *H. pylori* will prefer to reside in the antrum where less acid is produced.

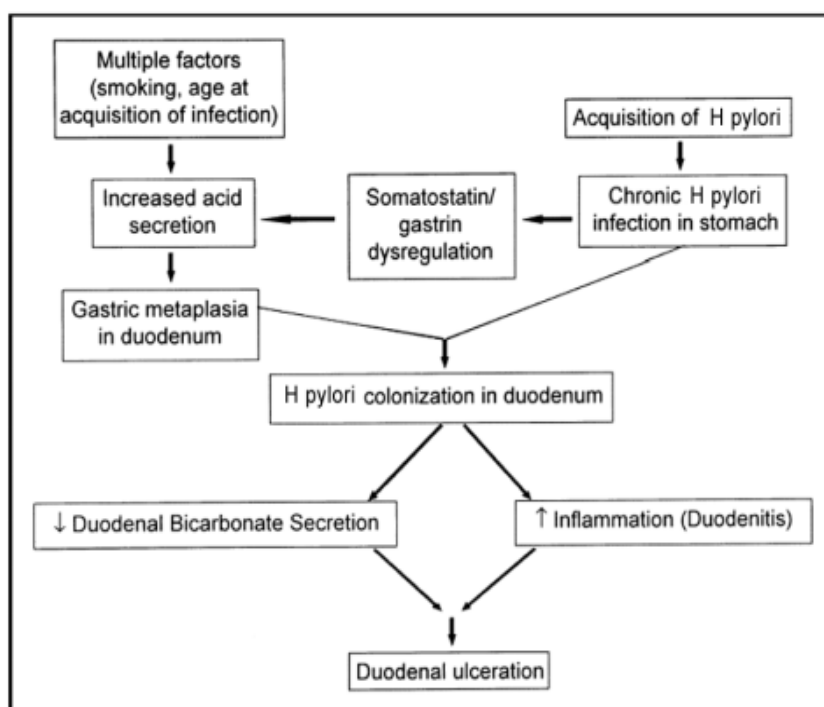


Figure 10. Model of duodenal ulcer pathogenesis. Persons infected with *cagA/tox A/H. pylori* strains develop enhanced mucosal inflammation, which may lead to heightened gastric acid secretion with development of gastric metaplasia, colonization by *H. pylori* in the duodenum, and subsequent duodenal ulcer formation.

The urease activity of *H. pylori* provide a means for the organism to burrow through the mucus overlying the gastric epithelium to bind to adhesions, and to colonize the alkaline environment adjacent to the membrane. It invades the gastric mucosa, while being able to evade the host immunity. The adhesions provide an interplay between bacterial and Lewis antigens, and help to determine different clinic-pathologic outcomes (Sheu et al. 2010). IL-1 and TNF- α gene clusters are important in defining the extent and severity of *H. pylori* associated gastritis. The common pan-gastritis may or may not be symptomatic, the antral predominant gastritis is associated with an increased risk of duodenal ulcer disease, and gastric body associated gastritis is associated with multifocal gastric atrophy and an increased risk of gastric cancer



(Shanks and El-Omar 2009). *H. pylori* is thought to be transmitted by the gastro0oral or the fecal-oral route. If one family member has an *H. pylori* infection, it has an impact on other family members and the community (Table 10).

There is a broad range of tests available to diagnose the presence of an *H. pylori* infection, put only upper endoscopy plus biopsy for histological examination or culture will provide a diagnosis of *H. pylori* plus *H. pylori* associated disease such as gastritis, peptic ulcer disease intestinal metaplasia, gastric cancer or mALT lymphoma (Guarner et al. 2010). The culture of the gastric biopsies also provides for testing for in vitro antibiotic sensitivity of the organism, as well as gene testing for antibiotic resistance, but the sensitivity is low. The rapid urease tests have better sensitivity than less histology. The non-tissue, non-endoscopy tests include blood, breath and stool antigen testing. The urea breath test is more than 75% sensitive and can be used both to diagnosis an *H. pylori* infection and to confirm its eradication. Testing for *H. pylori* antigens in stool is also useful before and after treatment, and has a greater than 95% sensitivity.

Table 10. The impact of one person in the family being positive for *H. pylori* on the rate of *H. pylori* infection by others in the family

-
- Hp positive parent
 - spouse 68% Hp⁺
 - children 40% Hp⁺
 - Hp negative parent
 - spouse 9% Hp⁺
 - children 3%Hp⁺
 - Community Risk
 - Adults - approximately 25-30% (depends on person's age)
 - Higher (30%) in older persons
 - >50% First Nations Canadians, new Canadians originally from high Hp prevalence areas
 - New Canadians from high prevalence countries
-



Table 11. Indications for Testing and Treatment of *Helicobacter pylori* infection

-
- Supported by evidence
 - Active peptic ulcer disease (gastric or duodenal ulcer)
 - Confirmed history of peptic ulcer (not previously treated for *H. pylori* infection)
 - Gastric MALT-lymphoma (low grade)
 - Following endoscopic resection of early gastric cancer
 - Uninvestigated dyspepsia (if *H. pylori* population prevalence high)
 - Controversial
 - Functional dyspepsia
 - GERD
 - Persons using NSAIDs, especially when first initiating NSAID treatment
 - Unexplained iron deficiency anemia or immune thrombocytopenic purpura
 - Populations at higher risk of gastric cancer (ie. Asians, Eastern Europeans, Mesoamericans)
-

GERD, gastroesophageal reflux disease; MALT, mucosa-associated lymphoid tissue; NSAIDs, nonsteroidal anti-inflammatory drugs.

In persons with an *H. pylori* infection plus dyspepsia, *H. pylori* eradication decreases their dyspepsia score, but has no effect on the person's quality of life (Bektas et al. 2009).

There are many conditions in the GI tract which are associated with *H. pylori* infection, the most important of which are dyspepsia, peptic ulcer disease, and gastric cancer (Table 12).

If the patient is *H. pylori*-positive, treat with triple therapy (PPI plus 2 appropriate antibiotics taken bid for 7–14 days). It is not always necessary to continue the PPI for longer. After the patient has been off PPI for 2 weeks, perform a urea breath test (UBT).²⁹ If the *H. pylori* has cleared, a delayed second UBT should be performed to completely exclude *H. pylori* infection³⁰, in which case PPI maintenance therapy would not be required. If the *H. pylori* has not cleared, a different triple therapy, or quadruple therapy would be needed, and the UBT is repeated to prove eradication of *H. pylori*. If the ulcer is not associated with *H. pylori*, or if the use of ASA or NSAIDs cannot be stopped, continue PPI maintenance therapy for life to reduce the risk of rebleeding.



Table 12 - GI and non-GI conditions which may be associated with *H. pylori* (Hp) infection

-
- Hp-associated GI Diseases
 - Non-ulcer dyspepsia
 - Acute/chronic gastritis
 - Atrophic gastritis – intestinal metaplasia- dysplasia – GCa (gastric cancer [non-cardia])
 - Duodenal and gastric ulcer (DU and GU) (only ~20% of Hp⁺ persons develop disease)
 - Accentuation of effect of smoking on PUD
 - Accentuation of ASA/NSAID effects on peptic PUD
 - Maltoma
 - Fundic gland polyps
 - Hypertrophic gastric folds
 - Protective against GERD (possible)
 - Halitosis
 - Carcinoid tumors
 - Colorectal cancer (possible)
 - Pancreatic cancer (possible)
 - Possible Hp-associated non-GI diseases
 - Head –otitis media, migraines, headaches
 - CNS – Parkinsonism, CVA
 - Heart – atherosclerotic diseases
 - Lung – chronic bronchitis, COPD, SIDS
 - Blood – ITP, iron deficiency
 - Skin – idiopathic chronic urticaria, acne, rosacea
 - Growth retardation in children
-

Abbreviations: CVA, Cerebrovascular accident; COPD, chronic obstructive pulmonary disease; DU, duodenal ulcer; GCa, gastric cancer; GERD, gastroesophageal reflux disease; GU, gastric ulcer; ITP, idiopathic thrombocytopenic purpura; PUD, peptic ulcer disease; SIDS, sudden infant death syndrome.

Adapted from: Hunt R. *AGA Institute Post Graduate Course* 2006; page 333-342.; and adapted from Graham DY. and Sung JJY. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006. page 1054.



Table 13. Recommended indications for *H. pylori* eradication therapy (ET) in the patient taking NSAIDs or ASA

Level of recommendation	Strength of Advice	
➤ Advisable	2	○ Reduce PUD formation
➤ Strong	2	○ Reduce recurrent PUD
➤ Strong	1	○ Reduce recurrent PUD bleeding (in ASA or NSAID high risk users)
➤ Advisable	2	○ ET does not prevent further PUD bleeding in high risk ASA/NSAID users on PPI

Modified from Lai LH & Sung JJY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(2): page 270.

Table 14. The annual incidence of NSAID-induced adverse event can be estimated by multiplying the baseline absolute risk (AR) with patient-specific relative risk modifiers

➤ Risk characteristic		
○ Baseline absolute risk (AR) for GI event (%)	-2.5 (1.5-4.5%)	2.5
○ Increase in risk:	Age >65 years	2.5
	Use of anticoagulants	2.5
	Use of steroids	2.0
	History of PUD	5.0
	High dose of NSAIDS	2.0
	Presence of <i>H. pylori</i>	1.5
○ Reduction in risk:	Therapy with PPIs	0.5

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2.2.4. Treatment

Peptic ulcers can be healed by acid suppression with a PPI or H2RA, but about 80% recur once anti-secretory therapy is discontinued. The strongest evidence that *H. pylori* infection causes peptic ulcer comes from randomized controlled trials that show eradication of the organism permanently cures the disease in most cases. Indeed antibiotic therapy alone can cure duodenal ulcer without the need for acid suppression. This evidence has led major guidelines worldwide to recommend *H. pylori* eradication therapy in infected patients with gastric and duodenal ulcer disease. Indeed, the relapse rate for duodenal ulcer disease after healing with acid suppression is 64% over 3–12



months. This falls to 14% in those receiving *H. pylori* eradication therapy. The relapse rate for gastric ulcer is 40% compared with 12% after *H. pylori* eradication. The number needed to treat (NNT) to prevent the recurrence of a duodenal ulcer was 2 (95% CI = 1.7 to 2.3). This is a very dramatic effect compared with the NNT for most other diseases but actually underestimates the true impact of *H. pylori* eradication, as many of the therapies included in the systematic review were substandard. When only proton pump inhibitor-based triple therapies or bismuth salt quadruple therapies were included, the relapse rate for duodenal ulcer patients fell to 8%. Many of the patients who relapsed still harboured *H. pylori* but a few patients had an ulcer relapse despite being *H. pylori* negative. This relates to the epidemiology of the association. If *H. pylori* is common, then a few patients will develop peptic ulcer disease through other causes and be infected by chance. Eradication of the organism in this setting will not cure the ulcer diathesis. A positive UBT is a surrogate marker for PUD (DU or GU), and eradication of this infection will remove this cause of PUD and its symptoms. Eradication of *H. pylori* will also reduce the adverse effects of NSAIDs and smoking on the mucosa of the stomach and duodenum.

Duodenal ulcer is typified by *H. pylori* infection and duodenitis and in many cases impaired duodenal bicarbonate secretion in the face of moderate increases in acid and peptic activity (Figure 7). The increased acid load resulting from *H. pylori* infection of the antrum is delivered to the duodenum, causing damage to the duodenal mucosa and eventually leading to the development of gastric metaplastic lesions. *H. pylori* bacteria can infect these islands of gastric mucosa, and the combination of increased acid delivery and *H. pylori* infection ultimately leads to ulcer formation (Figure 10). Gastric ulcer often occurs with decreased acid-peptic activity, suggesting that mucosal defensive impairments are more important.

Thus, the treatment of peptic ulcer disease associated with an *H. pylori* infection is the eradication of *H. pylori*.

H. pylori eradication has benefits beyond the relief of the dyspepsia. These benefits include the removal of the approximately 15% lifetime risk of PUD, and 1% risk of developing gastric cancer or mucosa-associated lymphoid tissue (MALT) lymphoma if the infection is left untreated. Treatment regimens approved by the Canadian Helicobacter Study Group achieve a minimum eradication rate (on an intention-to-treat basis) of at least 80%. First-line triple therapy consists of a PPI plus two antibiotics (clarithromycin and either amoxicillin or metronidazole) administered twice daily for one week (Table 1). Quadruple therapy is also considered to be a first-line treatment.

A prepackaged triple therapy combination containing lansoprazole, clarithromycin and amoxicillin trihydrate is commercially available as Hp-PAC®. PMC (PPI plus metronidazole and clarithromycin) prepackaged combination is not available commercially. The prevalence of Metronidazole-resistant *H. pylori* in Canada is about 20% and resistance to amoxicillin is less than 1%, thus use of amoxicillin-containing regimens is increasing.

If one triple-therapy regimen fails to eradicate *H. pylori*, the patient should be re-treated with a different antibiotic combination, for two weeks rather than one, or with a quadruple therapy (PPI, bismuth, metronidazole plus tetracycline) rather than triple



therapy. With increasing prevalence of resistance of *H. pylori* to treatment with metronizadole or clarithromycin, second line therapy is increasingly required, including levofloxacin. After successful *H. pylori* eradication, the risk of re-infection is only about 1% per year.

All PPIs have similar efficacy in triple therapy regimens for *H. pylori* eradication. Twice daily PPI dosing, however, is more efficacious than once daily dosing (when used in a PAC or PMC triple-therapy regimen). *H. pylori* eradication therapy with triple therapy (PAC and PMC) for 7 days is as efficacious as therapy for 10 or 14 days. *H. pylori* eradication therapy with triple therapy (PAC and PMC) for 10 days is as efficacious as 14 days. Continued treatment with a PPI after a course of *H. pylori* eradication therapy does not produce higher ulcer healing rates than eradication therapy alone in infected patients with uncomplicated DU. This does not apply to GU, where PPI therapy for 6-8 weeks is recommended.

The discovery of *H. pylori* has changed the life cycle of peptic ulcer disease (PUD). However, PUD does not completely disappear after elimination of *H. pylori* infection. Some ulcers recur even after successful eradication of *H. pylori* in non-NSAIDs users. In addition, the incidence of *H. pylori*-negative, non-NSAID PUD (idiopathic PUD) is reported to increase with time. Moreover, *H. pylori*-positive ulcers are not always *H. pylori*-induced ulcers because there are two paradoxes of the *H. pylori* story: the existence of *H. pylori*-positive non-recurring ulcer, and recurring ulcer after cure of *H. pylori* infection. Taken together, it is clear *H. pylori* infection is not the only cause of peptic ulcer disease. Therefore, it is still necessary to consider the pathophysiology and the management of the ulcers, which may exist after elimination of *H. pylori* infection.



Table 15. Useful Background: *H. pylori*

-
- Meta-analysis does not show a statistical difference in *H. pylori* eradication rates using wither triple quadruple therapy (RR = 1.002; 95% CI 0.936-1.073) (Luther J Schoenfeld P, et al. The American Journal of Gastroenterology 2008: S396).
 - Meta-analysis shows 93% ER with sequential therapy versus 74% for clarithromycin-based triple therapy (Jafri N, et al. Annals of Internal Medicine 2008: 2220-2223), particularly in persons with clarithromycin-resistant strains of *H. pylori*, but non of the *H. pylori* treatment guidelines (yet) endorse sequential therapy (Chey 09).
 - Met-analysis has shown superiority of a 10-day course of levofloxacin-based triple therapy is a 7 day course of bismuth-based quadruple therapy (rr = 0.51; 95% CI: 0.34-0.75) for persistent *H. pylori* infection (Saad R Schoenfeld P, et al. The American Journal of Gastroenterology 2006: 488-96)
 - Rifampin has been used as an alternative to alrithromycin, with ER of 38-91% (Chey WD, Wong BC. The American Journal of Gastroenterology 2007: 1808-1825) but there may be rare but serious adverse effects (myelotoxicity and ocular toxicity).
 - Furazolide used in place of clarithromycin, metronidazole or amoxicillin gives ER of 52-90% (Chey WD, Wong BC. The American Journal of Gastroenterology 2007: 1808-1825).
-

To ensure eradication of *H. pylori*, UBT or endoscopic biopsy may be repeated at least 30 days after completion of eradication therapy. Retesting may be particularly important if patient suffered of complicated ulcers (bleeding or perforation). It may also be necessary to prove that eradication has occurred before looking for new causes of dyspepsia in the occasional patient who experiences recurrent dyspepsia after the use of an approved eradicated regimen.

3. NSAIDs, Coxibs, ASA

NSAIDs can cause damage to the gastroduodenal mucosa via several mechanisms, including the topical irritant effect of these drugs on the epithelium, impairment of the barrier properties of the mucosa, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow and interference with the repair of superficial injury (Figure 8, 9). In addition, the presence of acid and, in some cases, *H. pylori* infection in the stomach and duodenum may contribute to the ability of NSAIDs to damage the mucosa.

Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin are among the most widely prescribed effective drugs for the treatment of pain and inflammation. The use of NSAIDs, however, is a well-known cause of gas- trointestinal (GI) adverse events, including dyspepsia, abdominal pain, nau- sea, erosive gastroduodenitis, ulceration, perforation, hemorrhage and even death. Nearly all patients who take aspirin



or traditional NSAIDs develop asymptomatic acute upper GI tract injury (erosions or ulcers) at some point in time. Interestingly, very few patients who develop serious complications have antecedent dyspeptic symptoms. Treatment of GI events caused by NSAIDs is also costly. Studies have shown that for each dollar spent on NSAIDs, an additional 55–125% is needed to treat GI events. Risk factors for serious GI complications are outlined in Table 5. This risk stratification is important to determine in every person on NSAIDs, so that the selection of which NSAID/Coxib may be established, and protective therapy with a proton pump inhibitor (PPI) may be prescribed (“co-therapy”).

Table 16. Risk factors for serious GI events associated with NSAID use

Clinical risk factors	Drug risk factors	Social risk factors
○ Advanced age ○ History of ulcer or ulcer complications ○ Major illness (e.g., heart disease, type & severity of arthritis) ○ Severe comorbidity & disability ○ <i>H. pylori</i> infection	○ Individual NSAID risk ○ High dose intake ○ Multiple NSAIDs ○ Concomitant corticosteroid ○ Concomitant anticoagulant/ antiplatelet drugs	○ Smoking ○ Alcohol

Although the mechanisms by which NSAIDs cause mucosal damage are not completely clear, they involve both topical injury and systemic effects. The complex elements that defend the gastroduodenal mucosa from damage are largely dependent on endogenous prostaglandins (PGs) synthesized in the GI mucosa. The two known isoforms of cyclo-oxygenase (COX), COX-1 and COX-2, direct the synthesis of PG from arachidonic acid. COX-1 is constitutively expressed in most cells and plays an important role in the GI mucosal protection, renal blood flow regulation and normal platelet function. In contrast, COX-2 is largely inducible by inflammation and is thought to generate prostaglandins that are responsible for pain and inflammation. In general, non-selective NSAIDs inhibit both COX-1 and COX-2 pathways leading to both beneficial (mucosal defense) and toxic outcomes. It has been postulated that the injurious effects of NSAIDs are due to the inhibition of COX-1 and loss of GI mucosal protection, and also due to increased risk of bleeding through inhibition of platelet function. There is a correlation between the risk of GI complications and the relative degree of inhibition of COX-1 and COX-2 isoenzymes. An NSAID with higher selectivity for COX-2 than COX-1 is associated with significantly less GI toxicity than other non-selective NSAIDs. The premise that preferential inhibition of COX-2 would maintain the therapeutic benefit of traditional NSAIDs with less GI toxicity due to sparing of COX-1 led to the development of more-selective COX-2 inhibitors. First generation coxibs



(celecoxib and rofecoxib), and second generation cox-ibs (etoricoxib, valdecoxib, parecoxib and lumiracoxib) have improved GI tolerance and less adverse events across a range of different GI safety assessments. In clinical trials, coxibs significantly reduced the risk of ulcers and ulcer complications compared to non-selective NSAIDs.

The safety profile of NSAIDs is variable and dependent on the class of NSAID with the selective COX-2 inhibitor class being among the safest. Aspirin doses as low as 10 mg/day can cause ulcers. Long-term use of aspirin alone is associated with 1.5–3 times increase in risk of GI complications even when used at low-dose (≤ 150 mg daily) or buffered or as enteric-coated formulations. The use of traditional non-selective NSAIDs increases the risk of serious GI complications by approximately 2.5–5-fold compared with patients not receiving these medications. There is a 2–4-fold increase in risk when low-dose aspirin is added to a non-selective NSAID compared to the use of low-dose aspirin alone. Among the classic NSAIDs, ibuprofen and etodolac are the least toxic. Naproxen, indomethacin, aspirin and diclofenac have intermediate toxicity, whereas ketoprofen and piroxicam are among the most toxic to the GI tract.

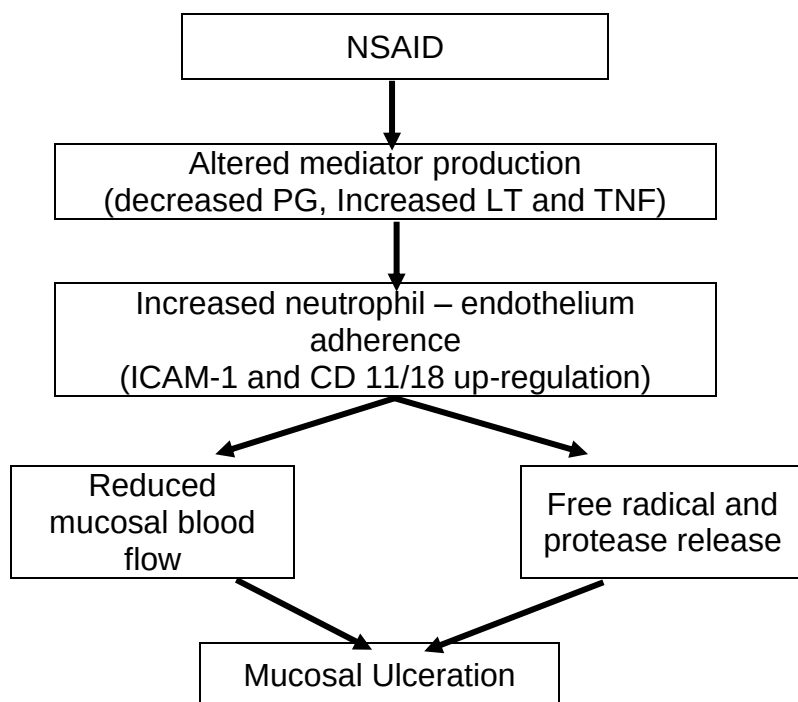


Figure 11. Role of changes in the gastric microcirculation in the pathogenesis of NSAID-induced ulceration. NSAIDs suppress prostaglandin (PG) synthesis, and cause an increase in the liberation of leukotriene (LT) B₄ and tumour necrosis factor (TNF). The net result is an increase in expression of various adhesion molecules, leading to neutrophil adherence to the vascular endothelium.



The prevalence of ulcer complications such as upper GI hemorrhage has not declined in the past decade, although *H. pylori* infection is declining in our Canadian population. Ulcer complications remain, mainly because of the aging population and increasing prevalence of arthritis, which is leading to an increased consumption of NSAIDs. To protect patients at risk, several strategies are advised, including the use of the lowest effective dose of NSAIDs, concomitant use of gastroprotective agents (e.g., acid antisecretory drugs, proton-pump inhibitors, or mucosal protective drugs) or alternative treatment with a coxib. Prevention of GI events is in particular indicated among patients with risk factors who require long-term treatment with NSAIDs, and use of a coxib and co-therapy with a PPI are the two most cost-effective treatments to decrease the risk of hospitalization for serious events (Table 17). The coxibs have decreased the risk of developing GI clinical events and complications in high-risk patients by more than 50% in large clinical trials. When economically possible, a coxib alone is preferable to a conventional NSAID plus a gastroprotective agent, but patients at high risk require a gastroprotective agent in addition to a coxib.

Table 17. Selection of NSAIDs and GI protective agents based on the key clinical factors

Risk of GI NSAID event		
Low		Average / high
➤ Not on aspirin, NSAID alone		○ Coxib or NSAID+PPI
➤ On aspirin, NSAID + PPI or coxib		○ NSAIDs +PPI or coxib +PPI

When deciding to place a patient on an NSAID, risk stratification must take into account the GI and renal risks, the presence of *H. pylori*, and importantly also the cardiovascular risks (Gupta and Eisen 2009). The use of an NSAID plus PPI, a COX-2 inhibitor, or a COX-2 inhibitor plus PPI does not prevent damage to the small or large intestine. The importance of cardiovascular risk of Coxibs became apparent with the APPROVE study. In the patient with both high GI and cardiovascular risk, an NSAID is given with ASA and a PPI. *H. pylori* is an independent and additive risk factor to the risk of NSAIDs and needs to be addressed (Table 18). Begin by taking a careful drug history for NSAID/ASA use, including low-dose ASA for cardioprotection, as well as other medications that may cause or aggravate dyspepsia, e.g., bisphosphonates, tetracyclines, calcium channel blockers.



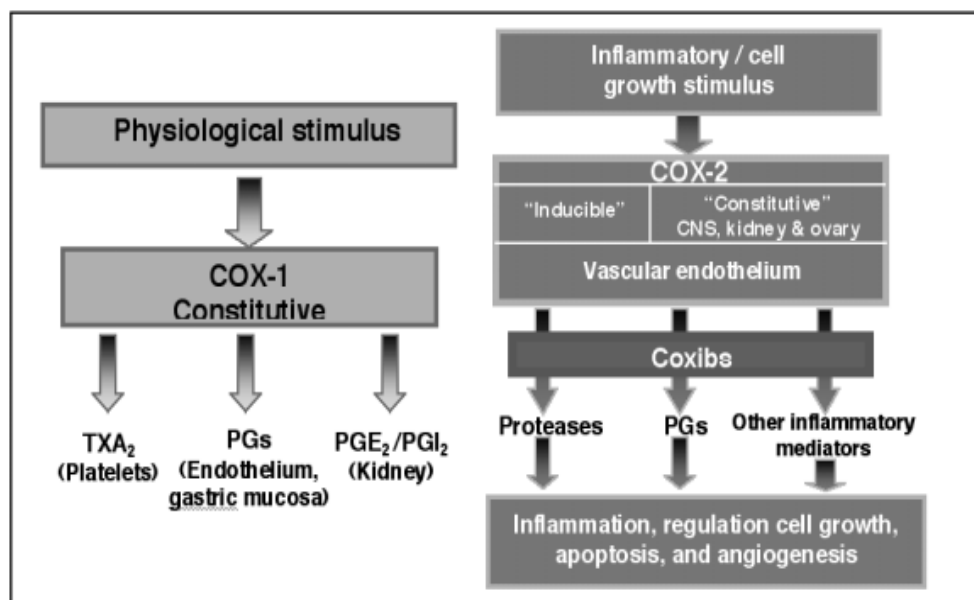


Figure 12. Proposed roles of the two known isoforms of COX and role of coxibs TXA₂, thrombozane A₂; PGE₂: prostaglandin E₂; PGs: prostaglandins; PGI₂: prostacycline; coxibs: COX-2 inhibitors.

Table 18. Reasons for *H. pylori* eradication therapy (ET) in the patient taking NSAIDs or ASA

- Reduce PUD formation
- Reduce recurrent PUD
- Reduce recurrent PUD bleeding (in ASA or NSAID high risk users) (ET does not prevent further PUD bleeding in high risk ASA/NSAID users on PPI)

Abbreviation: ET, eradication therapy

Adapted from: Lai LH., and Sung JJY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(2): page 270.

The vulnerable inflammatory phenotype of atherosclerosis is associated with a Th1 type immune response. The traditional NSAIDs and selective COX-2 inhibitors enhance this Th1 response by reducing prostanoids and promoting pro-atherogenic cytokines and plaque instability. It is proposed that this is the mechanism by which these classes of drugs enhance the cardiovascular risk (Padol and Hunt 2009; Rainsford 2010).

An expert panel has developed an algorithm to guide us in the appropriate use of PPIs, NSAIDs, and ASA in those persons with high-or-low-risk of gastrointestinal



cardiovascular disease (Alimentary Pharmacology expert panel, 2009). Gastrointestinal risk was stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants) (Table 19 and 20). High CV risk was arbitrarily defined as the requirement for low dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H.Pylori*, and if the infection is present, eradication therapy should be given. The practitioner must become familiar with the appropriate class of medication to use based on the GI plus CVS.

Table 19. GI risk stratification for NSAID GI toxicity

-
- High risk
 - History of a previously complicated ulcer, especially recent
 - Multiple (>2) risk factors
 - Moderate risk (1-2 risk factors)
 - Age >65 years
 - High dose NSAID therapy
 - A previous history of uncomplicated ulcer
 - Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants
 - Low risk
 - No risk factor
-

Abbreviations: CV, cardiovascular risk; NSAIDs, Nonsteroidal anti-inflammatory drugs
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Table 20. Recommendations for avoiding peptic ulcers (gastric or duodenal) associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a function of low, moderate and high gastrointestinal, as well as low and significant cardiovascular risk (CV) (e.g. required use of ASA plus NSAID)

	Low GI Risk	Moderate GI Risk	High GI Risk
➤ Low CV Risk (no ASA)	○ An NSAID with a low ulcerogenic potential at the lowest effective dose ○ Avoid multiple NSAIDs	○ NSAID plus PPI ○ Misoprostol ○ COXIB	○ COXIB plus PPI ○ Misoprostol
➤ Significant CV Risk (requires ASA)	○ NSAID plus a PPI	○ A combination of an NSAID and a PPI	○ Avoid NSAIDs and COXIB



Abbreviations: COXIB , COX-2 inhibitor; CV, cardiovascular risk; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

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Over a one-year interval, about 3% of NSAID users will develop a GU/DU. The possibility of NSAID-induced gastric complications should be discussed with patients, including the signs and symptoms of GI bleeding, e.g., dyspepsia, coffee ground emesis, melena. Patients at high risk may be offered gastric protective therapy with standard doses of PPI. Alternatively, misoprostol 200 µg QID may be offered, but the tolerability of this agent is limited by GI adverse effects.¹⁸ The risk of developing an NSAID-associated ulcer is greater in persons over the age of 65, in those who use more than one NSAID, higher doses of NSAIDs, in patients receiving concomitant steroids or anticoagulants, and in those with a history of ulcer disease and coexisting ischemic heart disease. Patients taking ASA with an NSAID are also at higher risk of ulcer complications. There is an additive effect between *H. pylori* infection and use of NSAIDs on the development of peptic ulcer and ulcer bleeding.¹⁹ For this reason, many experts recommend that persons beginning long-term NSAIDs should be screened for *H. pylori* and treated if found to be positive (Table 21).¹ Compared to regular NSAIDs, COX-2 inhibitors may reduce the risk of complicated peptic ulcer bleeding by 50 to 70%.^{15,16,17} However, reports of cardiovascular complications with use of COXIBs have limited their use and challenged their safety. Standard dose PPI therapy for 4-8 weeks produces higher healing rates in NSAID-associated ulcer than H2RAs or 800 mcg misoprostol when NSAIDs are continued. Whenever possible, the NSAID should be stopped. Standard dose PPIs are more efficacious than standard dose H2RAs or 400 mcg misoprostol (but not 800 mcg misoprostol) for the prevention of NSAID-associated gastric and duodenal ulcers. There is no difference in ulcer recurrence and bleeding rates between COX-2 selective NSAIDs and the combination of PPI and conventional NSAIDs in patients with previous NSAID-associated upper GI bleeding. Continuous acid inhibition, preferably with a PPI, may be needed in select patients with DU/GU not associated with *H. pylori* infection. This is especially true when the ulcer is complicated by bleeding or perforation, or when the patient continues ASA/NSAID use or experiences frequent recurrences of dyspepsia.



Table 21. Key points to consider regarding NSAIDs and gastroprotection

-
- Concomitant PPI use reduces the risk of development of NSAID induced endoscopic lesions such as ulcers
 - Concomitant PPI use is strongly recommended for high risk NSAID users
 - It is not known whether concomitant PPI use reduces the risk of clinically significant GI events such as hemorrhage and perforation
 - PPI co-therapy in high risk NSAID users is equivalent to COX-2 therapy in preventing NSAID induced endoscopic lesions
 - PPI used is effective as secondary prevention of ulcer complications in patients needing antithrombotic therapy with aspirin or clopidogrel
 - As alternatives to PPIs, misoprostol and H2RAs can be used in the prevention of NSAID related ulcers and their complications, and their use is cost effective
 - PPU co-therapy is effective in the healing and prevention of recurrence of ulcers in patients maintained on long-term NSAID therapy
-

Adapted from Arora et al. Clinical Gastroenterol and Hepatology 2009; 7: 725-735.

It is now recognized that NSAIDs and coxibs may damage the upper and the lower GI tract. They both also carry risk for cardiovascular damage, such as myocardial infarction and stroke. Therefore, the risk stratification must be in two dimensions, the GI as well as the cardiovascular systems. Carefully consider the need for gastroprotection in every NSAID user over the age of 65 years. The situation is even more complex, considering the need for some persons to be on anticoagulants or antiplatelet agents. Furthermore, it has been suggested that some PPI's interfere with the therapeutic benefit of clopidogrel. In patients with eradicated *H.pylori* but still on ASA/NSAIDs, standard dose PPIs (all agents have similar efficacy) are effective in reducing ulcer risk and in promoting healing. In *H.pylori* negative patients who have a history of ulcer bleeding on low-dose ASA alone, the combination of low-dose ASA and a PPI is associated with a lower risk of recurrence of ulcer complications at 1 year as compared to clopidogrel (an antiplatelet agent) alone.

4. Choices During Pregnancy and Lactation

Some women of reproductive potential, may try to manage their dyspeptic symptoms with nonprescription antacids, barrier agents, H2RAs and PPIs. These medications are considered to be generally safe to use during pregnancy and lactation, (FDA pregnancy class B, except for omeprazole which is class C) with the caveat that the symptoms are from a condition in the upper GI tract and not from other pregnancy associated conditions (e.g. constipation, cholelithiasis, urinary tract infection or hypertension). If a diagnostic test for *H.pylori* (serology, endoscopy, UBT[with the ¹³C isotope]) were done during pregnancy or lactation, treatment for the *H. pylori* infection should be postponed until after pregnancy and lactation. There is no need to test the infant for *H.pylori* if the mother is infected.



5. Proton Pump Inhibitors (PPIs)

The PPIs are generally considered to be a very safe class of medications. The few suggested associations of long-term use of PPIs and complications is given in Table 22 and 23. Retrospective epidemiological studies detail an association between the use of PPIs and an increased risk of hip fractures, and raise the possibility that this risk is increased with the dose and duration of PPI. There are numerous factors for the development of osteoporosis, and when these were taken into account in a Canadian cross-sectional study and appropriate consideration of confounding variables were taken into account, PPIs did not add to the risk of osteoporosis (Targownik et al., 2010).

The antiplatelet function of clopidogrel may be modestly reduced by PPIs, but there is no difference in cardiovascular outcome in those who do, or don't use PPIs (*Lancet* 2009).

Table 22. PPIs are associated with alterations in gastric histology in *H. pylori* negative and positive persons

-
- *H. pylori* negative persons
 - Older persons have an increased risk of moderately severe gastritis.
 - PPIs may improve (and certainly do not worsen) pre-existing gastritis
 - PPIs do not cause atrophic gastritis
 - *H. pylori* positive persons
 - *H. pylori* causes antral or body acute or chronic gastritis, atrophy and metaplasia
 - *H. pylori*- associated chronic gastritis may progress (to gastric atrophy, intestinal metaplasia, and gastric cancer)
 - *H. pylori* plus PPIs may cause progression or acceleration from gastric antrum-predominant chronic gastritis, to body-predominant chronic gastritis
 - *H. pylori* eradication probably causes regression of gastric atrophy or intestinal metaplasia
 - Gastric body-predominant atrophic gastritis is a risk factor for gastric cancer
-

(Thomson et al, 2009)

Table 23. PPIs change the bioavailability or metabolism of some drugs

-
- PPIs reduce gastric acid, and thereby reduce the bioavailability of drugs requiring intragastric acidity to maximize their absorption and bioavailability (ketoconazole, itraconazole, indinavir).
 - PPIs alter the hepatic clearance of some drugs.
 - PPIs may show a rare class action effect on Vitamin K antagonist.
 - PPIs may differ on their possibility of causing drug interactions.
-

(Thomson et al, 2009)



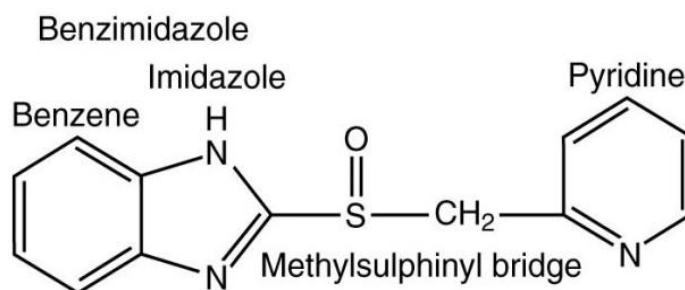
Table 24. The importance of physiological hypergastrinemia associated with the use of PPIs

- PPIs modestly increase serum gastrin concentration in persons who are *H. pylori* negative or positive
- *H. pylori* infection, even without use of PPIs, increases serum gastrin concentration
- PPIs do not increase risk of gastric or esophageal cancer, but increases apoptosis
- PPIs increase ECL cell numbers, and possibly also increase linear or micronodular hyperplasia, but the different PPIs have varying effects in causing physiological hypergastrinemia
 - Lansoprazole > Omeprazole > Pantoprazole

(Thomson et al, 2009)

The long-term use of PPIs is suspected but has not been convincingly proven to cause or accelerate the progression of pre-existing chronic gastritis, corpus gastric atrophy or intestinal metaplasia. The long-term use of PPIs has not been convincingly proven to cause ECL cell hyperplasia or carcinoid tumors. PPI use is associated with parietal cell hyperplasia and up to 4-fold increased incidence of fundic gland polyps (FGP). FGP also occur in the presence of *H. pylori* infection, and eradication of *H. pylori* or stopping long-term use of PPIs is associated with regression of FGP. Sporadic FGP is rarely associated with dysplasia, but never gastric adenocarcinoma, up to date. Dysplasia may occur in 25-44% of gastric polyps in persons with familial adenomatous polyposis. PPI use is associated with the development of fundic gland polyps (FGP). FGP occur in the presence of *H. pylori* infection. Eradication of *H. pylori* or stopping PPI is associated with regression of FGP. FGP may occasionally become dysplastic, but almost exclusively in persons with familial adenomatous polyposis.

PPIs may mask symptoms or heal early gastric cancer, but there is no data on survival. PPIs are not associated with an increased risk of latent iron deficiency, or iron deficiency. In elderly patients who may already have gastric atrophy (possibly from *H. pylori* infection), PPIs used long-term may reduce serum vitamin B12 concentrations.

**Figure 13.** Structure of proton pump inhibitors (PPIs).

- PPIs consist of two heterocyclic moieties, a benzimidazole ring, and a pyridine, connected by a methylsulphonyl bridge. PPIs are weak bases (pKa 4-5) that



accumulate and activate in acidic spaces within the body that have a pH less than 4.

- Once activated within the parietal cell canaliculus, the PPI binds covalently with certain cysteine residues within the α -subunit of the inserted H^+,K^+ -ATPase.

Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-14, pg 824, Ninth Edition, 2010.

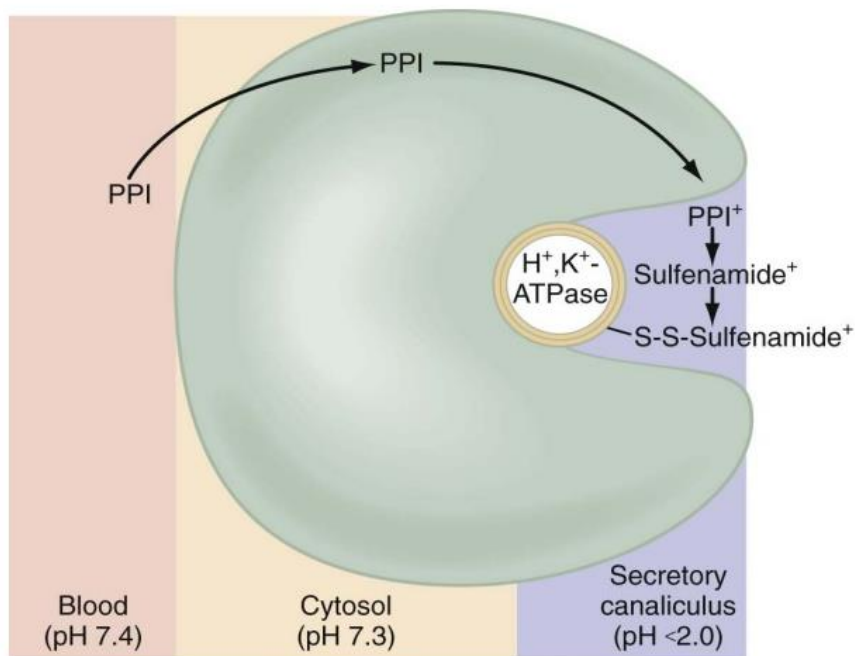


Figure 14. Model illustrating the mechanism of action of proton pump inhibitors (PPIs).

- PPIs reach the parietal cell from the bloodstream, diffuse through the cytoplasm, and accumulate in the acid environment of the secretory canaliculus.
- In the canaliculus, the PPI becomes protonated and trapped as a sulfenic acid followed by conversion to a sulfenamide.
- The sulfenamide binds covalently by disulfide bonds to one or more cysteines of the H^+,K^+ -ATPase to inhibit the enzyme.
- Whereas all PPIs bind to cysteine 813, omeprazole also binds to cysteine 892, lansoprazole to cysteine 321, and pantoprazole to cysteine 822.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-15, pg 825, Ninth Edition, 2010.

6. Upper GI Bleeding

Upper GI bleeding is a common and potentially fatal condition of duodenal and gastric ulcers. Bleeding peptic ulcers need to be distinguished from bleeding esophageal varices, secondary to portal hypertension. Even in the patient with known cirrhosis, UGIB is still usually due to peptic ulcer disease.



6.1 Goals of GI therapy

The goals of therapy in the patient with UGIB include: (ABCs) to resuscitate and save the patient's life and to prevent hypoxia-related damage to other organs; to make a diagnosis, to heal the underlying lesion; to perform ENT where appropriate; and to prevent recurrences. The distribution of the endoscopic type of bleeding ulcers is clean-based, 55%; a flat pigmented spot, 16%; a clot, 8%; and active bleeding, 12% (Enestvedt BK et al, 2008:422-9).

Other common sources of bleeding include erosive gastroduodenitis, esophagitis, Mallory-Weiss tears, angiodysplasia, Dieulafoy lesions and neoplasia. In most cases, bleeding stops spontaneously. However a minority rebleeds or continues to bleed despite attempts at hemostasis. This subpopulation accounts for most of the morbidity, mortality and resource consumption associated with upper gastrointestinal hemorrhage. Risk stratification allows targeted application of medical, endoscopic and surgical therapy. Despite remarkable advances in each of these domains, however, approximately 1 in 20 patients who present with upper gastrointestinal bleeding will die over the course of their hospitalization. When the patient vomits coffee ground-appearing blood or fresh red blood, the bleeding arises from the upper GI tract, proximal to the ligament of treitz. The passage per rectum of black stools containing blood (melena) arises from relatively slow bleeding of small amounts of blood from the upper GI tract, small intestine, or from the right side of the colon. If the patient passes fresh red blood per rectum, they may be rapidly losing large amounts of blood from the upper GI tract, or more slowly losing smaller amounts of blood from the lower GI tract.

When the patient presents with an UGIB, clinical risk stratification is performed. If the patient is high risk then prompt endoscopy is performed to further stratify the risk from the endoscopic appearance of the bleeding lesion.

A negative NG aspirate in the patient who presents with melanoma or hematoschezia reduces the likelihood of an upper GI source of the bleeding, but because of curling of the tube or duodenal bleeding which does not reflux into the stomach, 15-18% of persons with an upper GI source for bleeding will have a non-bloody aspirate.

6.2. Presentation and Risk Stratification

Bleeding from the upper gastrointestinal tract (proximal to the ligament of Treitz) manifests typically with overt hematemesis or coffee ground emesis, or with passage of melena per rectum. Brisk hemorrhage with rapid transit can present with maroon stool, hematochezia or features of hemodynamic instability. In all cases, the priority at initial assessment is to ensure hemodynamic stability and initiate appropriate volume resuscitation before conducting a detailed history and physical examination.

Key features of the history include: symptoms of hemodynamic instability (such as presyncope); prior upper gastrointestinal and liver disease with or without hemorrhage; other blood loss suggestive of an underlying bleeding diathesis; use of medications known to cause gastrointestinal injury (such as aspirin and NSAIDs); alcohol consumption; and family history of gastrointestinal pathology. On physical



examination, key features include serial assessment of postural vital signs, thorough examination of the abdomen, careful inspection of the skin and mucus membranes for telangiectasia, assessment for the stigmata of chronic liver disease, and digital rectal examination. A rapid estimate of blood loss can be made at the bedside: 50% loss of blood volume is suggested by systolic blood pressure < 100 mm Hg, a pulse rate > 100 BPM and a Hgb < 100 g/L. In all cases of overt hemorrhage, care must be taken to exclude respiratory or nasopharyngeal sources of blood loss. Passage of a nasogastric tube for aspirate can be informative; a biliary aspirate suggests a source of bleeding distal to the ampulla of Vater, while a bloody aspirate suggests a high-risk lesion and increased risk of mortality.

An upper GI series (e.g., barium swallow) must not be performed in the patient with UGIB. The diagnostic accuracy is poor in this setting, it may obscure a clear field for subsequent esophagogastroduodenoscopy, and endoscopic hemostatic therapy (EHT) cannot be performed if the field of vision is obscured by barium. All patients with UGIB should be referred for Esophagogastroduodenoscopy (EGD) after they are stabilized. The timing will depend on the suspected severity of bleeding, the likely cause and the patient's general condition, but ideally should be done within 12–24 hours of the presentation of the patient.⁶ Prompt EGD will identify the lesion in about 90% of patients. The most common EGD finding is a peptic ulcer or erosions. Inability to make a diagnosis is usually due to profuse bleeding.

Table 25. A simple clinical method to estimate volume depletion

	Class I	Class II	Class III	Class IV
➤ Blood loss (mL)	<750	750-1000	1500-2000	>2000
➤ Blood loss (% blood volume)	<15	15-30	30-40	>40
➤ Heart (beats/min)	<100	>100	>120	>140
➤ Blood pressure	Normal	Normal	Decreased	Decreased
➤ Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
➤ Ventilatory rate (breaths/min)	14-20	20-30	30-40	>35
➤ Urine output (mL/hr)	>30	20-30	5-15	Negligible
➤ Mental status	Slightly anxious	Midly enxious	Anxious and confused	Confused and lethargic
➤ Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood



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Prognosis may be established at the time of EGD. A patient with a clean-based ulcer who is stable, reliable, otherwise healthy and who has family support and transportation available may be discharged home from the emergency room after endoscopy. Obtain two biopsies for *H. pylori* from the gastric antrum. Obtain two additional biopsies for *H. pylori* from the gastric body in patients who have recently been on acid suppression therapy.

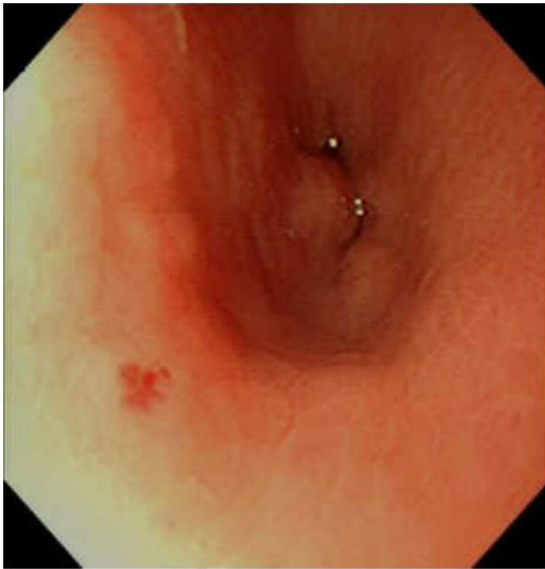


Figure 15. Angiodysplasias

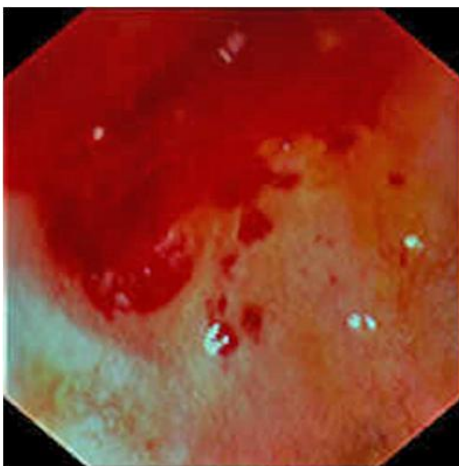
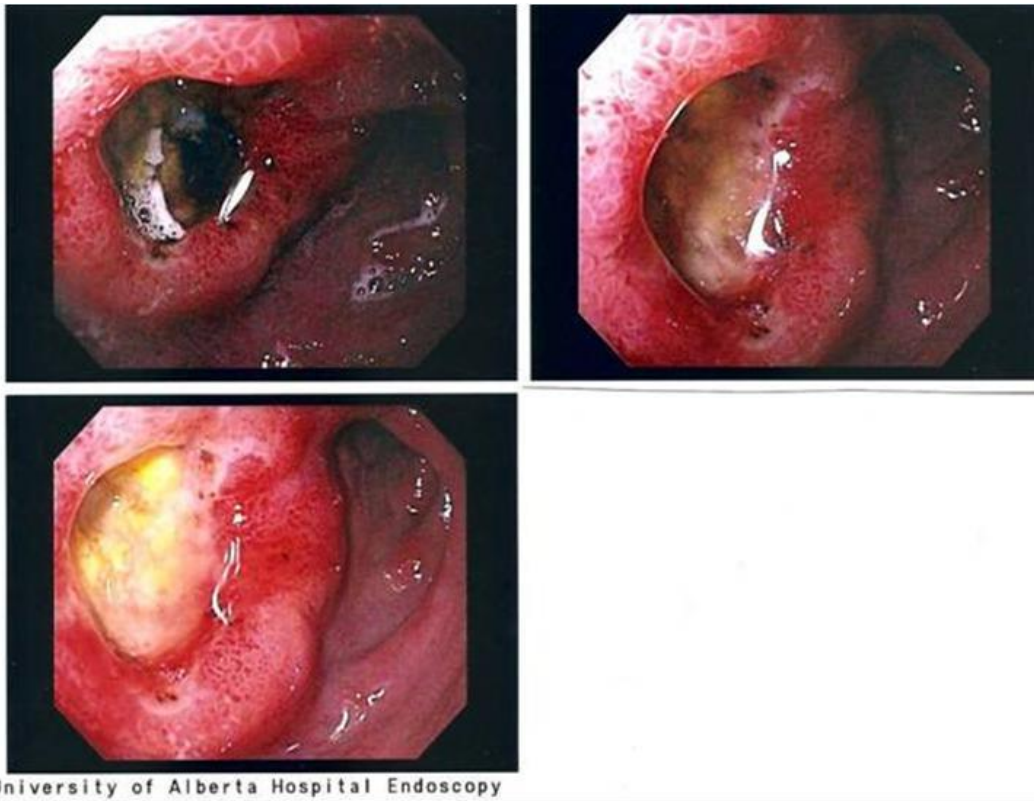


Figure 16. Upper GI bleed





Figure 17. Upper GI bleed



University of Alberta Hospital Endoscopy

Figure 18. Ulcer, possibly *H. pylori* associated

Upper gastrointestinal endoscopy (ideally within 24 hours of presentation) is a key component of patient assessment, and is often essential to diagnosis, prognosis and treatment. In most cases, an experienced endoscopist can localize the source of bleeding and estimate the risk of rebleeding. Of note, the Forrest classification of peptic ulcer stigmata (first reported in 1974) has withstood the test of time as a



powerful predictor of the risk of rebleeding (Table 26). By combining clinical and endoscopic criteria, clinicians can estimate risk with even greater accuracy. The Rockall score combines five domains (age, comorbidity, hemodynamic stability, bleeding source and Forrest classification) to predict rebleeding and mortality. Patients at low risk can be discharged home from the emergency department for outpatient follow-up.

Table 26. The rates (%) of rebleeding, surgery and mortality, without and with endoscopic hemostatic therapy (ET), using the Forrest classification of bleeding peptic ulcers

Forrest Classification:		Rebleeding Rate (%)		Surgery Rate (%)		Mortality rate (%)	
EGD appearance	Prevalence	No ET	ET (~70%↓)	No ET	ET (~80%↓)	No ET	ET (~50%↓)
➤ Active Bleeding (Ib, oozing)*	18	55	20	35	7	11	<5
➤ Visible vessel (IIa); not bleeding	17	43	15	34	6	11	<5
➤ Adherent clot (IIb)	15	22	5	10	2	7	<3
➤ Flat pigmented spot (IIc)	15	10	<1	6	<1	3	<1
➤ Clean ulcer base (III)	35	<5	<1	<1	<1	<1	<1

*Forrest 1a, active bleeding (spurting)

Abbreviation: ET, endoscopic hemostatic therapy

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Gastric and duodenal ulcers are the most common lesions in Canadian patients with nonvariceal UGIB. After EHT, the early rates of rebleeding, surgery and mortality are respectively reported to be 14.1%, 6.5% and 5.4%.¹³ In the GI bleed patient, the short-term mortality may be increased by co-morbid conditions such as diabetes¹⁴, and in the elderly¹⁵ where 30-day mortality in octogenarians may exceed 40%.¹⁶ Post interventional complications¹⁷ and hypoalbuminemia¹⁸ may also add to the mortality.

In bleeding esophageal varices, endoscopic variceal band ligation or sclerotherapy is highly effective in stopping bleeding and preventing rebleeding. Band ligation is preferred because there are fewer complications. For bleeding gastric varices, the tissue adhesive cyanoacrylate may be carefully applied. Endoscopic triage provides for assessment of the risk of the UGIB.⁸ In the more serious lesions seen in EGD, such as an ulcer with an adherent clot, visible vessel or active bleeding, EHT must be used. EHT involves coaptive thermal coagulation, injection of a large volume (30ml) of epinephrine and saline, or a sclerosing agent and/or a mechanical technique (banding, hemoclip, staples, sutures). In nonvariceal bleeding, a combination of injection (e.g., epinephrine), thermal or mechanical therapies should be used.

Table 27. Similarities and differences in the clinical features of NVUGIB in elderly versus younger persons

-
- Similarities
 - Presenting manifestations of bleedings: hematemesis (50%); melena (30%); hematemesis and melena (20%)
 - Peptic ulcer disease most common etiology
 - Safety and efficacy of endoscopic therapy
 - Differences (in elderly patients)
 - ↓ Antecedent symptoms (abdominal pain, dyspepsia, heartburn)
 - ↑ Prior aspirin and NSAID use
 - ↑ Presence of comorbid conditions
 - ↑ Hospitalization, rebleeding, death
-

Abbreviation: NVUGIB, non-variceal upper GI bleeding

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In the patient with UGIB due to esophageal varices (5-30% of all cases of UGIB), adding octreotide plus infusion for 2-5 days for EHT improves the control of bleeding. Also, adding ceftriaxone or quinolones reduces bacterial infection and mortality (DeFranchis, 2005). Recurrent esophageal variceal bleeding in the Child-Pugh class A or B cirrhotic, which occurs despite repeated endoscopic variceal banding or maintenance use of nonselective beta blocker may require the placement of TIPS (83% vs 11%, likely due to the TIPS shunt stenosis), with no difference in rebleeding, hepatic encephalopathy or death (Henderson et al., 2006). Gastric varices due to splenic vein



thrombosis can be cured by splenectomy.

Endoscopic hemostatic therapy has been shown to reduce rebleeding, surgery and death among patients with high-risk endoscopic stigmata (Forrest classification Ia, Ib or IIa). Both injection therapy (saline +/- 10,000 epinephrine) and thermal coagulation therapy to ablate the bleeding vessel are effective. The combination of injection therapy plus thermal coagulation therapy is more effective than either intervention alone. In patients with adherent clots (Forrest classification IIb), management is controversial.

Aggressive irrigation to dislodge the clot and treatment of the underlying lesion is generally accepted. Clinical trials from expert centres have shown better outcomes when a cold snare is used to remove the clot, but many clinicians are reluctant to use this technique for fear of precipitating a brisk bleed. The use of endoscopic clips for hemostasis is a promising technique undergoing assessment in clinical trials.

For high risk lesions (active bleeding, visible vessel, adherent clot), endoscopic hemostatic therapy is performed, with good results for the reduction in the risk of rebleeding, need for surgery, and death. Note the very high rate of these complications. The patient-related adverse prognostic variables are not meant to predict the patient with these high risks, before EGH is performed. In the patient with high risk of lesions treated by EHT, the EHT is followed by 3 days of IV PPIs, and then switched to oral PPIs. For low risk lesions, the patient is started directly on oral once-a-day PPI.

Acid suppression can improve clot stability and platelet aggregation. Accordingly, medical therapy of non-variceal upper gastrointestinal hemorrhage is focused on achieving sustained and substantive elevation of gastric pH. Clinical trials of intravenous histamine-2-receptor antagonists have been disappointing, in part due to early induction of pharmacologic tolerance. However, an intravenous bolus of omeprazole followed by an intravenous infusion for 72 hours has been shown in several well-designed clinical trials to reduce the risk of rebleeding after endoscopy in patients with high-risk endoscopic lesions (Forrest classification Ia, Ib and IIa). Meta-analyses pooling these trials have also shown intravenous proton pump inhibitors to be associated with significant reductions in surgery and mortality. RCTs show that adding bolus plus infusion of PPI to endoscopic hemostatic therapy (EHT) significantly decreased bleeding (NNT, 12) surgery (NNT, 28) and death (NNT, 45) (Laine L, et al. Clin Gastroenterol Hepatol 2009; 33:47). In the ICU patient on a mechanical ventilator, IV H2-receptor blocker or PPI through the nasogastric tube is superior to sucralfate to reduce stress when bleeding (Cook DJ, et al. The New England Journal of Medicine 1998; 791-7; Conrad SA et al. Crit Care Med 2005; 33: 760-5).

Several controversies persist in the medical management of non-variceal upper gastrointestinal hemorrhage. First, the empiric use of proton pump inhibitors in patients prior to endoscopy has intuitive appeal but has not been tested in clinical trials. High doses of oral proton pump inhibitors may also be effective, but no rigorous head-to-head comparison with intravenous dosing has assessed clinical outcomes. Intravenous infusion of somatostatin analogs such as octreotide may also reduce rebleeding, and may be useful in patients with significant bleeding facing delays to endoscopy. Other agents such as tranexamic acid and recombinant factor VII can be considered in refractory



patients, but have not been tested in clinical trials.

For patients who rebleed after an initial attempt at endoscopic hemostasis, repeat endoscopy to reassess the lesion and apply further endoscopic treatment as needed is appropriate. However, routine second-look endoscopy in patients with no evidence of recurrent bleeding is not advocated.

Table 28. Patient-related adverse prognostic variables which may be used for risk stratification in persons with acute NVUGIB

-
- Increasing age
 - Red blood in the emesis or stool
 - Increasing number of comorbid conditions (especially renal failure, liver failure, heart failure, cardiovascular disease, disseminated malignancy)
 - Shock – hypotension, tachycardia, tachypnea, oliguria on presentation
 - Increasing number of units of blood transfused
 - Onset of bleeding in the hospital
 - Need for emergency surgery
 - Use of anticoagulants, glucocorticosteroids
-

Abbreviations: NVUGIB, non-variceal upper GI bleeding ; UGIB, upper GI bleeding

Table 29. Factors to consider when performing EGD in pregnant women

-
- A strong indication is always needed, particularly in high-risk pregnancies
 - Whenever possible, endoscopy should be deferred until the second trimester
 - The lowest possible dose of sedative medication should be used (wherever possible FDA category A or B drugs)
 - Procedure time should be short
 - To avoid inferior vena cava or aortic compression, the patient should be positioned in the left pelvic tilt or left lateral position
 - Presence of fetal heart sounds should be confirmed before sedation and after the procedure
 - Obstetric support should be immediately available
 - No endoscopy should be performed in patients with obstetric complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)
-

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NVUGIB may occur during pregnancy, and the management is the same: stabilize, EGD, EHT, depending upon the cause of the bleeding, followed by IV or po PPIs. There are special factors to consider when performing EGD in pregnant women (Table 29). Also, there are similarities and differences to consider in the clinical features of NVUGIB in elderly (>65 years) versus younger persons (Table 28).



In some persons who present with upper/lower GI bleeding, or chronic iron deficiency anemia, they have no diagnosis after carefully performed EGD/colonoscopy. They are considered to suffer from obscure GI bleeding, and there are numerous diagnostic methods which may be used to determine the cause of this obscure bleeding (Table 30).

6.3. Surgery

Between 5% and 10% of patients who present with acute upper gastrointestinal bleeding will require surgery because of continued or recurrent hemorrhage. Although this proportion is gradually declining, it remains substantial as improvements in medical and endoscopic therapies are offset by the increasing age and comorbidity of patients admitted with gastrointestinal bleeding. The decision to perform surgery must be individualized, but consider factors such as patient comorbidity, transfusion requirements, the nature of the bleeding lesion and the anticipated success of further endoscopic therapy. Surgery should be considered early in patients at high risk of complications such as perforation (e.g., large, deep anterior duodenal ulcers).



Figure 19. Gastrojejunostomy

Gastric Surgery may be performed in the setting of the patient with an Upper GI bleed, gastric cancer, and for weight reduction. Obesity will be discussed in the chapter on nutrition, but it is useful to consider bariatric surgery here within the context of the rate of common complications arising from gastric surgery performed for any

reason.

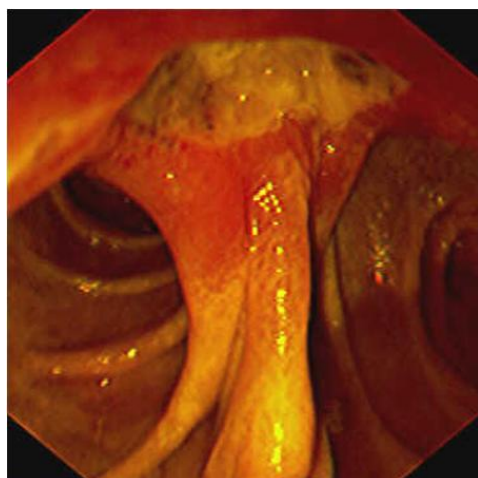


Figure 20. Gastric Anastomotic Ulcer



Table 30a. Bariatric procedures

➤ Specific procedures

- Gastric bypass (Roux-en-Y)
 - Anastomotic leak with peritonitis
 - Stomal stenosis
 - Marginal ulcers (ischemia)
 - Staple line disruption
 - Internal and incisional hernias
 - Nutrient deficiencies (usually iron, calcium, folic acid, vitamin B12)
 - Dumping syndrome
 - Gastroplasty
 - GERD
 - Stomal stenosis
 - Staple line disruption
 - Band erosion
 - Gastric banding
 - Band slippage
 - Erosion
 - Esophageal dilation
 - Band infections
 - Biliopancreatic diversion
 - Anastomotic leak with peritonitis
 - Protein-energy malnutrition
 - Vitamin and mineral deficiencies
 - Dehydration
-

Table 30b. Complications for each bariatric procedure, and complications common to all bariatric surgical procedures

➤ Complications common to all bariatric surgical procedures

- CNS
 - Psychiatric disturbance
 - Lung
 - Atelectasis and pneumonia
 - Deep vein thrombosis
 - Pulmonary embolism
 - CVS
 - GI
 - Anemia
 - Diarrhea
 - Ulceration
 - GI bleeding
 - Stenosis
 - Gallstones
-



-
- Metabolic
 - Bone disease
 - Too rapid weight loss
 - Surgical
 - Wound infection
 - Failure to lose weight
 - Mortality (0.5-1%)
 - GI
 - Anemia
 - Diarrhea
 - Ulceration
 - GI bleeding
 - Stenosis
 - Gallstones
 - Metabolic
 - Bone disease
 - Too rapid weight loss
 - Surgical
 - Wound infection
 - Failure to lose weight
 - Mortality (0.5-1%)
-

Abbreviation: CNS, central nervous system

Adapted from: Klein S. 2006 AGA Institute Post Graduate Course: page 175.

The three most common bariatric surgical procedures include adjustable gastric bands (AGB), sleeve gastrectomy (SG), and roux-en-Y gastric bypass (GBP). Laparoscopic AGB provided less of more than 50% of excess weight in 84% of adolescents with a BMI > 35, as compared with 12% in a lifestyle group (O'Brien et al. 2010). The improvement in T2DM is more frequent with gastric bypass than banding, with rapid normalization of glucose metabolism (decrease in insulin resistance and increase in insulin secretion) occurring even before weight loss (Laville and Disse 2009). There may even be a decline in diabetes-associated death. Natural Orifice Transluminal Endoscopic Surgery (NOTES), endoscopy and endoluminal surgery are being developed as surgical bariatric procedures (Tsesmeli and Coumaros 2010). GBP appears to be the superior procedure, and weight loss may be just as much due to changes in gastrointestinal hormones as to restriction or malabsorption (Bueter et al. 2010). Unfortunately, these procedures are associated with multiple complications (Table 31a&b). It is a useful exercise to consider the mechanisms responsible for the nutrient deficiencies which may develop after bariatric surgery, let alone any type of gastric surgery which may be used for example for peptic ulcer disease or for gastric malignancy (Table 32).



Table 31. Mechanisms or causes of iron- and B12-deficiency associated anemia, diarrhea, metabolic bone disease, and recurrent gastric ulceration in a patient having had a Billroth II partial gastrectomy for peptic ulcer disease (PUD), gastric cancer (GCA) or morbid obesity (bariatric surgery) and Roux-en-Y

-
- Iron
 - Pre-surgery iron deficiency
 - Decreased intake from post-op symptoms (anorexia, early satiety)
 - Decreased acid leads to decreased pepsin and decreased meat (iron) digestion
 - Decreased acid: inhibits the acid-mediated solubilizing and reducing of inorganic dietary iron (Fe^{3+} [ferric] .. Fe^{2+} ferrous])
 - Decreased absorption of Fe^{2+} , Ca^{2+} , B12, bypassing site of maximal absorption
 - Can be slow bleeding at surgical site
 - Bile gastritis
 - Gastric stump cancer
 - B12
 - Pre-surgery deficiency
 - Decreased intake
 - Loss of stimulated co-ordinated release of pancreatic “R” factor
 - Decreased intrinsic factor
 - Loss of HCl/pepsinogen to liberate food B12
 - Bacterial overgrowth syndrome
 - Diarrhea
 - Magnesium-containing antacids, PPI’s
 - Dumping
 - Retained antrum ($\uparrow$ gastrin)
 - Hypergastrinemia, HCL hypersecretion ($\uparrow$ volume, mucosal damage)
 - Bypassed duodenum
 - Unmasked celiac disease
 - Unmasked lactose intolerance
 - Unmasked bile acid wastage
 - Primary or secondary (unmasked) pancreatic insufficiency
 - Bacterial overgrowth syndrome (BOS)
 - Metabolic bone disease
 - Pre-existing osteoporosis $\downarrow$ Ca^{2+} solubilization
 - $\downarrow$ vitamin D or Ca^{2+} intake
 - Bypass of site of maximal absorption of Ca^{2+} (duodenum)
 - Binding Ca^{+2} (unabsorbed fatty acids)
 - Peptic ulceration (previous peptic ulcer disease [PUD])
 - $\uparrow$ gastrin – ZES, incomplete vagotomy, gastric retention, afferent loop syndrome
 - *H. pylori* infection



- NSAIDs, ASA use
- “Stump” Cancer
- Ischemia at anastomosis
- Bile gastritis
- Presentations of ZES (Zollinger Ellison Syndrome)
 - PUD – severe, multiple, unusual sites; GERD-like symptoms
 - Diarrhea
 - Recurrent ulceration (with or without gastric surgery)
 - Associated MEN I syndrome
 - Thick gastric folds

Abbreviations: BOM, bacterial overgrowth syndrome; GCa, gastric cancer; MEN, multiple endocrine neoplasia ; PPIs, proton pump inhibitor; PUD, peptic ulcer disease; ZES, Zollinger-Ellison syndrome

6.4. *Obscure GI Bleeding*

Understandably, at the time of active bleeding from the upper or lower GI tract, endoscopic visualization of the site and cause of bleeding may be obscured by the presence of blood. Even when EGD and colonoscopy are performed again under ideal circumstances, the cause of bleeding may be obscure. In those persons with recurrent episodes of bleeding or with unexplained iron deficiency anemia, further diagnostic methods may need to be used (Table 33), and particularly small bowel lesions such as vascular abnormalities, polyps, or ulcers may be the culprit.

Table 32. Diagnostic methods for determining the cause of obscure GI bleeding

- Endoscopy
 - Capsule endoscopy (CE)
 - Double balloon enteroscopy (DBE)
 - Push enteroscopy (PE)
 - Intraoperative endoscopy
 - Esophagogastroduodenoscopy (EGD)
 - Colonoscopy
- Small bowel contrast X-ray
 - Small bowel single contrast
 - Small bowel double contrast (enteroclysis)
- CT/MRI
 - CT angiography
 - CT/MRI enteroscopy
 - CT-enteroclysis



- Angiography
 - Elective (no acute bleeding)
 - With acute bleeding
 - Scintigraphy
 - Erythrocyte scintigraphy (RBC scan)
 - Meckel's scintigraphy
 - Video capsule endoscopy
-

Adapted from: Heil U. and Jung M. *Best Practice & Research Clinical Gastroenterology* 2007; 21(3): page 402.

6.5. Conclusions

Appropriate management of acute upper gastrointestinal hemorrhage entails early resuscitation and triage, careful clinical assessment, early endoscopy, intravenous proton pump inhibitors infusion (if indicated) and access to a skilled surgical team. Given the high prevalence of upper gastrointestinal bleeding, each acute care hospital and health care system should develop institution-specific protocols for its management. These protocols should address aspects of triage and multidisciplinary care including access to a therapeutic endoscopist skilled in endoscopic hemostasis and trained support to assist with urgent endoscopy. Despite remarkable advances in medical and endoscopic therapy, non-variceal upper gastrointestinal hemorrhage continues to impose a significant disease burden.



Chapter 5: Gastritis and Gastric Neoplasia

A.B.R. Thomson and R.H. Hunt



1. Gastritis

1.1. Introduction

The term “gastritis” has been used variously and incorrectly to describe symptoms referable to the upper gastrointestinal tract, the macroscopic appearances of inflammation or injury in the stomach at endoscopy and the histologic features of inflammation or injury to the gastric mucosa at microscopy. Unfortunately, there is a very poor correlation between an individual’s symptoms and any abnormalities evident at endoscopy or microscopy. Upper gastrointestinal tract symptoms are best considered under the term “dyspepsia,” while endoscopic features such as erythema, hypertrophy, friability, petechial hemorrhages and erosions should be described as such and correlated with the histological features of inflammation and damage. Only the histological features compatible with inflammation may be correctly used with the term gastritis, which will be the subject of the present chapter (Table 1).

Gastritis is defined as inflammation of the gastric mucosa (Figure 1), and the use of the term should therefore be based solely on an examination of gastric mucosal biopsies. Gastric mucosal biopsies should be obtained if there is endoscopic evidence of any mucosal abnormality, including erosions, ulcers, thickened folds, polyps or masses, or if there is a suspicion of *H. pylori* infection (Figure 2) or damage due to the ingestion of NSAIDs. Indeed, it has been proposed that an endoscopy performed without mucosal biopsies is an incomplete examination. In addition to specific lesions or abnormalities, biopsies should also be taken from the antrum (2 biopsies) and body of the stomach (2 biopsies) and some authors also recommend a fifth biopsy from the gastric angulus or incisura to identify possible *H. pylori* infection in patients who have recently received acid suppression therapy.

Strictly, the term ‘gastritis’ should be used only to describe changes characterized by a mucosal infiltrate of inflammatory cells while changes attributable to the injurious effects of NSAIDs, alcohol and bile, for example, should be termed a chemical or reactive gastropathy. However, even a chemical gastropathy may be accompanied by inflammation and both entities will, therefore, be addressed.

Acute gastritis is characterized by an inflammatory infiltrate that is predominantly neutrophilic and is usually transient in nature. Inflammation may be accompanied by mucosal hemorrhage and superficial mucosa sloughing and, when severe, acute erosive gastritis may be associated with gastrointestinal bleeding (Figure 3). Acute gastritis may cause epigastric pain, nausea and vomiting but it may also be completely asymptomatic.

Chronic gastritis is characterized by an infiltrate of lymphocytes, plasma cells, or both, that may also be associated with intestinal metaplasia and atrophy of the epithelium. In intestinal metaplasia, the normal gastric epithelium is replaced by metaplastic columnar absorptive cells and goblet cells; these are usually small-intestinal in morphology although features of a colonic epithelium may be present. The development of atrophic gastritis and intestinal metaplasia is considered to be premalignant although the incidence of gastric cancer in gastric intestinal metaplasia



is unknown and surveillance is not widely practised. In the Western world, histologic changes of chronic gastritis occur in up to 50% of the population in later life although the incidence of gastric cancer is falling, almost certainly due to the decreasing prevalence of *H. pylori* infection. Chronic gastritis rarely causes symptoms although it can be associated with nausea, vomiting and upper abdominal discomfort.

In addition to elements of chronicity, gastritis can also be categorized on the basis of identifiable etiology (e.g., infection, graft-versus-host disease, autoimmune, chemical gastropathy) or on the basis of histological appearance (e.g., granulomatous, eosinophilic, lymphocytic, hypertrophic) although, in practice, the categorization of gastritis may address both of these elements.

Gastritis is not itself often a cause of dyspepsia, unless there is *H. pylori*- or NSAID- associated peptic ulcer disease. Gastritis is a diagnosis made from the histological examination of gastric biopsies obtained on EGD. There are numerous causes of histologically diagnosed gastritis, and the importance of knowing the cause of the gastritis is to treat the underlying condition. It must be stressed that even when the cause of the gastritis is treated, such as in the person with dyspepsia and a chronic *H. pylori* infection, curing the infection as well as the gastritis may have little benefit on the patient's dyspepsia (therapeutic gain only about 13%, versus 50% if there is *H. pylori* eradication in the person with *H. pylori* associated peptic ulcer disease).

1.2. Gastritides with Identifiable Etiology

1.2.1. Infectious Gastritides

1.2.1.1. Viral

Cytomegalovirus (CMV) infection of the gastrointestinal tract usually occurs in immunocompromised individuals. CMV gastritis may be associated with epigastric pain and fever and the gastric mucosa may be edematous and congested, with erosions or ulceration at endoscopy. The characteristic histological finding is "owl-eye," intranuclear inclusions in cells of the mucosal epithelium, vascular endothelium and connective tissue.

Herpes infection with the H. simplex, H. varicella or H. zoster virus occurs by reactivation of a prior infection; again, this is seen most commonly in the immunocompromised patient, and leads to nausea, vomiting, fever, chills, fatigue and weight-loss. At endoscopy, the gastric mucosa has a cobblestone appearance due to multiple superficial linear ulcers and small raised ulcerated plaques, while histology shows numerous cells with ground-glass nuclei and eosinophilic, intranuclear inclusion bodies surrounded by halos.



Table 1. Causes of histologically-diagnosed gastritis.

-
- Drugs, chemicals, radiation
 - Medications
 - Aspirin, NSAIDs, COXIBs
 - Bisphosphonates, K⁺ tablets
 - Drugs, chemicals
 - Alcohol, bile, cocaine, chemotherapy, radiotherapy, red peppers, pickles
 - Infection
 - Bacterial - *H. pylori*, Mycobacteria
 - Viral-CMV, HSV
 - Fungal
 - Parasitic
 - Graft-versus-host disease (GVHD)
 - Autoimmune gastritis (pernicious anemia)
 - Ischemia
 - Atherosclerosis
 - Sepsis
 - Burns
 - Shock
 - Mechanical ventilation
 - Associated with liver disease – GAVE, PHG
 - Trauma/foreign body
 - Nasogastric or gastrostomy tubes
 - Bezoar
 - Prolapse / sliding hiatal hernia/paraesophageal hernia
 - Cameron ulcer (ulcer in hiatus hernia)
 - Infiltration/ tumor
 - Lymphocytic/ collagenous
 - Granulomatous
 - Eosinophilic
 - Tumor
 - Miscellaneous
 - Gastritis cystica profunda
 - Ménétrier's disease (hyperplastic, hypersecretory gastropathy)
-

Abbreviations: CMV, cytomegalovirus; GAVE, gastric antral vascular ectasia; GVHD, graft-versus-host disease; HSV, herpes simplex virus; PHG, portal hypertensive gastropathy



Adapted from: Lee EL, and Feldman M. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 1068; and printed with permission: Francis DL. *Mayo Clinic Gastroenterology and Hepatology Board Review*; 2008:67.

1.2.1.2. Bacterial

H. pylori is the most common gastric bacterial infection worldwide and, surprisingly, it remained almost unrecognized until the seminal work of Barry Marshall and Robin Warren (see previous chapter). The prevalence of *H. pylori* infection in the Western world is about 20-30% (25% in Canada) prevalence increases with age and, in the developing world, it may exceed 80%. *H. pylori* can be found in 90% of patients with chronic antral gastritis and most *H. pylori*-infected individuals have associated gastritis. Although many *H. pylori*-infected individuals have no symptoms, *H. pylori* is associated with an increased risk of developing peptic ulcer disease, gastric cancer and gastric 'MALT' lymphoma.

Although it initially causes antral gastritis, *H. pylori* may affect both antral and body-fundic mucosa. At endoscopy, the mucosa may appear coarse and reddened with thickened rugal folds but, with longer-standing infection, it may become thinned, flattened and atrophic. Chronic *H. pylori* gastritis is characterized by an infiltrate of lymphocytes and plasma cells in the lamina propria and lymphoid aggregates with germinal centres; a variable, active gastritis is characterized by neutrophils in the glandular and surface epithelial layer. *H. pylori* organisms reside in the superficial mucous layer, over the mucosal surface, and in gastric pits; they can usually be seen with a standard hematoxylin and eosin stain but special stains, such as the Warthin-Starry silver stain, acridine orange fluorescent stain and Giemsa stain may be needed if organisms are sparse.

Over time, the initial antral-predominant gastritis progresses to a pangastritis and then to atrophic gastritis and intestinal metaplasia – precursors to the development of gastric cancer (the "Correa hypothesis"). Eradication of *H. pylori* infection usually with regimens comprising two antibiotics and an acid antisecretory agent, is associated with a decreased risk of peptic ulceration and its complications and, probably, with a decreased risk of gastric cancer and gastric MALT lymphoma.

Phlegmonous (suppurative) gastritis is a rare bacterial infection of the submucosa and muscularis propria and is associated with massive alcohol ingestion, upper respiratory tract infection, and immune compromise; it has a mortality rate in excess of 50%. At endoscopy, the mucosa may show granular, green-black exudates and, at histology, there is an intense polymorphonuclear infiltrate with gram-positive and gram-negative organisms. Emphysematous gastritis, due to *Clostridium welchii*, may lead to the formation of gas bubbles, along the gastric contour on x-ray. Treatment requires gastric resection or drainage and high-dose systemic antibiotics.

Mycobacterium tuberculosis gastritis is rare; ulcers, masses, or gastric outlet obstruction may be seen at endoscopy and biopsies show necrotizing granulomas with acid-fast bacilli. *Mycobacterium avium* complex gastritis is very rare, even in immunocompromised individuals; gastric mucosal biopsies show foamy histiocytes containing acid-fast bacilli.



Actinomycosis and syphilis are very rare causes of gastritis, although the incidence of gastric syphilis has increased in the US over the last two decades. In actinomycosis, endoscopy may reveal appearances suggestive of a gastric malignancy; biopsies show multiple abscesses containing *Actinomyces israelii*, a gram-positive filamentous anaerobic bacterium. In syphilis, endoscopy may show multiple serpiginous ulcers while biopsies show severe gastritis with a dense plasma cell infiltrate in the lamina propria, as well as some neutrophils and lymphocytes, gland destruction, vasculitis and granulomata.

1.2.1.3. Fungal and Parasitic

Candida and *Histoplasma*, the most common, albeit rare, fungal causes of gastritis are associated with impaired immune status; gastric phycomycosis (zygomycosis) is exceedingly rare but usually fatal. Parasitic causes of gastritis include *Cryptosporidia*, *Strongyloides stercoralis*, *Anisakis* (from raw marine fish), *Ascaris lumbricoides* and *Necator americanus* (hookworm).

1.2.2. Graft-Versus-Host Disease (Gvhd)

The stomach and esophagus are affected less often than small intestine and colon by GVHD, which usually follows allogeneic bone marrow transplantation. Acute GVHD occurs between days 21 and 100 after transplantation and, if it affects only the stomach, it is associated with nausea, vomiting and upper abdominal pain. Endoscopic findings are non-specific and histology shows cell necrosis (apoptotic bodies — intraepithelial vacuoles containing karyorrhectic debris and fragments of cytoplasm) in the neck region of the gastric mucosa.

1.2.3. Autoimmune Gastritis

Autoimmune gastritis, comprising less than 10% of chronic gastritis cases, is caused by one or more autoantibodies to parietal cell components, including intrinsic factor and the acid-producing proton pump ($H^+,K^+-ATPase$). It is associated with other autoimmune disorders such as Hashimoto's thyroiditis and Addison's disease. Mucosal atrophy, with loss of parietal cells, leads to decreased production of acid and intrinsic factor; about 10% of these patients develop low serum vitamin B12 levels and pernicious anemia.



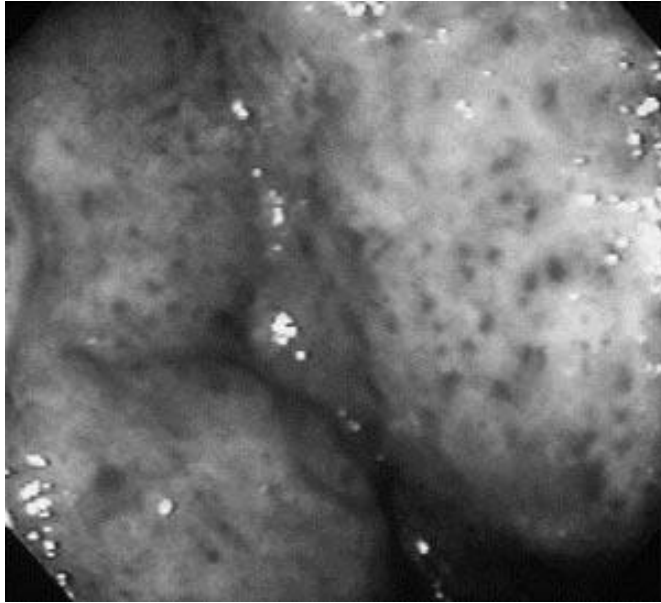


Figure 1. Fundal (Type A) gastritis

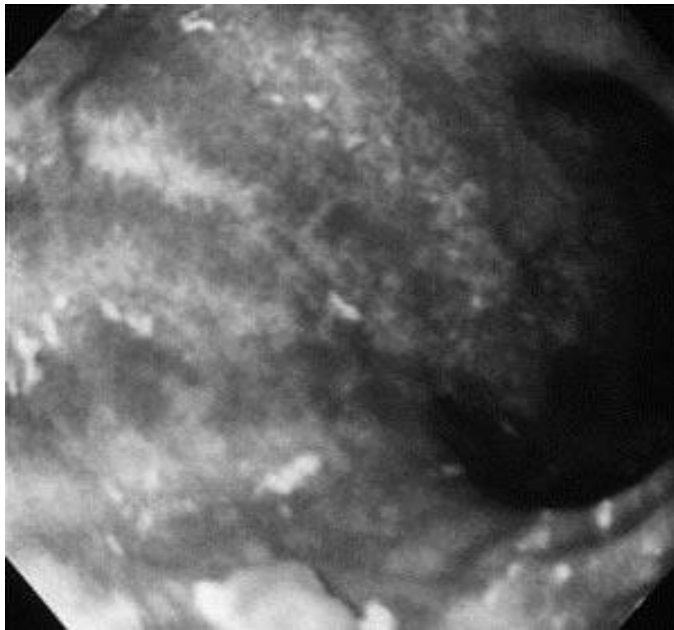


Figure 2. Chronic *H. pylori* gastritis



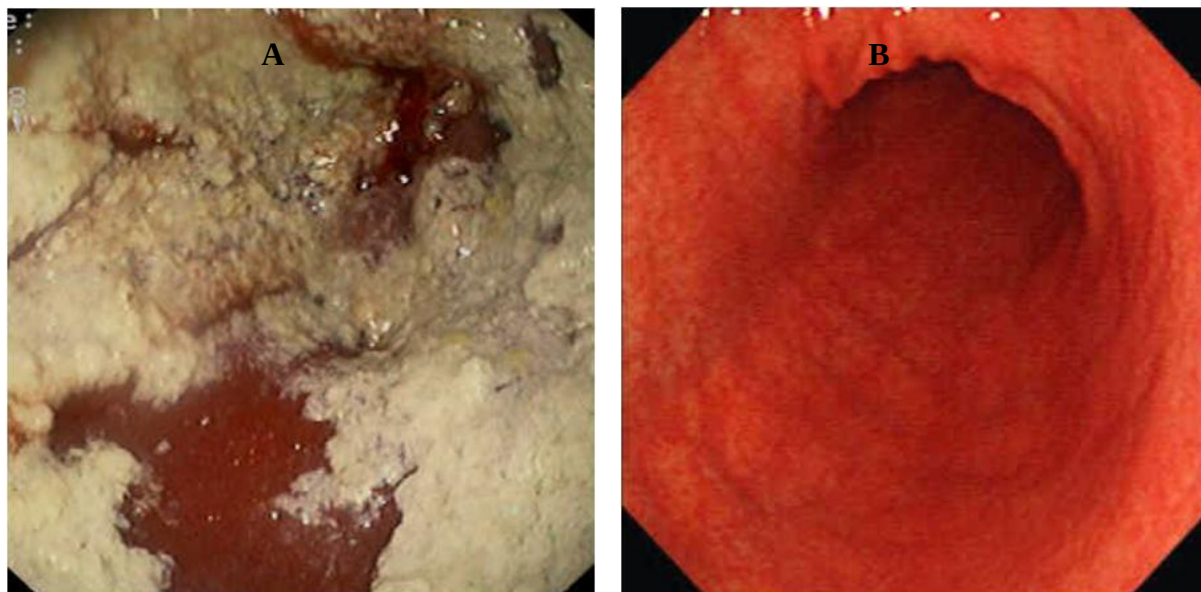


Figure 3. A) Candidiasis. B) Gastric atrophy

1.2.4. Chemical Gastropathy (Reactive Gastropathy)

A number of different agents can produce gastric mucosal injury, characterized at endoscopy by hemorrhagic lesions and erosions (necrosis to the level of the muscularis mucosa) or ulcers (necrosis extending deeper than the muscularis mucosa). Biopsies show the typical changes of foveolar hyperplasia including an elongated, corkscrew appearance to the gastric pits, depletion of surface, mucin-containing cells, subepithelial hemorrhage and minimal inflammatory cell infiltrate.

Aspirin (ASA) and other NSAIDs are the most common causes of a chemical gastropathy; cyclo-oxygenase-2 selective inhibitors (COX-2 or coxibs) are less likely to cause injury. While the patient's history of consuming NSAIDs is important to establish the diagnosis of NSAID-associated gastropathy, there are histological features which suggest the etiology. Bile reflux gastritis has become far less common as partial gastrectomy (Billroth I and II) is now performed only rarely; however, bile gastritis also occurs after cholecystectomy or sphincteroplasty, or, occasionally, in the absence of prior surgery. Other causes of a chemical gastropathy include medications (e.g., potassium chloride supplements, bisphosphonates), alcohol, ischemia (chronic mesenteric insufficiency), cocaine, stress (in intensive care settings) and gastric bezoars. Portal hyper- tension produces a congestive gastropathy, with vascular ectasia but, again, only a minimal inflammatory infiltrate.



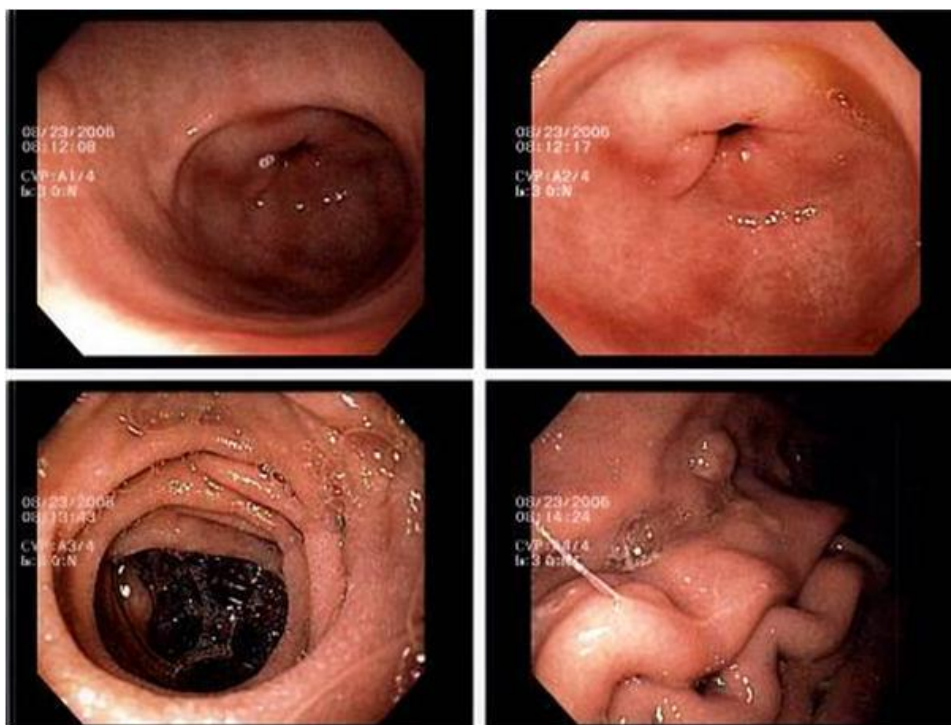


Figure 4.
Thick gastric
folds, gastric
polyp

1.3. Gastritides Identified by Histological Appearance

1.3.1. Granulomatous Gastritides

Crohn disease is the most common cause of a granulomatous gastritis although the differential diagnosis includes sarcoidosis, foreign bodies, Churg-Strauss syndrome (granulomatous vasculitis), Whipple's disease, Langerhans cell histiocytosis (eosinophilic granuloma) and lymphoma.

Crohn disease of the stomach is uncommon, particularly in the absence of disease elsewhere in the gastrointestinal tract. Endoscopy may show mucosal reddening and nodules with or without overlying erosions and ulcers that may be elongated or serpiginous. Histological features include non-caseating granulomata, ulceration, chronic inflammation and submucosal fibrosis. Sarcoidosis of the stomach can be difficult to distinguish endoscopically and histologically from Crohn disease and the diagnosis must be based on the presence of other systemic features.

Xanthogranulomatous gastritis is characterized, histologically, by the presence of foamy histiocytes, inflammatory cells, multinucleated giant cells, and fibrosis and may extend into adjacent organs and simulate malignancy.

1.3.2. Gastritis with Specific Diagnostic Features

Collagenous gastritis has been reported in association with collagenous colitis and lymphocytic colitis; it is very rare. At endoscopy, non-specific findings include mucosal hemorrhages, erosions and nodularity while histology shows a chronic gastritis (plasma cells and intra-epithelial lymphocytes), focal atrophy and focal collagen deposition (20–75 μ m) in the lamina propria.

Lymphocytic gastritis is thought, by some, to be related to varioliform gastritis, which is associated with thick mucosal folds, nodularity and aphthous erosions at endoscopy. It has been described in association with *H. pylori* infection and, also,



celiac disease (celiac sprue). Histology shows an infiltrate of the lamina propria in the antrum or body by plasma cells, lymphocytes and rare neutrophils, and a marked intraepithelial infiltrate with T lymphocytes.

Eosinophilic gastritis is associated with peripheral eosinophilia and eosinophilic infiltration of the stomach, involving one or more layers of the gastrointestinal tract (mucosa, muscle or subserosa). Endoscopy may show pylori obstruction, prominent gastric folds, nodularity or ulceration, and histology is characterized by eosinophilic infiltration (> 20 per high power field), eosinophilic pit abscesses, necrosis and epithelial regeneration. Severe disease and symptoms may require corticosteroid therapy.

1.3.3. Hypertrophic Gastropathies

There are numerous causes of thickened gastric folds seen on endoscopy or diagnostic imaging (Table 2). Ménétrier's disease is associated with protein-losing gastropathy and hypochlorhydria whereas hyperplastic, hypersecretory gastropathy is associated with increased or normal acid secretion and hyperplasia of the parietal and chief cells, with or without protein loss. Endoscopy, in both cases, typically shows irregular hypertrophic folds involving the body of the stomach, although there is a polypoid variant that resembles multiple hyperplastic gastric polyps. The characteristic histological features are foveolar hyperplasia with cystic dilation; inflammatory infiltrates may be present, as in hypertrophic lymphocytic gastritis, but this is variable. Ménétrier's disease may resolve spontaneously; symptomatic treatment includes acid antisecretory agents (H₂-RAs, PPIs), anticholinergics and a variety of other, empirical therapies, including octreotide and corticosteroids. Gastric resection for refractory protein loss, hemorrhage or obstruction is a last resort. Zollinger-Ellison syndrome, due to ectopic secretion of gastrin, responds well, symptomatically, to high-dose PPI therapy and, if a gastrinoma can be identified, surgery may be curative.

Table 2. Causes of thick gastric folds seen on an upper GI series or EGD

-
- Folds not actually thickened (barium study is wrong – ie. varices)
 - Malignant infiltration – adenocarcinoma, lymphoma, MALT lymphoma, linitis plastica
 - Benign infiltration -granulomas: e.g. sarcoidosis, TB, Crohn's severe gastritis (ethanol, *H. pylori*), Menetriers disease (hyperplasia) eosinophilic gastritis, lymphocytic gastritis, acute *H. pylori* gastritis
 - Multiple gastric polyps (HNPCC, FAP, fundic glands)
 - Hypersecretion (Zollinger-Ellison Syndrome)
 - Fundal varices
 - Worms
-

Abbreviations: EGD, esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; GI, gastrointestinal; TB, tuberculosis





Figure 5. Hypertensive gastropathy



Figure 6. NSAID gastropathy

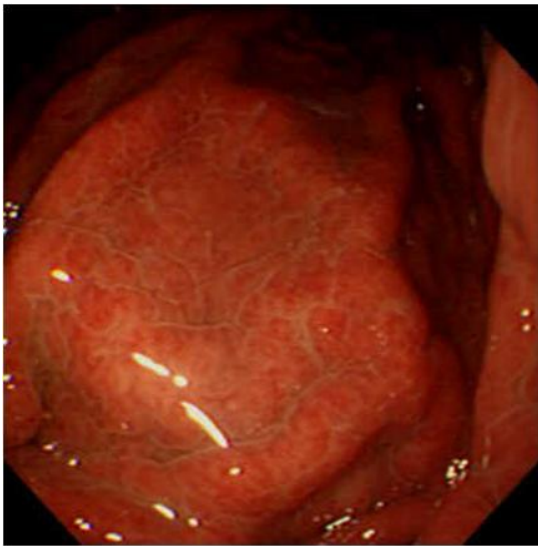


Figure 7. Portal hypertensive gastropathy



Figure 8. Watermelon stomach



Table 3. Potential causes of inadequate PPI response

-
- **Drugs**
 - Non-adherence to PPI
 - PPI not given 30 minutes before breakfast (or first meal of the day in shift worker)
 - Other medication (nitrites, calcium channel blockers)
 - Rapid metabolism of PPI
 - Reduced bioavailability
 - **Lifestyle**
 - Large volume regurgitation and need for other drugs
 - Posture (bending, lack of head of bed elevation)
 - Increased BMI / increased waist girth
 - Previous myotomy, hemigastrectomy
 - Delayed gastric emptying
 - Other causes of esophageal symptoms
 - Esophagus
 - Other causes of esophagitis
 - non-acid GERD
 - motility disorders; DES; achalasia
 - functional, hypersensitive
 - pill esophagitis, NERD, esophageal cancer, skin disease with esophagitis (Epidermolysis dissecans, Mucocutaneous candidiasis), eosinophilic esophagitis, infectious esophagitis (candida, HSV, CMV)
 - Stomach-- Hypersecretory state, nocturnal acid breakthrough, gastroparesis
 - Small Intestine-- Bile reflux
 - Colon – GERD associated with IBS
 - Other diagnoses (ie. Heart disease)
-

Abbreviations: CMV, cytomegalovirus; DES, diffuse esophageal spasm; GERD, gastroesophageal reflux disease; HSV, herpes simplex virus; IBS, irritable bowel syndrome; NERD, normal esophagus reflux disease; PPI, proton pump inhibitor

1.3.4. Miscellaneous Gastritides

Gastritis cystica profunda is a rare sequela of partial gastrectomy with gastro-jejunostomy but it may also develop in the absence of prior gastric surgery. Endoscopy typically shows multiple exophytic gastric masses, which on section reveal multiple cysts. At histology, foveolar hyperplasia is accompanied by cystic glands that extend through the muscularis mucosae into the submucosa and muscularis propria. It may be associated with chronic atrophic gastritis, hyperplasia or primary gastric stump cancer after surgery.



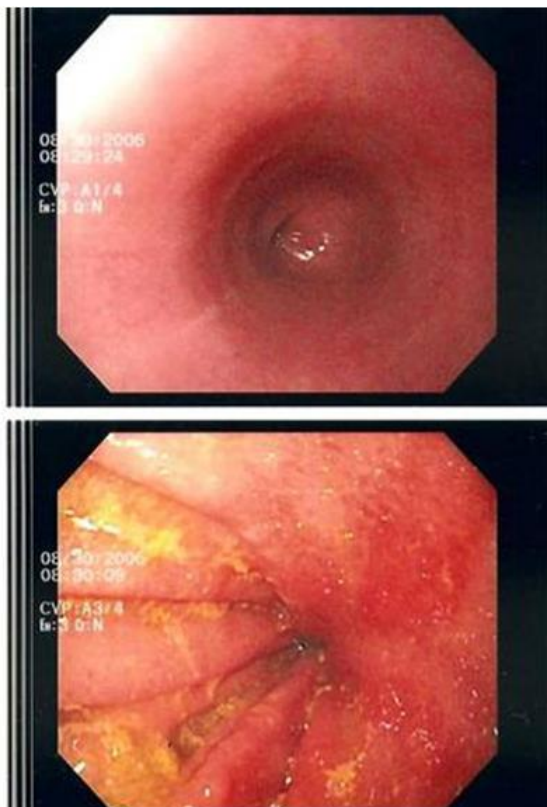


Figure 9. Bile gastritis

2. Gastric Polyps and Gastric Malignancy

There are numerous types of gastric polyps (Table 4) which are usually incidental findings with little risk of developing into cancer. *Gastric polyps* are gastric epithelial or non-epithelial protrusions observed either endoscopically or radiologically. The non-epithelial polyps arise from the mesenchymal tissue of the submucosa (such as a leiomyoma). The epithelial polyps are most common, and are often multiple, hyperplastic polyps. Infrequently, adenomatous or villous adenomatous polyps, which are often singular, occur. Duodenal adenomatous polyps may also be found in patients with Familial Adenomatous Polyposis (FAP)

Syndrome.

Individuals with a parent or sibling with gastric cancer are three times as likely to develop gastric cancer as the general population. People born in a country where gastric cancer is common (e.g., Japan or Eastern Europe) are also at increased risk, even if they have lived in North America for many years. Although regular screening is not warranted in either case, minor symptoms should be promptly and thoroughly investigated.

In the USA over 20,000 new cases of gastric adenocarcinoma are diagnosed annually, with the majority detected at an advanced stage with 1- and 5-year survival rates of 30% and 10%, respectively. In Canada there were 2,800 new gastric cancer cases in 2001 (8 per 100,000) and 1,950 deaths.

There are numerous risk factors associated with the development of gastric adenocarcinoma (Table 5). The incidence of gastric adenocarcinoma has been falling dramatically in North America from ~ 30 per 100,000 in the 1930s to 6–8 per 100,000 at present. There is a disparity in adenocarcinoma incidence between first- and second-generation immigrants, suggesting both genetic and lifestyle or environmental factors together contribute to the risk for cancer. Genetic factors that increase the risk include low gastric acid secretory status and the presence of pro-inflammatory genes such as interleukin-1 β , which is associated with gastric acid hyposecretion. Several lifestyle factors including diet and smoking increase the risk of gastric cancer but these are potentially modifiable. Infection with *H. pylori* is strongly associated with gastric malignancy and cancer develops in about 1% of those infected.



Table 4. The endoscopic characteristics and diagnostic criteria for types of benign gastric polyps

Polyp type	Location	Size	Endoscopic appearance	Pathological features	Comments
Fundic gland (75%)	Fundus and upper body	<1 cm	Smooth, glassy, transparent; usually multiple polyps are found	○ <i>Helicobacter pylori</i>-associated gastritis is rare	○ Associated with PPI use, may regress ○ Dysplasia found in patients with FAP ○ Fundic gland polyp: distorted glands and microcysts lined by parietal and chief cells; no or minimal inflammation
Hyperplastic (20%)	Random, adjacent to ulcers or stoma sites, or in the cardia if related to acid reflux	Generally <1 cm	Small polyps have a smooth dome; large polyps are lobulated, and erosions are common	○ Atrophic gastritis with intestinal metaplasia ○ <i>Helicobacter pylori</i>-associated gastritis (25%), dysplasia is rare (<3%) and found in polyps <2 cm	○ <i>Hyperplastic</i> elongated, cystic, and distorted foveolar epithelium, marked regeneration; stroma with inflammation, edema, and smooth muscle hyperplasia
Adenoma	Incisura angularis, found in the antrum than fundus	<2 cm	Velvety, lobular surface; exophytic, sessile or pedunculated; usually solitary (82%)	○ Atrophic gastritis with intestinal metaplasia ○ May be accompanied by coexistent carcinoma	○ <i>Adenoma dysplastic intestinal- or gastric-type epithelium with variable architecture</i>
Inflammatory fibroid	Submucosal, found near the pyloric sphincter	Median 1.5 cm; generally <3 cm	Single, firm, sessile, well-circumscribed, ulceration is common	○ Pernicious anemia commonly found; atrophic gastritis ○ Genetic mutations are common	○ <i>CD34+ spindled stromal cells, inflammatory cells, and thin-walled vessels in a myxoid stroma</i>



Polypoid lesion	Gastric location	Size	Endoscopic appearance	Pathological features	Comments
Peutz-Jeghers	Random	<1 cm	Pedunculated with a velvety or papillary surface	○ Normal ○ Risk of adenocarcinoma rare in gastric polyps	
Juvenile	Found more in the body than in the antrum	Variable	More rounded than hyperplastic polyps; superficial erosions; multiple polyps are usually found	○ Normal ○ Polyps may exclusively involve stomach risk of adenocarcinoma but rare in gastric polyps	
Xanthoma	Antrum, lesser curvature, prepyloric	<3 mm	Can be multiple in groups; sessile, pale-yellow nodule or plaque	○ Chronic gastritis ○ No association with hyperlipidemia	○ Xanthoma aggregates of lipid-laden macrophages in the lamina propria
Pancreatic heterotopia	Antrum, prepyloric	0.2-4.0 cm	Solitary; dome-shaped with central dimple; smooth surface	○ Normal ○ Very rare instances of associated pancreatitis, islet-cell tumors, adenocarcinoma	○ <i>Pancreatic heterotopia</i> normal components of pancreatic parenchyma
Gastrointestinal stromal tumor	Random, submucosal	Variable (median 6 cm)	Well-circumscribed; overlying mucosa may be ulcerated	○ Normal ○ 25% are malignant; risk of aggressive behaviour depends on size and mitotic count	○ CD117+, CD34+ spindle cell or epithelioid cell tumor with variable pattern, mitoses, and stroma



Polypoid lesion	Gastric location	Size	Endoscopic appearance	Pathological features	Comments
Carcinoid	Body and fundus	<2 cm, larger if sporadic	Hypergastrinemic lesions: firm, yellow, broad-based and multiple. Sporadic lesions: large and single	- Autoimmune atrophic gastritis with intestinal metaplasia parietal cell hyperplasia in ZES normal mucosa if lesion is sporadic - Associated with hypergastrinemia, autoimmune atrophic gastritis, ZES or MEN	<i>Carcinoid</i> nodular proliferation of neuroendocrine cells >500 µm in diameter

Abbreviations: FAP, familial adenomatous polyposis; MEN, multiple endocrine neoplasia; ZES, Zollinger-Ellison syndrome

Adapted from: Carmack SW, et al. *The American Journal of Gastroenterology* 2009;104(6): 524-532.; and Carmack SW, et al. *Nat Rev Gastroenterol Hepatol* 2009;6(6): 331-34.

Table 5. Risk factors associated with the development of gastric adenocarcinoma

- Genetic--First degree relative with gastric cancer (hereditary diffuse gastric cancer) (2-3 fold increased risk): with mutations in E-cadherin CDH1 gene
- HNPCC >> APC
- Polyps--adenomatous gastric polyps (HNPCC, APC), Peutz-Jeghers syndrome, hamartomas, Menetrier's syndrome
- *Gastric atrophy*--*H.pylori* infection, pernicious anemia, chronic atrophic gastritis, subtotal surgical resection with vagotomy for benign gastric ulcer disease
- Diet-- salted, pickled or smoked foods, low intake of fruits and vegetables
- Life Style--Smoking (EtOH is not an independent risk factor)
- Esophageal --Barrett's esophagus (cancer of cardia)

Abbreviation: HNPCC, hereditary nonpolyposis colon cancer

Adapted from: Houghton JM and Wang TC. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006: pg 1149.



2.1. Environmental Risk Factors

Dietary factors that contribute to gastric cancer include a high dietary salt and nitrate/nitrite intake, low fruit and vegetable intake, and the use of tobacco. The INTERSALT Cooperative Research Group (39 populations, 24 countries) confirmed an association between stomach cancer mortality and 24-hour urinary sodium excretion, and 24-hour urinary nitrate excretion, in both men and women.

Persons with the highest intake of vegetables have a significantly reduced risk of gastric cancer compared to those who consume no vegetables. Similar but weaker protective effects have also been observed for consumption of green and cruciferous vegetables.

Current smoking adversely influences the risk for gastric cancer, and this risk increases with the intensity and duration of cigarette smoking.



Figure 10.
Carcinoma of the
gastric cardia



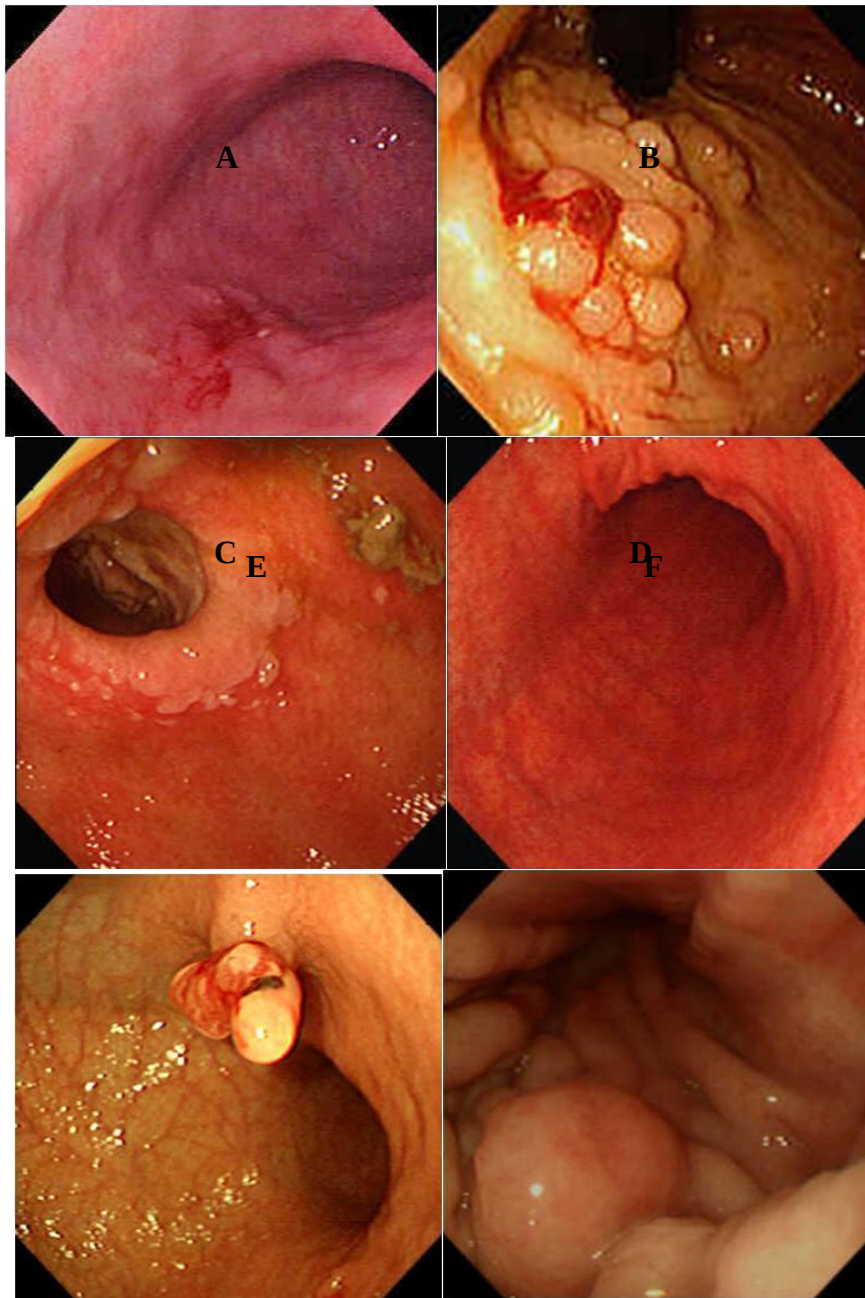


Figure 11. A) Early gastric cancer. B) Fundic gland polyps in FAP. C) Gastric atrophy D) Gastric polyps. E) Intestinal metaplasia in stomach. F) Gastric lymphoma.

In 1994, the International Agency for Research on Cancer (WHO) classified *H. pylori* as a group 1 carcinogen based on numerous studies that confirmed the association between *H. pylori* infection and gastric cancer rather than by direct cause and effect. Nested case-control studies showed an increase in the risk of cancer (odds ratios 2.5–6.0) while meta-analyses of cohort or case- controlled studies reported summary odds ratios for gastric cancer in those infected with *H. pylori* of 1.92–2.24. Younger individuals had a higher risk for gastric cancer than



older patients, presumably because of their having a longer duration of exposure. Infection with *H. pylori* is strongly associated with gastric malignancy and cancer develops in about 1% of those infected. Eradication of *H. pylori* reduces the risk of recurrence of early gastric cancer. Population studies have not proven that the eradication of *H. pylori* prevents the development of gastric cancer, but it may be that treatment of the infection must begin at a much earlier age before the progression of the inflammatory process has occurred (Table 6).

2.2. Gastritis, Intestinal Metaplasia and Gastric Cancer

2.2.1. Adenocarcinoma

Almost a decade before *H. pylori* was isolated, Correa proposed the concept of an inflammatory cascade initiated by an acute gastritis progressing to a chronic atrophic gastritis as the basis for gastric carcinogenesis. *H. pylori* infection is the most common cause of chronic gastritis. In a proportion of patients with chronic atrophic gastritis, intestinal metaplasia develops and, in a much smaller proportion, dysplasia and subsequently cancer (Table 5). Recent studies have shown the importance of inflammation, arising from the initial *H. pylori* infection with resultant gene polymorphisms, which increase the risk of gastric cancer. Patients with the interleukin-1 gene cluster polymorphism, which may enhance production of the proinflammatory cytokine interleukin-13, are at increased risk of *H. pylori*-induced hypochlorhydria and gastric cancer. Thus, host genetic factors that affect interleukin-1 β production and hypochlorhydria may influence gastric cancer risk in those infected with *H. pylori*. In relatives of index cases of gastric cancer who had *H. pylori* infection, atrophy and hypochlorhydria were significantly more common than in non-infected relatives.

Table 6. The annual risk of progression of gastritis to gastric cancer

Pathology	Risk of GCa per year	Recommended EGD/Biopsy follow-up
➤ Atrophic Gastritis	○ 0.1%	- None
➤ Intestinal Metaplasia	○ 0.3%	- 2-3 years
➤ Mild to moderate dysplasia	○ 0.6%	- 1 year
➤ Severe dysplasia	○ 6.0%	- Definitive therapy (EMR)

Abbreviation: EGD, esophagogastroduodenoscopy ; EMR, endoscopic mucosal resection

Adapted from: De Vries AC, et al. *Gastroenterology* 2008;134:945-52.



The presence of other pro-inflammatory polymorphisms, including interleukin-13, interleukin-1 receptor antagonist, tumour necrosis factor- α and interleukin-10, confer an increasingly greater cancer risk. Such exciting advances in the genetics of gastric cancer promise a means to identify early those who are at risk of this serious malignancy.

2.2.2. Neuroendocrine Tumors

Table 7. Secretory products and clinical characteristics of foregut, midgut and hindgut carcinoids (neuroendocrine tumors).

Location	Secretory products	Clinical characteristics	Carcinoid syndrome
○ Foregut-Stomach, duodenum, pancreas	Serotonin, histamine	Indolent except type 3 gastric carcinoid	Rare
○ Mid gut- Jejunum, ileum, appendix, ascending colon	Serotonin, prostaglandins, polypeptides	Often multiple, usually in ileum	Classic, but present in <10% of cases
○ Hindgut- Transverse, descending, and sigmoid colon and rectum	None	Indolent except in colon	Rare

Printed with permission: Rancis, Dawn L. *Gastritis. Mayo clinic Gastroenterology and Hepatology Board Review*. Page 87.

2.3. Diagnosis and Staging of Gastric Cancer

Diagnosis of gastric cancer should be suspected in patients over the age of ~ 50 years with epigastric symptoms of new onset, including early satiety, anorexia, nausea and vomiting, and especially when there are associated alarm symptoms of anemia, weight loss etc. However, by this stage the disease is likely to be advanced. Confirmatory diagnosis is usually made at endoscopy when biopsies and the intraluminal extent can be determined. Routine barium meal is of little value in diagnosis although the tumour will often be seen. Ultrasound may sometimes be helpful and abdominal CT scan can be used to determine the extent of disease and any metastatic spread. Gastric cancer may spread within the abdomen, for example to the ovaries (Krukenburg tumour).



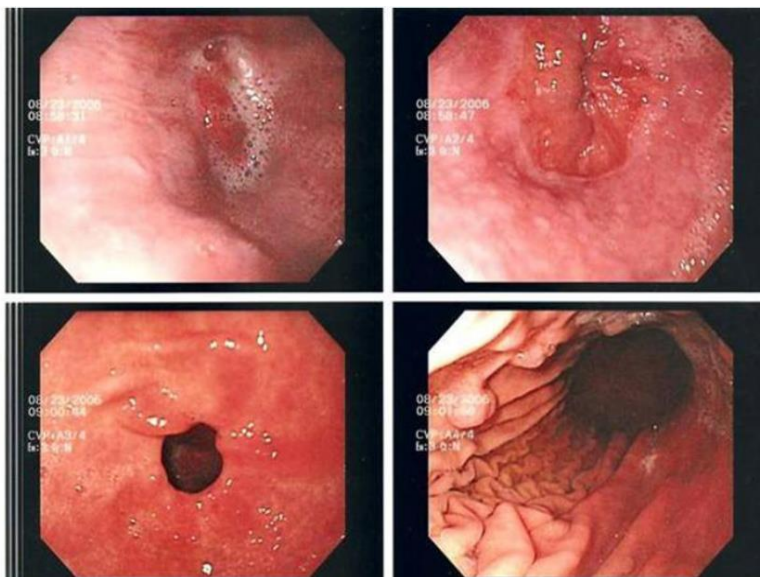


Figure 17. Fundic gastric polyps

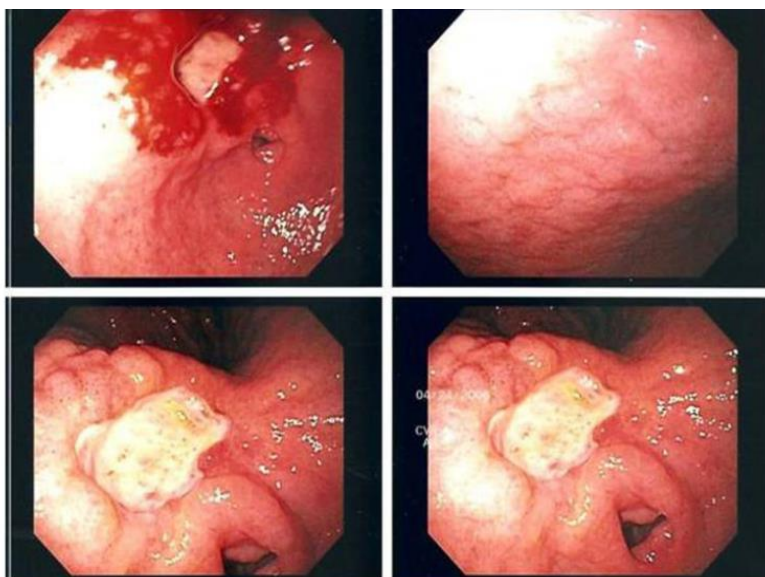


Figure 18. GU, possible gastric Ca

While the guidelines for dyspepsia take into account the need to attempt to prevent a missed diagnosis of gastric cancer, in fact persons with gastric polyps are usually asymptomatic, and those with gastric cancer usually present with alarm symptoms such as weight loss or bleeding, rather than with dyspepsia. Nonetheless, it is important to appreciate that there are many causes of thickened gastric folds and types of gastric polyps. The finding of thickened gastric folds or polyps on an upper GI series mandates the performance of an EGD to obtain multiple biopsies, which will allow for a diagnosis to be made and an appropriate management plan established. For the purpose of providing the patient with a prognosis, it is important for the endoscopist to provide the macroscopic type of the gastric cancer (Table 8).

While gastric cancer is usually diagnosed late and there is no universally-accepted reference standard chemotherapy, meta-analyses of randomized trials have shown a benefit for first-line combination therapy (Power et al. 2010). Clinocopathologic factors have been identified with improved survival, and targeted



therapy with for example anti-angiogenic and anti-Her₂ therapy, may in a subset of patients provide survival for more than two years.

Staging of the tumour is usually undertaken to determine prognosis and progress of the cancer. The widely used TNM (Tumour, Node, Metastasis) system is usually used and can help decide on the best course of treatment. Staging determines characteristics of the tumour and the extent of spread to other parts of the body.

Table 8. Macroscopic types of gastric cancer

Type	Japanese classification	Paris classification
0	Superficial, flat tumors with or without minimal elevation or depression	Superficial polypoid, flat/depressed, or excavated tumors
0I	Protruded 	Polypoid
0IIa	Superficial and elevated 	Non-polypoid and nonexcavated, slightly elevated
0IIb	Flat 	Non-polypoid and nonexcavated, completely flat
0IIc	Superficial and depressed 	Non-polypoid and nonexcavated, slightly depressed without ulcer
0III	Excavated 	Nonpolypoid with a frank ulcer
1	Polypoid tumors that are sharply demarcated from the surrounding mucosa and are usually attached on a wide base	Polypoid carcinomas that are usually attached on a wide base
2	Ulcerated carcinomas that have sharply demarcated and raised margins	Ulcerated carcinomas that have sharply demarcated and raised margins
3	Ulcerated carcinomas that have no definite limits and infiltrate into the surrounding wall	Ulcerated, infiltrating carcinomas that have no definite limits
4	Diffusely infiltrating carcinomas in which ulceration is not usually a marked feature	Nonulcerated, diffusely infiltrating carcinomas
5	Carcinomas that cannot be classified into any of the above types	Unclassifiable advanced carcinomas



According to Japanese classification of gastric carcinoma, for the combined superficial types, the type occupying the largest area should be described first, followed by the next type (e.g. IIc+III). Types 0 I and 0 IIa are distinguished from each other by lesion thickness: type 0 I lesions have thickness more than twice that of the normal mucosa and type 0 IIa lesions have a thickness up to twice that of the normal mucosa and type 0 IIa lesions have a thickness up to twice that of the normal mucosa. Modified from data presented in the Japanese classification of gastric carcinoma and the Paris endoscopic classification of superficial neoplastic lesions.

Printed with permission: Yamamoto H. *Nature Clinical Practice Gastroenterology & Hepatology* 2007;4(9): page 513.

2.4. Treatment of Gastric Cancer

Treatment of gastric cancer is usually surgical, although a palliative endoscopic procedure with tumour debulking may be considered in patients unfit for a definitive procedure. Surgical approaches involve partial, or sometimes total, gastrectomy depending on the location and extent of the tumour. The procedure may also involve removal of any lymph nodes involved in the malignancy. The more radical procedures will involve complex anastomosis to maintain continuity of the gut and esophago-jejunal anastomosis in the case of total gastrectomy. Careful long-term follow up of such patients is essential to maintain optimal nutritional status.

Radiation therapy and chemotherapy may also be used depending on the extent and stage of the tumour. Current chemotherapeutic agents may include epirubicin, cisplatin, 5-fluorouracil while the newer generation of chemotherapeutic agents, such as gemcitabine, irinotecan and paclitaxel and the recent introduction of “biological” or immunological treatments or vaccines, which block growth signals, inhibit angiogenesis, stimulate the body's own immune system etc., offer new hope for patients with a condition that has traditionally carried a very poor outlook.

Because of the dismal prognosis of gastric cancer unless it is diagnosed early (such as may occur in Japan with gastric cancer screening programs), it is important to recognize the risk factors which are associated with the development of gastric adenocarcinoma (Table 10). There are no Canadian guidelines for screening for gastric cancer, and in our community those at highest risk of developing gastric cancer are those with a family history, and those with a personal history of an *H. pylori* infection for many years, such as First Nations persons, or new Canadians from high endemic risk areas. If a type of gastritis with a high risk of progression to gastric cancer happens to be identified (Table 6), the patient may be entered into a surveillance (follow-up) program.

2.5. Gastric Cancer Prevention

A healthy diet, rich in fruits and vegetables and low in salt, pickles, nitrates and nitrites is likely to carry a reduced risk of gastric cancer. It is not clear to what extent heredity is important although numerous reports of familial gastric cancer are documented. The common originating factor may still be infection with *H. pylori* in a household. New information on genetics will help clarify this. An important question



that is not yet answered is whether widespread eradication of (or vaccination against) *H. pylori* infection will reduce or prevent gastric cancer. A large number of trials with differing endpoints is under way but it seems clear that treatment would need to be given relatively early in life before intestinal metaplasia and dysplasia have occurred for cancer to be prevented. Guidelines in Canada recommend that *H. pylori* infection be eradicated whenever detected.

Table 9. Risk Factors Including Protective Factors for Gastric Adenocarcinoma

➤ Definite	○ <i>Helicobacter pylori</i> infection ○ Chronic atrophic gastritis ○ Intestinal metaplasia ○ Dysplasia ○ Adenomatous gastric polyps ○ Cigarette smoking ○ History of gastric surgery (esp. Billroth II) ○ Genetic factors ○ Family history of gastric cancer (first-degree relative) ○ Familial adenomatous polyposis (fundic gland polyps) ○ Hereditary nonpolyposis colorectal cancer ○ Peutz-Jeghers syndrome ○ Juvenile polyposis
➤ Probable	○ High intake of salt ○ Obesity (adenocarcinoma of cardia only) ○ Snuff tobacco use ○ History of gastric cancer ○ Pernicious anemia ○ Regular aspirin or NSAID use (protective)
➤ Possible	○ Low socioeconomic status ○ Menetrier's disease ○ High intake of fresh fruits and vegetables (protective) ○ High ascorbate intake (protective)
➤ Questionable	○ Hyperplastic and fundic gland polyps ○ High intake of nitrates ○ High intake of green tea (protective)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug

2.6. Other Gastric Malignancies

- *Gastric lymphoma* is a rare tumour representing between 2 and 7% of gastric malignancies. Lymphoma may be primary or secondary from a more generalized lymphoma arising in other organs. Secondary lymphoma must be managed



as part of the systemic disease.

- *Mucosa-associated lymphoid tissue lymphoma* (MALT) is increasingly recognized and may also be associated with *H. pylori* infection. Treatment may lead to remission of the disease but the patient remains at risk of a recurrence in the event of reinfection.
- *Familial adenomatous polyposis*, may involve the stomach and in patients in whom this is detected in the rectum and colon, a full gastrointestinal survey with endoscopy and radiology is necessary with appropriate ongoing surveillance where indicated.
- *Neuroendocrine tumors*

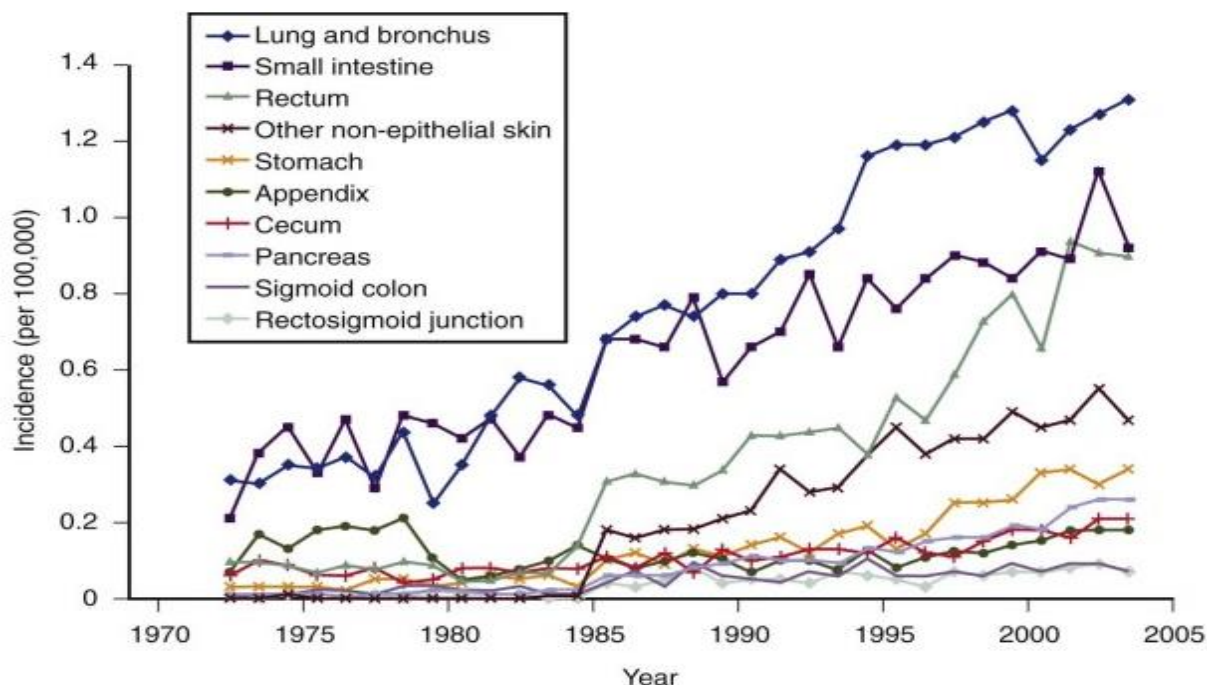


Figure 19. Incidence of different subtypes of neuroendocrine tumors, 1970 to 2005, from the Surveillance Epidemiology and End Results (SEER) data base., Note the significant increase in most subtypes of neuroendocrine tumors since the 1970s.(From Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008; 9:61-72.).

3. Miscellaneous Gastric Diseases

- *Gastric volvulus* is a rare cause of acute upper abdominal pain and vomiting and can be partial (antral) or total (entire stomach). These obstructions can arise by themselves, or as torsion within a hiatus hernia. Volvulus within a hernia is not uncommon in the elderly and may be asymptomatic. The belief that twisting obstruction poses an important risk to the blood supply is probably unjustified. Gastric aspiration is followed by surgical relief of the volvulus in those who present with obstruction.





Figure 20. Acute Gastric Dilation

- *Acute dilation* of the stomach can arise after any form of upper abdominal surgery, including cholecystectomy, and especially after vagotomy, after childbirth and in diabetic coma. The causes are uncertain. Vomiting of relatively clear gastric contents is succeeded by the production of dirty brown or feculent material and the development of abdominal distention. Prompt decompression with a large-bore stomach tube and intravenous fluid replacement are required. After a variable interval the condition should then resolve spontaneously (Figure 20).
- *Gastric rupture* is a rare, acute, nontraumatic, spontaneous rupture of the stomach, which is catastrophic and poorly understood. The majority of ruptures occur on the lesser curvature. They have also been reported to occur during upper gastrointestinal radiography using barium, sodium bicarbonate ingestion, nasal oxygen therapy, cardiopulmonary resuscitation and labour, and during the postpartum period.
- *Hypertrophic pyloric stenosis* is an idiopathic condition that may occur in infants or adults. The muscle of the pyloric canal is unduly hypertrophied. Infantile hypertrophic pyloric stenosis is more common in boys than in girls (the sex ratio is approximately 10:1), is a frequent anomaly (its incidence is about 3 per 1,000 live births) and is thought to be due to a combination of genetic predisposition and some abnormality of fetal or early postnatal development. Symptoms usually develop in the first few weeks after birth and characteristically consist of copious projectile vomiting of the gastric contents after feeding. On examination there is usually visible gastric peristalsis; a lump can be felt abdominally in the region of the pylorus. Barium-meal examination is not usually necessary but will confirm the presence of a narrow segment, 1–2 cm long, at the pylorus. The condition must be distinguished clinically from esophageal atresia (which involves difficulties with swallowing, with onset at birth) and duodenal obstruction/atresia (which involves bile-stained vomitus). A minor proportion of all cases settle in the first two to three months with conservative management with anticholinergic drugs, but most patients will require early surgery with Ramstedt's procedure (pyloromyotomy).
- *Gastric diverticula* occur most commonly near the cardia on the lesser curve, but occasionally are found in the prepyloric region. They seldom cause symptoms. Their principal importance lies in the likelihood of confusion with gastric ulceration on barium radiography.



- *Pseudolymphoma* is localized lymphoid hyperplasia of the stomach. The lesions are raised, flat or nodular folds, and are often associated with gastric ulceration. The etiology of this condition remains unclear, but *H. pylori* infection has been implicated. It is difficult to exclude lymphoma using radiology or endoscopic biopsy, thus, a resected specimen is required for diagnosis.
- *Gastric bezoars* are persistent concretions found in the stomach and consist of a variety of substances, most commonly plant and vegetable fibres (phytobezoars), persimmons (disopyrobezoars) or hair (trichobezoars). They most commonly occur in patients with previous gastric surgery or delayed gastric emptying and often produce symptoms including early satiety, abdominal fullness and epigastric pain. They may also occur in patients with behavioural disorders and the mentally challenged, especially when institutionalized. They can be complicated by gastric ulcer, secondary anemia and bleeding. Treatment methods include endoscopic removal or destruction, oral enzymatic therapy to dissolve the bezoar and metoclopramide.



Abbreviations

CE	Capsule endoscopy
COPD	Chronic obstructive pulmonary disease
COXIBs	COX-2 inhibitors
CV	Cardiovascular risk
CVA	Cerebrovascular accident
DBE	Double balloon enteroscopy
EGD	Esophagogastroduodenoscopy
EGG	Electrogastogram
ET	Endoscopic hemostatic therapy
ET	Eradication therapy
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
GAVE	Gastric antral vascular ectasia
GVHD	Graft-versus-host-disease
H2RA	H2 receptor antagonist
HCl	Hydrochloric acid
Hp	<i>Helicobacter pylori</i>
ITP	Idiopathic thrombocytopenic purpura
MRI	Magnetic resonance imaging
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVUGIB	Non-variceal upper GI bleeding
OR	Odds ratio
PE	Push enteroscopy
PHG	Portal hypertensive gastropathy
PPIs	Proton pump inhibitors
PUD	Peptic ulcer disease
SHR	Endoscopic stigamata of recent hemorrhage.
SIDS	Sudden infant death syndrome
SPECT	Single photo emission computed tomography
TSH	Thyroid ultrasound
UGIB	Upper GI bleeding
US	Ultrasonography
ZES	Zollinger Ellison syndrome



Chapter 6: The Small Intestine Intestinal Digestion
and Absorption in Health

A.B.R. Thomson and H.J. Freeman

1. Anatomy

The small intestine is a specialized abdominal tubular structure with an adult length of about 6 m, depending on the method of measurement. The proximal portion, the *duodenum*, consists of the: bulbar, descending, transverse and ascending portions. Most of the duodenum is retroperitoneal, wrapped around the head of the pancreas. As a result, inflammatory or neoplastic masses in the pancreas sometimes compress the duodenum. From the ligament of Treitz, the jejunum are suspended on a mesentery crossing from left upper to right lower quadrants. Then, the small intestine enters the large intestine at the ileocecal “valve.” The latter is not a true valvular structure but a physiological sphincter that acts to reduce cecal reflux into the small intestine.

The plicae circulares are more evident in proximal jejunum compared to distal ileum. The narrower ileal lumen is more prone to obstruction. Lymphoid follicles (aka Peyer’s patches) are visualized along the length of small intestine, particularly in distal ileum. Although the proximal duodenum derives some arterial supply from the celiac axis and its branches, and the rest of the small intestine derives mainly from the superior mesenteric artery. Veins follow the arterial supply, with the superior mesenteric vein flowing into the portal vein. Lymphatic drainage also follows these vascular structures flowing into lymph nodes and eventually the cisterna chyli, thoracic duct and left subclavian vein. Extrinsic innervation derives from the vagal nerve parasympathetic, while upper thoracic sympathetic fibers also supply the small intestine. Gut neurons project from the intestine to innervate the prevertebral sympathetic ganglia.

The intestinal wall is comprised of the mucosa, muscularis propria, submucosa and serosa. The serosa is a layer of mesothelial cells extending from the peritoneum. The muscularis propria includes both the outer longitudinal and inner circular layers separated by ganglion cells of the myenteric plexus (Auerbach’s plexus). The submucosa consists of a connective tissue framework, plus lymphocytes, plasma cells, mast cells, eosinophils, macrophages and fibroblasts. There are also numerous ganglion cells and nerve fibers (Meissner’s plexus) as well as vascular and lymphatic structures in the submucosa. The mucosa is separated from submucosa by a layer of muscle cells, the muscularis mucosae. The epithelial layer of the mucosa is divided into villus and crypt regions. Villi are fingerlike projections extending into the small intestinal lumen. They are longer in the jejunum compared to the ileum. Villi are covered with enterocytes which are specialized for digestion and absorption, along with goblet cells and intraepithelial lymphocytes. Cells from several adjacent crypts migrate into each villus and differentiate during their migration and eventual extrusion from the villus with a turnover of four to six days.

Stem cells, located in the base of crypts, are pluripotent cells that do not migrate from the crypt bases. Undifferentiated crypt cells are the most common crypt cells that may proliferate rapidly, but they have poorly developed structure, including intracellular organelles and microvilli. Paneth cells are characterized by eosinophilic granules that remain in the crypt bases and contain growth factors, digestive enzymes and antimicrobial peptides. Goblet cells are epithelial cells that contain visible mucins that may be discharged into the intestinal lumen, and play a role in



immune defense. Enteroendocrine cells contain secretory granules that may influence epithelial function through enterocyte basolateral membrane receptors. Enterocytes are polarized epithelial cells containing apical and basolateral membrane domains. The apical, microvillus brush border membrane faces the lumen, contains a complement of digestive enzymes, transporters and ion channels, different from those on the basolateral membrane. The enterocytes are connected by junctional complexes, forming a permeability barrier to the contents of the intestinal lumen. This polarized distribution of membrane proteins permits vectorial transport that differs in various regions of the small intestine. The basolateral membrane also has nutrient and electrolyte transporters as well as receptors for growth factors, hormones and neurotransmitters. Intestinal immune system includes M-cells and intraepithelial lymphocytes (IELs). M-cells are epithelial cells overlying lymphoid follicles that bind, process and deliver pathogens directly to lymphocytes, macrophages or other components of the immune system. IELs are specialized memory T-cells that migrate from the peripheral circulation to intercalate between the basolateral membranes of epithelial cells.

There is a complex vascular and lymphatic network extending through the villus core that is involved in signal and nutrient trafficking to and from the epithelial cell layer. The enteric nervous system (ENS) is even more complex, forming a myenteric and submucosal plexus, as well as containing intrinsic sensory neurons, interneurons for reflex activities and motor neurons that mediate actions of the enteric smooth muscle, glands and blood vessels. The interstitial cells of Cajal (ICC), have pacemaker activity with development of slow waves that electrically couple to smooth muscle cells. This leads to propulsive activity that promotes luminal movement of material from the proximal into the distal intestine.

2. Motility

The main function of the small intestine is digestion and absorption of nutrients. The role of small bowel motility is to mix food products with digestive enzymes (chyme), to promote contact of chyme with the absorptive cells over a sufficient length of bowel and to propel undigested material into the colon. Food in the stomach is churned into smaller and smaller particles. Once those particles are < 2 mm in size, they are pushed into the duodenum by co-ordination of contraction of the antrum and the relaxation of the pylorus. The rate of emptying of the stomach may be slowed by inhibition occurring from the duodenum or from the ileum. Receptors in the mucosa sense calories, osmolality, acid, fatty acid concentrations and slow emptying when these are high. Fatty acid in the ileum release glucagon-like peptide (GLP-1 or -2), peptide tyrosine-tyrosine (peptide YY); these peptides also slow gastric emptying by a process called the “ileal break”. Well-organized motility patterns occur in small intestine to accomplish these goals in the fed as well as the fasting. During fasting, there is a migrating motor complex (MMC) which starts in the lower esophagus. Sweeping through the stomach, it removes debris and residual material not emptied with the last meal. This MMC is characterized by a front of intense spiking activity (phase III activity) that continues to migrate down the entire small intestine. As the activity front reaches the terminal ileum, another front develops in the gastroduodenal area and progresses down the intestine. The



purpose of phase III myoelectric and contractile activity is to sweep remnants of the previous meal into the colon, and prevent stagnation and bacterial overgrowth.

During meals, this MMC cycle is interrupted, and the motility pattern in the small bowel becomes an irregular spiking activity called the “fed pattern.” This fed pattern of motility mixes but does not seem to move intestinal contents forward to any great extent but does mix these contents with digestive juices, spreading them again and again over the absorptive surface of the brush border. Diarrhea can occur when this normal fed pattern is replaced by aggressive propulsive rather than mixing contractions.

An overview of the motor function of the gastrointestinal tract (GIT) will be given, and in later sections motility will be considered in specific organ-related sections such as esophagus, stomach, small intestine and colon. The enteric nervous system (ENS) is comprised of efferent intrinsic and extrinsic motor neurons, interneurons, and afferent sensory neurons. The extrinsic afferent innervation of the intestine is supplied by the vagus nerve; over 80% of the vagal fibers are afferent, 20% are efferent (motor). The sensory aspect will be discussed with a consideration of the pain arising from IBS, the so-called irritable bowel (colon) syndrome.

The ENS has two major plexuses, the myenteric and the submucosal plexus (Figure 4). The ENS receives input from the central nervous system (CNS) and the autonomic nervous system (ANS). Enteric nerve cell bodies receive input from the sympathetic and parasympathetic components of the ANS. The myenteric plexus (Auerbach’s plexus) runs between the inner circular and outer longitudinal smooth muscle and most of the nerves of this plexus project to these muscle layers. The submucosal plexus (Meissner’s plexus and Schabadasch’s plexus) runs between the inner circular muscle and the mucosa, and its nerves project to the mucosal nerves, as well as to the myenteric plexus.

The reflexes arising in the ENS begin from chemical or mechanical stimulation. Intrinsic primary afferent neurons (IPANs) are activated, and in turn the IPANs activate the enteric primary afferent neurons (“sensory”, although not normally consciously perceived) in the submucosal and myenteric plexuses, which are integrated through interneurons, and produce a motor or secretory reflex response. Serotonin-containing enterochromaffin cells may be involved in the mucosal sensing of stimuli. There are numerous neurotransmitters in the GIT (Table 1).

Acetylcholine, tachykinins (e.g. substance P and neurokinins), and other peptides are released from the excitatory motor neurons, whereas the inhibitory motor neurons release nitric oxide (NO), adenosine triphosphate (ATP), VIP (vasoactive intestinal polypeptide), and PACAP (pituitary adenyl cyclase-activating peptide). Nitric oxide (NO) synthase synthesizes NO from arginine. NO diffuses rapidly from the activated neuron and binds to guanylyl cyclase on the myocyte membrane. Guanylyl cyclase converts GTP in the myocyte cytoplasm to cGMP, which relaxes the smooth muscle.



Table 1. Neurotransmitters in GI tract

➤ Myenteric plexus	○ GABA (γ -aminobutyric acid)
	○ Serotonin
➤ Submucosal plexus	○ VIP, CGRP, SP, ACh
➤ Endocrine cells	○ Somatostatin
➤ ANS Ganglia	○ Serotonic
	○ NYP (Neuropeptide Y), Somatostatin
➤ Excitatory, motor	○ ACh, SP, NKA
➤ Inhibitory, motor	○ NO, ATP, VIP, PACAP, β -NAD

Abbreviations: ANS, Autonomic Nervous System; ACh, Acetylcholine; NPY, Neuropeptide Y; SP, substance P; CGRP, calcitonin gene-related peptide; NKA, Neurokinin A; NO, Nitric Oxide; PACAP, Pituitary adenyl cyclase-activating peptide; VIP, Vasoactive Intestinal Polypeptide.

The intrinsic motor neurons are both excitatory and inhibitory. They respond to slow as well as fast neurotransmitters. The fast excitatory neurotransmitter is acetylcholine, the slow excitatory transmitter, substance P. The fast inhibitory neurotransmitters are nitric oxide (NO), ATP and β -NAD (nucleotide β -nicotinamide adenine dinucleotide), and the slow inhibitory neurotransmitter is VIP. Polarized reflexes also result from the presence of a bolus in the intestinal lumen. The “law of the intestine” is the result of the ascending excitatory reflex and the descending inhibitory reflex of the excitatory and inhibitory motor neurons.

The myocytes form a syncytium, with each myocyte connecting with another through cell-to-cell contacts, called gap junctions. There is both electrical as well as mechanical connection, so the myocytes in each layer work as a contractile unit. In the GI tract, the muscle contractions may be tonic or phasic. These are confusing terms, because when we speak of the small intestine, for example as having tone, this is really a long-lasting tonic contraction. A phasic contraction is short in duration (about 1 to 5 seconds), and this is what we mean when we say the intestine is undergoing a contraction.

Intestinal tract smooth muscle has a basic electrical rhythm (BER), a slow wave of electrical potential, also known as pacemaker potential. The interstitial cells of Cajal (ICC, in the longitudinal or circular muscle) generates the BER, and this pacemaker potential is higher proximally than distally, e.g. 12 slow waves per minute in the duodenum, 7 in the ileum. The ICC (interstitial cells of Cajal) are specialized mesenchymal cells that are placed closely to the myocytes and to the axons of neurons.



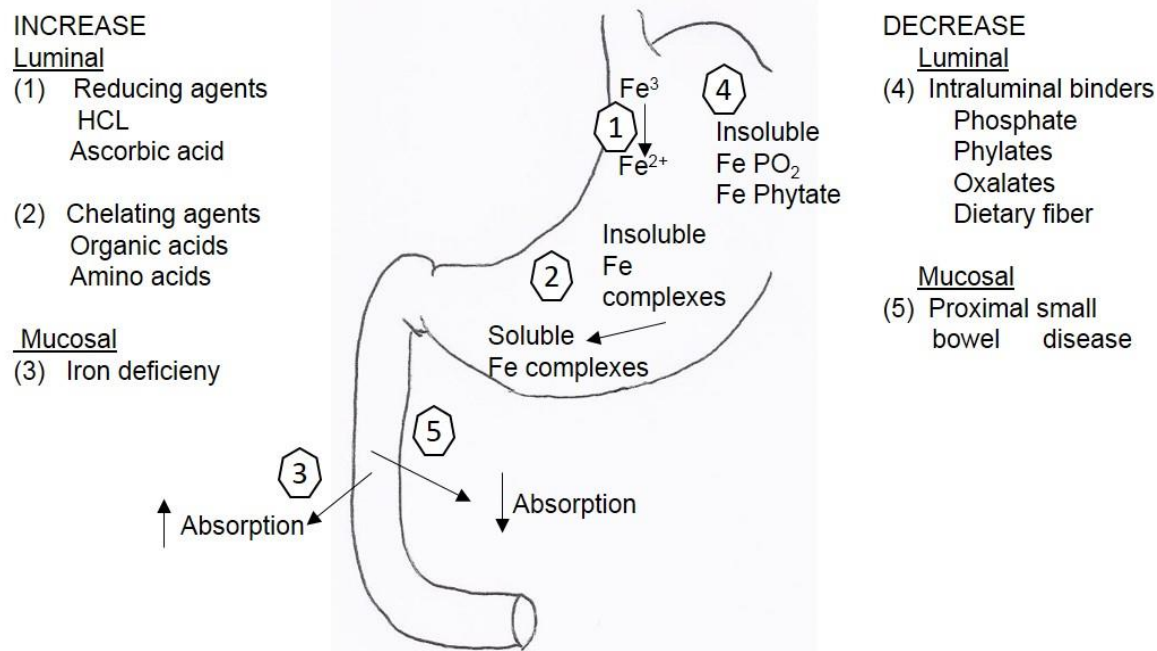


Figure 1. Factors that effect iron absorption. Nonheme ion absorption is affected both by intraluminal factors (1, 2 and 4) and by the total iron body content (3) as well as by small bowel disease (5). Heme iron absorption is altered only by those factors that affect the mucosa itself (3 and 5).

Source: Alpers DH. Absorption of water-soluble vitamins, folate, minerals, and vitamin D. In: Sleisenger MH, Fordtran JS (eds.), *Gastrointestinal disease: pathophysiology, diagnosis, management*. 3d ed. Philadelphia: WB Saunders, 1983:835.

3. Nutrient Absorption

3.1. Iron

Iron is available for duodenal absorption from vegetables (non-heme iron, Fe^{3+}) and from meat (heme iron [Fe^{2+}], ingested as myoglobin and hemoglobin). Heme iron (ferrous, Fe^{2+}) is ingested as myoglobin and hemoglobin. In the presence of gastric acid, the globin molecule is split off myoglobin and hemoglobin, and its Fe^{2+} absorbed. Both heme and nonheme iron are absorbed most rapidly in the duodenum. Heme iron is better absorbed (10–20%), and is unaffected by intraluminal factors or dietary composition. Only 1-6% non-heme iron is absorbed, and absorption is influenced by luminal events such as gastric pH and binding substances in food (polytate, phosphate, phophoproteins). The average dietary intake of iron is 10–30 mg/day. Men absorb 1–2 mg/day, while menstruating women and iron-deficient persons absorb 3–4 mg/day. Non-heme iron (in the ferric, [Fe^{3+}] state), when ingested into a stomach unable to produce acid, forms insoluble iron complexes, which are not available for absorption (Figure 2).



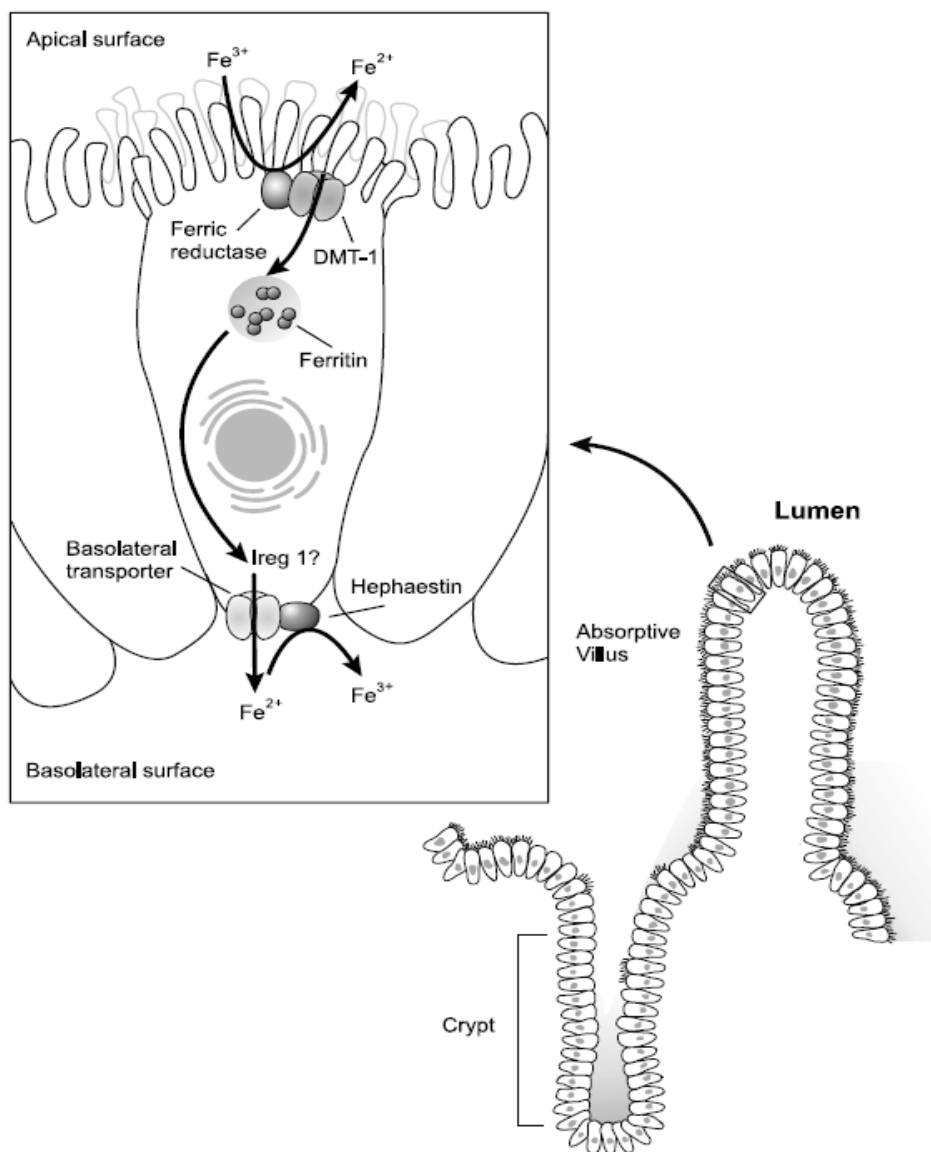


Figure 2. Intestinal absorption of iron. Iron is being transported across the brush-border membrane (BBM) by DMT (duodenal metal-transporter), and across the basolateral membrane possibly by Ireg 1, in conjunction with hephaestin, a ceruloplasmin-like molecule. Ferrereductase already in the BBM reduces Fe^{3+} to Fe^{2+} for transport by DMT. Absorption of iron is regulated by the amount of iron in the diet, body iron stores and by the activity of the bone marrow erythropoiesis.

In the presence of gastric acid and reducing agents (such as ascorbic acid, some sugars and amino acids). Ferric reductases in the BBM also reduces Fe^{3+} to Fe^{2+} . The Fe^{2+} is actively transported across the BBM by DMT₁ (divalent metal transporter 1), which is mostly in enterocytes at the top of the villus. DMT₁ is a proton symporter that also transports cobalt and manganese (Figure 3).



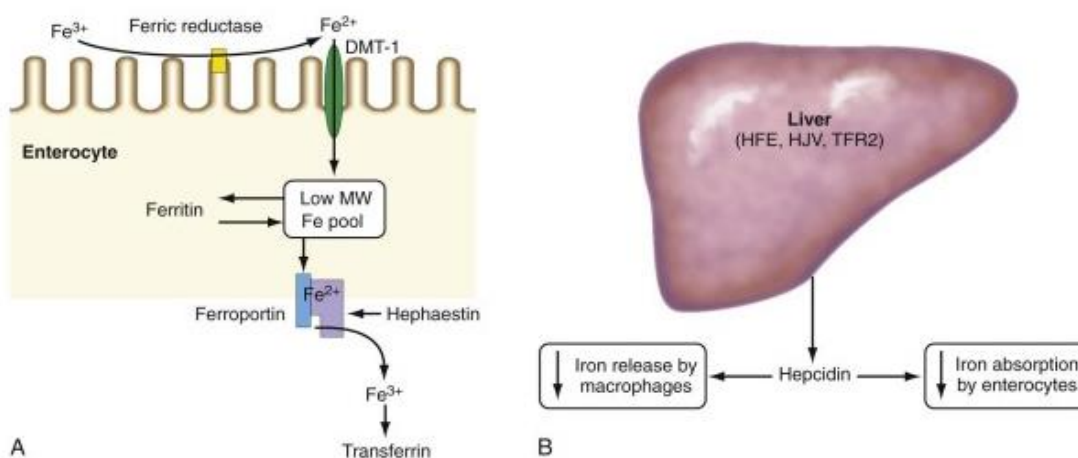


Figure 3. Iron absorption pathway in duodenal enterocytes and the role of hepcidin.

- A, Duodenal enterocytes are the major site of iron absorption.
- Before uptake, dietary ionic iron requires reduction from the ferric (Fe^{3+}) to the ferrous (Fe^{2+}) state.
- This is accomplished by ferric reductases that are expressed on the luminal surfaces of enterocytes.
- Ferrous iron is taken up by the apical transporter, DMT-1. Iron may be stored within the cell as ferritin, and then lost with the sloughed senescent enterocyte, or transferred across the basolateral membrane to the plasma.
- This process occurs via the transporter ferroportin and requires oxidation of iron back to the ferric state by the ferroxidase hephaestin.
- B, Hepcidin is produced by the liver and secreted into the blood.
- HFE protein, hemojuvelin (HJV), and transferrin receptor 2 (TFR2) may participate in the hepatic iron-sensing mechanism that regulates hepcidin expression.
- Hepcidin reduces iron release by macrophages (and thereby increases macrophage iron stores)
- Hepacidin also reduces iron absorption by duodenal enterocytes to reduce the amount of dietary iron in the circulation.
- In *HFE*-related hereditary hemochromatosis, loss of functional HFE protein leads to aberrant hepatocellular sensing of plasma iron, inappropriately low levels of hepcidin, diminished macrophage iron stores, and greater duodenal iron absorption. MW, molecular weight.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 74-1, page 1241, Ninth Edition, 2010.



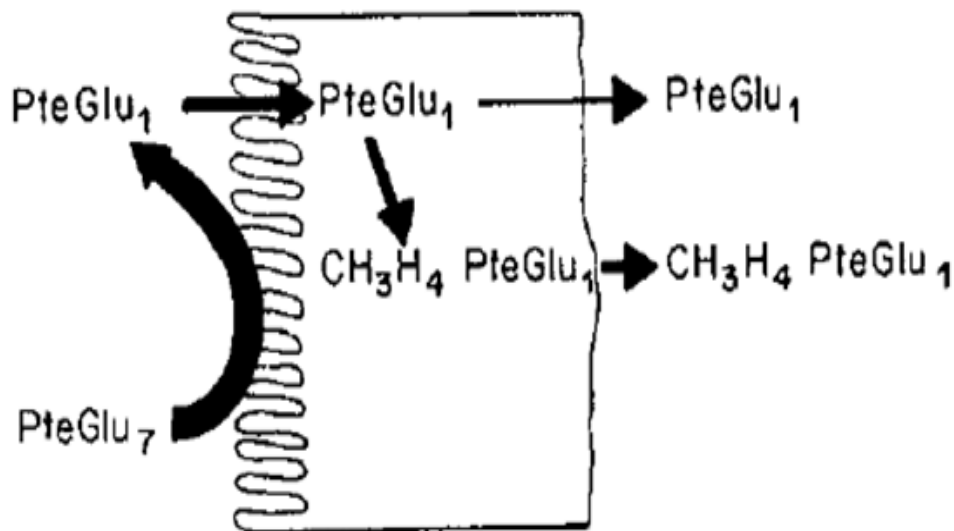


Figure 4. Proposed scheme of the digestion and absorption of dietary pteroylglutamates. Hydrolysis of polypteroylglutamates (shown here as PteGlu_7) probably occurs outside the intestinal epithelial cell. The overall rate of absorption into the mesenteric circulation is governed by the rate of transport of the monoglutamyl product (PteGlu_1). At physiologic doses, a substantial amount of PteGlu_1 is reduced and then methylated to $\text{CH}_3\text{H}_4\text{PteGlu}_1$ in the intestinal cell before release into the circulation.

Source: Rosenberg IH. Folate absorption and malabsorption. *N Eng J Med* 1975;293:1303.



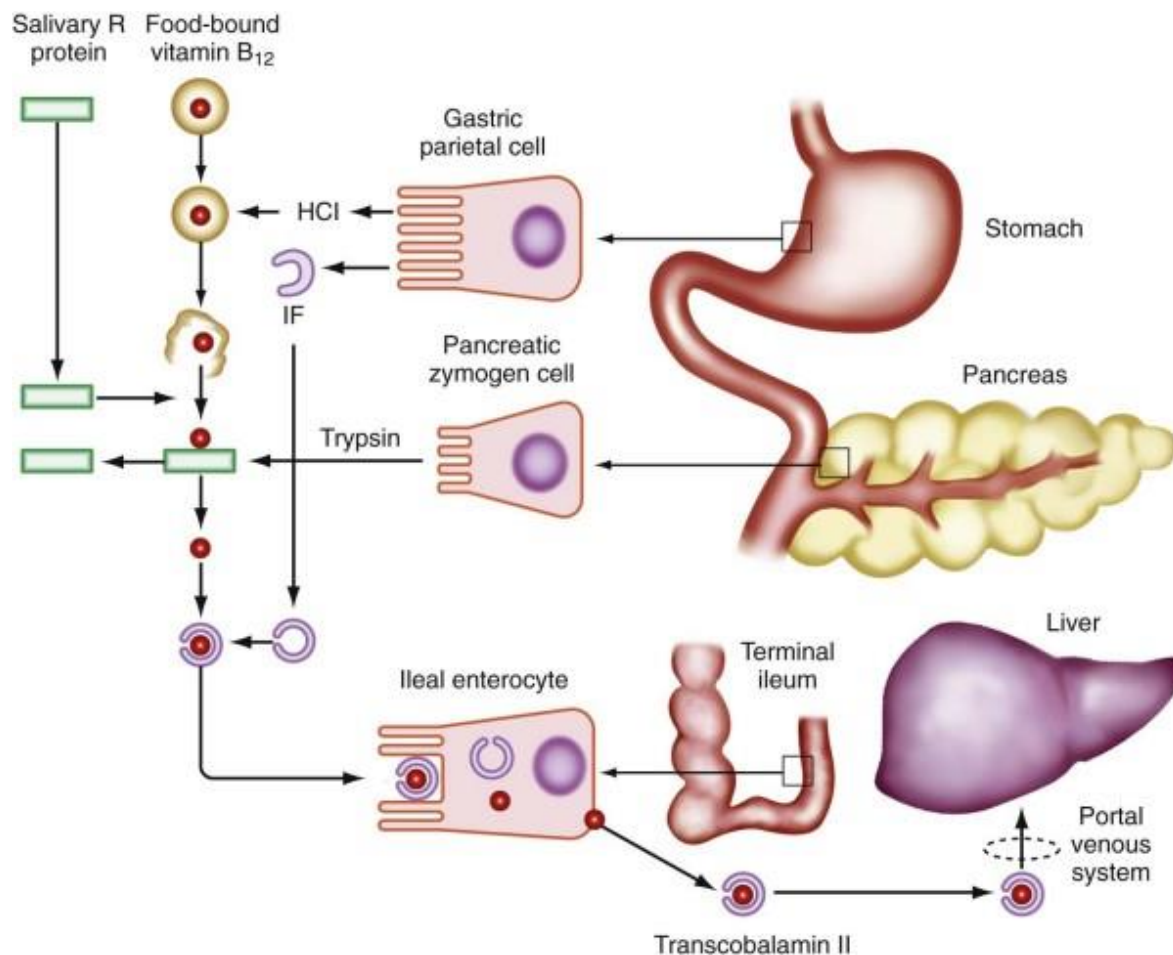


Figure 5. Absorption of Cbl (Cbl) requires proteolysis and intrinsic factor (IF).

- The intrinsic factor secreted is far in excess of that needed for binding the available Cbl. protein derived from saliva is also present in great abundance.
- Cbl binds initially to R protein in the stomach at acid pH.
- Only after R protein is degraded by protease does Cbl bind to IF. After Cbl is absorbed in the ileum, it is bound to transCbl II (Kalser MH., 1985).

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-18, pg 1719, Ninth Edition, 2010.

Since transfer of Cbl from R protein to IF depends upon ambient pH, pancreatic insufficiency (with deficient bicarbonate production) or the Zollinger-Ellison syndrome (with excess HCl production) interferes with this process and may result in Cbl deficiency. Loss of the ileum from injury, disease (Crohn disease) or surgical resection will result in Cbl malabsorption and deficiency. In the ileum, the IF-Cbl complex (but not free Cbl) binds to a BBM receptor, is absorbed, and in the cytosol of the ileocyte the Cbl is released from the IF. After trafficking across the enterocytes, Cbl is transported across the BLM and into the blood, bound to circulating proteins known as transCbls.



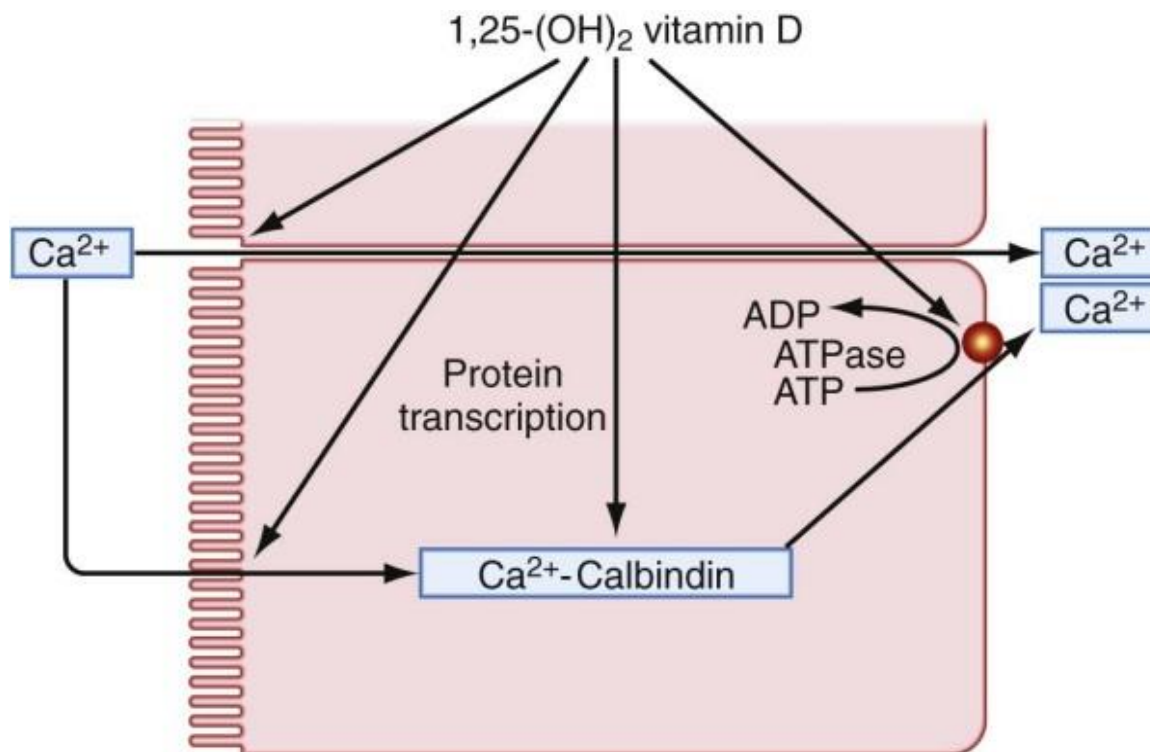


Figure 6. Mechanisms of calcium transport across the intestinal epithelium

- A paracellular route allows bidirectional flux.
- Transport into the epithelial cell occurs via specific channels down an electrochemical gradient.
- A critical step is the binding to calbindin, which then presents calcium for export via a calcium-dependent adenosine triphosphatase (ATPase) on the basolateral membrane.
- Each of these processes appears to be influenced by 1,25-(OH)₂ vitamin D, although its maximal effect is on synthesis of fresh calbindin. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-20, pg 1719, Ninth Edition, 2010



Table 2. Comparison of Calcium and Magnesium absorption

	Calcium	Magnesium
• Site of Maximal Absorption	Duodenum, jejunum and proximal	Ileum
• Enhancing effect of 1, 25 (OH) ₂ vitamin D on absorption:		
- Proximal	+	+
- Distal	+	-

3.2. Digestion and Absorption of Fat:

The overall process of the digestion and absorption of fat, triglycerides, cholesterol, phospholipids and bile acids consists of five distinct phases, related to the respective functions of the stomach, pancreas, hepatobiliary, intestinal mucosa, and lymphatics (Figure 13 and 14 and Table 4). Physiologically, these involve (1) gastric emulsification of dietary triglyceride (TG) (2) pancreatic lipolysis of TG to fatty acid (FA) and monoglyceride (MG); (3) bile micellar solubilization of FA and MG with bile acids, as well as the synthesis of BA from cholesterol; (4) uptake into the enterocytes, with reesterification of the MG with FA to form TG, and chylomicron formation in the presence of cholesterol, cholesterol esters, phospholipids and protein; and delivery of chylomicrons in lymphatics to the body for utilization of fat.

The average North American diet contains 60–100 g of fat each day, mostly in the form of neutral fat or triglycerides. The fat in masticated food is emulsified, and undergoes some lipolysis by gastric lipase. In the proximal intestine, TG comes under hydrolytic attack by pancreatic colipase and lipase, producing glycerol, FA and MG. Pancreatic lipase acts only at oil-water interfaces and requires a large surface area. Pancreatic colipase is required to achieve the necessary close contact of lipase with the triglyceride molecule. *E. coli* lipase is secreted as pro-colipase from the pancreas, followed by trypsin activation. Following the entry of food and particularly fat into the duodenum, cholecystikinin (CCK) is released from mucosal cells, causing gallbladder contraction.

Table 3. Key Steps in the Absorption of Lipids

- Stomach
 - Emulsification to increase the stability of lipid droplets
 - Lipase breaks down TG to FA and DG; DG further enhances emulsification
- Pancreas and duodenal lumen
 - Further hydrolysis of TG by pancreatic lipase, further enhanced by biliary BS and lecithin
 - In presence of colipase, the lipase moves closer to the emulsification droplet, closer to the hydrolytic sites of lipase
 - At pH~7, lipolysis of FA from α , and α_3 position of TG, releasing MG+FA



- Dietary cholesterol is esterified. Pancreatic cholesterol esterase releases FA and cholesterol. These are absorbed, and re-esterified in the enterocyte cytosol.
- Hepato-biliary Phase
 - BS and PL from bile enhance pancreatic hydrolysis, and AT BS concentrations above CMC, simple micelles are formed, solubilizing FA, MG, FSV, and CHOL
 - Once the CMC of the BS has been reached, simple micelles form
 - Simple micelles incorporate FA, MG, PL and form mixed micelles
 - Mixed micelles act as a reservoir for the solubilized products of the digestion of dietary lipids, and aid their diffusion across the UWL.
- Enterocyte
 - Once the micelle has diffused across the UWL just external to the BBM, the lipid products solubilized in the micelle either dissociate from the lipophilic micelle into the lipophilic BBM, or the lipid components of the micelle dissociate from the micelle into an aqueous phase, and from there pass into and through the BBM.
 - The BS which were part of the micelles diffuse back to the bulk phase in the intestinal lumen, where they solubilize further luminal lipid, and shuttle it back once again to the BBM; very little BS is absorbed in the proximal intestine, allowing the BS concentration to remain above the CMC, and micelles to be formed and reformed to continuously optimize the solubilization of the lipolytic products.
 - The products of lipolysis (FA, MG) may diffuse across the lipolytic BBM, or may bind to the BBM lipid-binding proteins, CD36 or FATP
 - Only a tiny amount of glycerol is absorbed, to be later used to synthesize TG in the cytosol. LCFA may bind directly to a FATP dimer in the BBM, or may bind first to BBM CD 36 and then to the dimeric FATP.
 - Once the LCFA is in the enterocyte cytosol, it binds to LACS, ACBP or I-FABP/L-FABP
 - I-FABP binds LCFA, and L-FABP binds MG and LPC
 - LCFA initially bound to LACS is transferred to ACBP; ACBP and FABP prevent LCFA from diffusing back across the BBM and out of the enterocyte
 - ACBP and FABP also shuttle LCFA to the ER for the resynthesis of TG, modulating intracellular lipid metabolism by regulating gene expression.
 - In the enterocyte, most absorbed LPC is reacylated to form PC and a small amount is hydrolyzed to form glycerol-3-phosphorylcholine, which is transported in portal blood to the liver
 - SCP-1 is involved in the microsomal conversion of squalene to lanosterol. SCP-2 is both involved in the microstomal conversion of



lanosterol to cholesterol, and the transport of cholesterol in lipid droplets to the mitochondria.

- During fasting, intracellular enterocyte glucose is used to form α -glycerophosphate, Acyl CoA plus α -glycerophosphate form first phosphatidic acid and then PL+TG.
- When adequate amounts of MG are present such as during a meal containing lipids, the MG pathway is active and inhibits the α -glycerophosphate pathway.
- Microsomal acyl coA-lipase synthesize Acyl coA from FA, acyl coA plus MG form DG, and then TG, through what is known as the monoglyceride pathway. With feeding of fat in the SER, the FA is acetylated with CoA in the presence of ATP to form acyl coA
- During the fed period, the monoglyceride pathway synthesizes about 96% of TG, whereas a tiny amount (~4%) of TG is formed during this absorptive period by acylation of the tiny amount of glycerol that is absorbed.
- The TG and PL are synthesized in the SER. In the RER the apolipoproteins are synthesized.
- CHOL in the enterocyte cytosol is from diet, biliary cholesterol, plasma lipoproteins, and newly synthesized cholesterol. The CHOL is esterified by ACAT and ACAT₂, and a lesser role by cholesterol esterase.
- The chylomicrons pass to the Golgi apparatus, and then to the enterocyte BLM
- The chylomicrons for vesicles with the BLM to move by exocytosis into the lacteals
- The gaps in the endothelial cells widen, and the chylomicrons move in the portal circulation
- Water soluble MCTs move from the enterocyte cytosol directly across the BLM, without the need for micellar solubilization, re-esterification, or chylomicrons
- When dietary levels of CHOL are high, ACAT is stimulated
- The RER apolipoproteins and the SER-synthesize TG, CHOL and PL ester from chylomicrons and VLDLs in the SER. The FA in the TG in chylomicrons are largely from the diet; the FA in the PL are used to form VLDLs. With feeding, chylomicrons predominate, whereas with fasting, VLDLs predominate
- The apolipoproteins formed in the enterocyte SER coat the chylomicrons (TG, PL, CHOL ester). Apo B is synthesized in the enterocyte Golgi cisternae, and then moves to the RER, where it is important for the synthesis and secretion of chylomicrons



- The lipid transfer activity of the microsomal triglyceride transfer protein initiates the addition of lipids (PL, TG) to the primordial chylomicron particle

Abbreviations

ACAT, acyl cholesterol acyl transferase
 ACBP, acyl CoA binding protein
 BS, bile salts
 CHOL, cholesterol
 CHOL, cholesterol
 CMC, critical micellar concentration
 DG, diglyceride
 ER, endoplasmic reticulum
 FA, fatty acid
 FATP, fatty acid transport protein
 FSV, fat soluble vitamin
 I-FABP, intestinal(-type) fatty acid binding protein
 LACS, long chain fatty acyl-CoA synthetase
 LCFA, long-chain fatty acid
 L-FABP, liver (-type) fatty acid binding protein
 LPC, lyso phosphatidyl choline
 LPC, lysophosphatidylcholine
 MCT, medium-chain length triglycerides
 MG, 2-monoglycerol
 MG, monoglyceride
 PC, phosphatidyl choline
 PL, phospholipids (Lecithin)
 RER, rough endoplasmic reticulum
 SER, smooth endoplasmic reticulum
 TG, triglyceride
 UWL, unstirred water layer
 VLDL, very-low-density lipoproteins



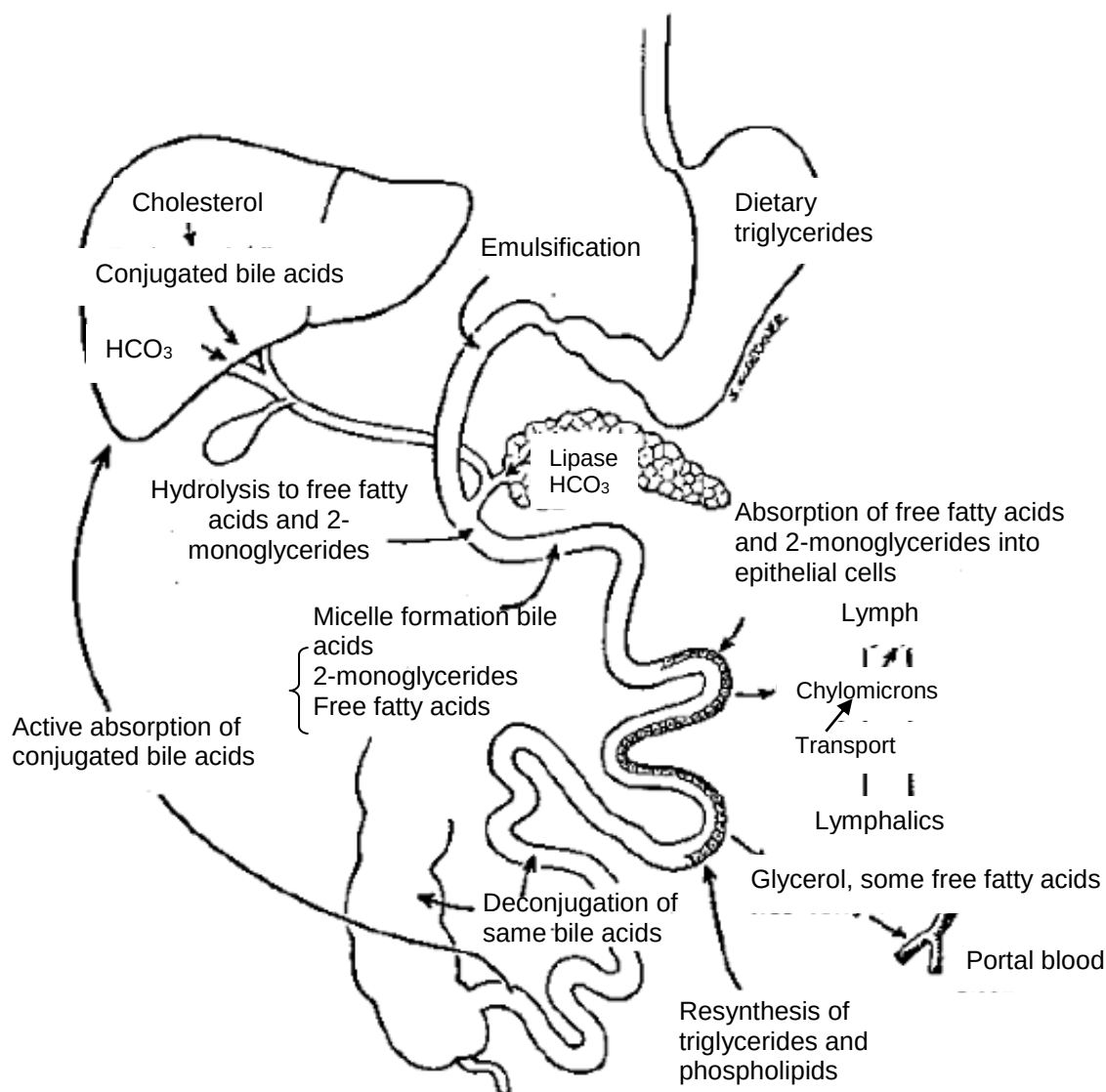


Figure 7. Diagram of the major steps in the digestion and absorption of dietary fat. These include (1) the lipolysis of dietary triglyceride (TG) by pancreatic enzymes; (2) micellar solubilization of the resulting long-chain fatty acids (FA) and β -monoglycerides (β MG; shown in figure as 2-monoglycerides) by bile acids secreted into the intestinal lumen by the liver; (3) absorption of the fatty acids and β -monoglycerides into the mucosal cell with subsequent re-esterification and formation of chylomicrons; and, finally, (4) movement of the chylomicrons from the mucosal cell into the intestinal lymphatic system. During the process of chylomicron formation, small amounts of cholesterol ©, cholesterol ester (CE), and phospholipid (PL) as well as triglyceride are incorporated into this specific lipoprotein fraction.

Adapted from: Wilson FA, Dietschy JM. Differential diagnostic approach to clinical problems of malabsorption. *Gastroenterology* 1971; 61:912.



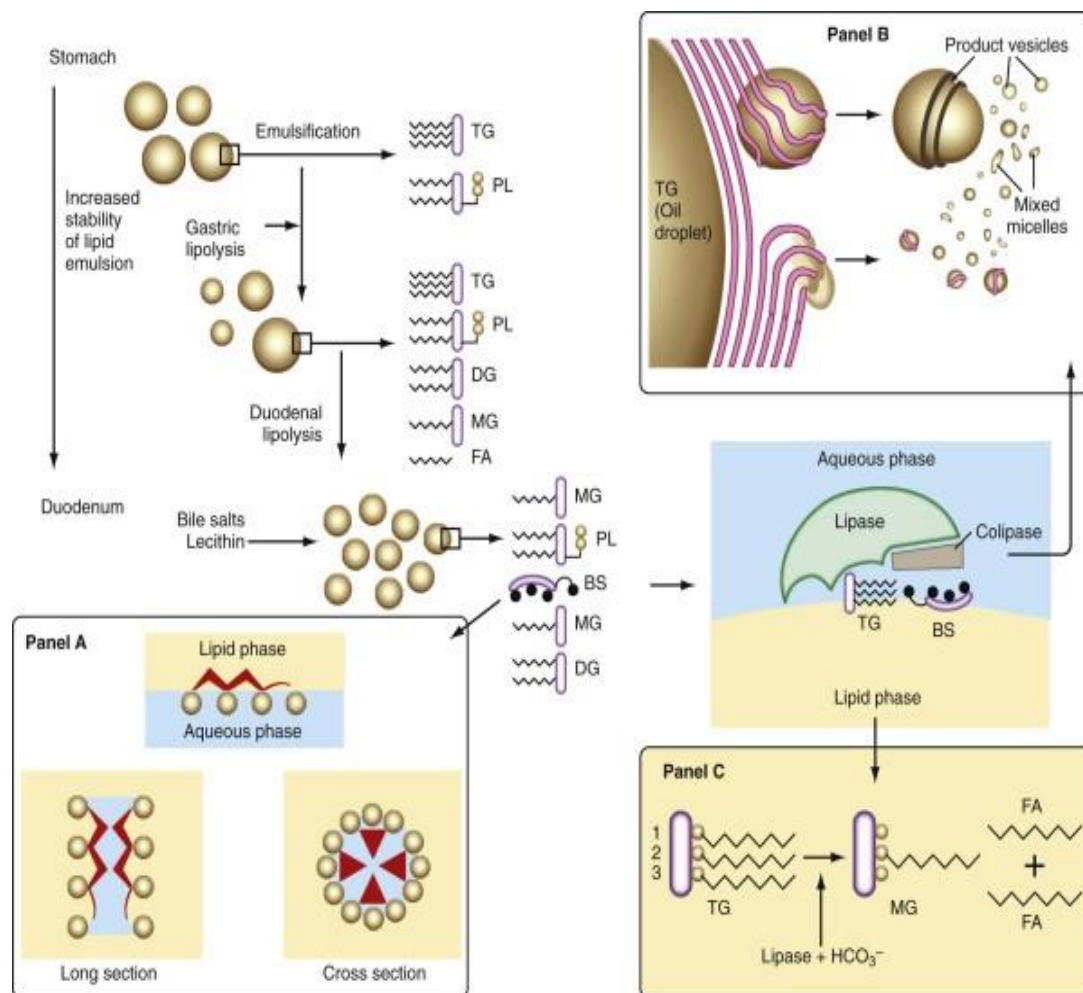


Figure 8. Steps in lipolysis.

- The initial step in lipolysis is to increase the stability of the fatty emulsion.
- Gastric lipase acts on triglycerides to yield fatty acids and diglyceride (diglyceride enhances emulsification).
- This step is enhanced in the duodenum by bile salts and phospholipid (lecithin), which enable lipase, in the presence of colipase, to act at the surface of the emulsion droplet to bring it close to the triglyceride molecule, whereupon monoglyceride and fatty acids are released.
- Lipolysis in the duodenum yields fatty acids (from the α_1 and α_3 positions) and monoglyceride and occurs in a rapid and efficient manner at nearly neutral pH.
- In *panel A* are diagrammatic representations of bile salt molecules (*top*) oriented at an oil-water interface with its hydrophobic sterolic backbone in the oil phase and its hydrophilic hydroxyl and either taurine or glycine conjugates in the aqueous phase. At concentrations above critical micellar concentration, bile salts aggregate as simple micelles in water, with their hydrophilic groups facing into the water.



- Three hydroxyl groups (cholate) are shown as *open circles* and an additional polar group represents either taurine or glycine.
- *Panel B* is a diagrammatic sketch of the dispersion of the products of lipolysis into lamellae at the surface of the oil phase, each about 4 to 5 nm thick, with water spacings up to 8 nm, and from there into vesicles of about 20 to 130 nm in diameter.
- In *panel C*, fatty acids and monoglyceride within the vesicles pass into mixed micelles.

Abbreviations: BS, bile salt; DG, diglyceride; FA, fatty acid; MG, monoglyceride; PL, phospholipid; TG, triglyceride.

This article was published in *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Feldman M, Friedman LS, Brandt LJ., Ninth Edition, Elsevier, Philadelphia, 2010, Figure 100-4, page 1700.

The topic of the absorption of bile acids, including enterohepatic circulation of bile acids, is covered in the Liver chapter.

3.3. Digestion and Absorption of Carbohydrates

Starch present in wheat, rice and corn is a polysaccharide whose molecular weight ranges from 100,000 to greater than 1,000,000. The straight chain of glucose molecules in starch is bridged by an oxygen molecule between the first carbon (C1) of one glucose unit and the fourth carbon (C4) of its neighbor (α -1,4 glucose link). This type of starch is called amylose. Similar in structure to glycogen (the major form of polysaccharide in animals), it makes up as much as 20% of the starch in the diet. The glucose-to-glucose bridge is of the alpha type – in contrast to the beta type, which connects glucose units in cellulose, an indigestible saccharide. These non-starch polysaccharides provide most of the “unavailable carbohydrate” in the diet, mainly as dietary fibers, (e.g., cellulose and hemicelluloses). Cellulose is comprised of non digested β -1,4-linked glucose in straight chains, and hemicelluloses is comprised of polymers of pentose and hexose with straight as well as branched chains. While amylases cannot break down the β -1,4 bond, some digestion is caused by colonic bacteria, resulting in short chain fatty acids (SCFAs) which are absorbed and become a source of energy. Other dietary fibers such as pectins, gums and alginates that may be partially hydrolyzed in the colon, while lignins are indigestible. Dietary fibers are active molecules that play an important role in altering the luminal content and mass, transit time and absorption of some nutrients.

The remaining 80% of the starch that humans ingest has a branch point every 25 molecules along the straight α -1,4 glucose chain. This starch is called amylopectin. These branches occur via an oxygen bridge between C6 of the glucose on the straight chain and C1 in the branched chain (α -1,6 branch points), which then continues as another α -1,4 glucose-linked straight chain (Figure 17).



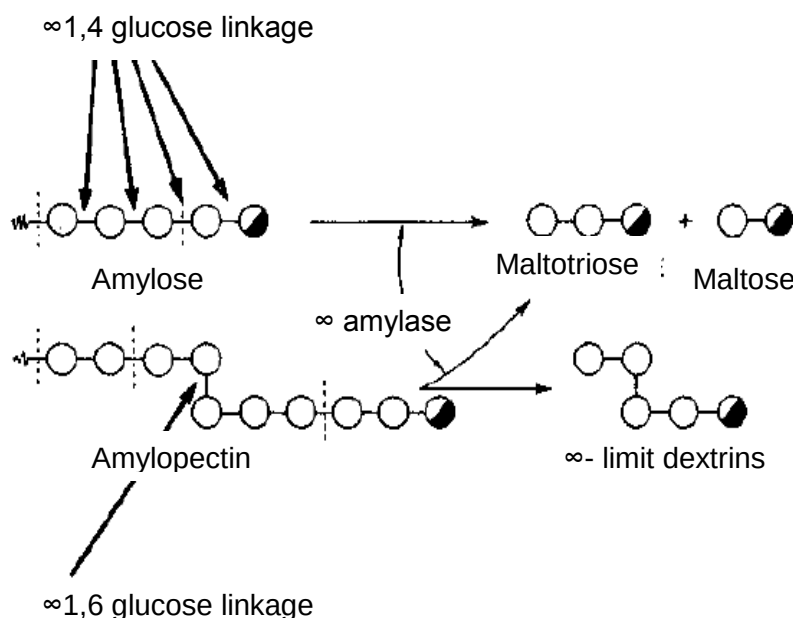


Figure 9. The action of pancreatic α -amylase on linear (amylose) and branched (amylopectin) starch. Circles indicate glucose residues and the reducing glucose unit.

Source: Gray GM. Mechanisms of digestion and absorption of food. In: Sleisenger MH, Fordtran JS (eds.), *Gastrointestinal disease: pathophysiology, diagnosis, management*. 3d ed. Philadelphia: WB Saunders, 1983:851.

Salivary and pancreatic α -amylases act on the interior α -1,4 glucose–glucose links of starch, but break down α -1,4 linkages close to a 1,6 branch point. Amylase proteins are encoded by a gene family on human chromosome 1 (i.e., AMY1 in the parotid gland, AMY2 in the pancreas). Salivary amylase acts in the mouth where slow chewing improves its action, while gastric acid leads to rapid inactivation of salivary amylase. Pancreatic amylase is the major enzyme of starch digestion and acts mainly within the intestinal lumen. The products of amylase digestion, are maltose and maltotriose. Since α -amylase cannot hydrolyze the 1,6 branching links and has relatively little specificity for 1,4 links adjacent to these branch points, large oligosaccharides containing five to nine glucose units and consisting of one or more 1,6 branching links are also produced by α -amylase action. These are called limit dextrins, and represent about 30% of amylopectin breakdown. The end products of amylase hydrolysis therefore are not single glucose molecules.

Digestion of the oligosaccharides, (including α -limit dextrins) occurs with the BBM enterocyte hydrolytic enzymes (Figures 10 and 11). BBM carbohydrases (disaccharidases and oligosaccharidases) hydrolyze sugars containing two or more hexose units (Table 3). They are present in highest concentration at the villous tips in the jejunum, and persist throughout most of the ileum, but not in the colon. Lactase (Lactase-phlorizin hydrolase, LPH) breaks down lactose into glucose and galactose. Maltase-Glucoamylase differs from pancreatic α -amylase since it sequentially removes a single glucose from the nonreducing end of a linear α -1,4 glucose chain, breaking down maltose into glucose.



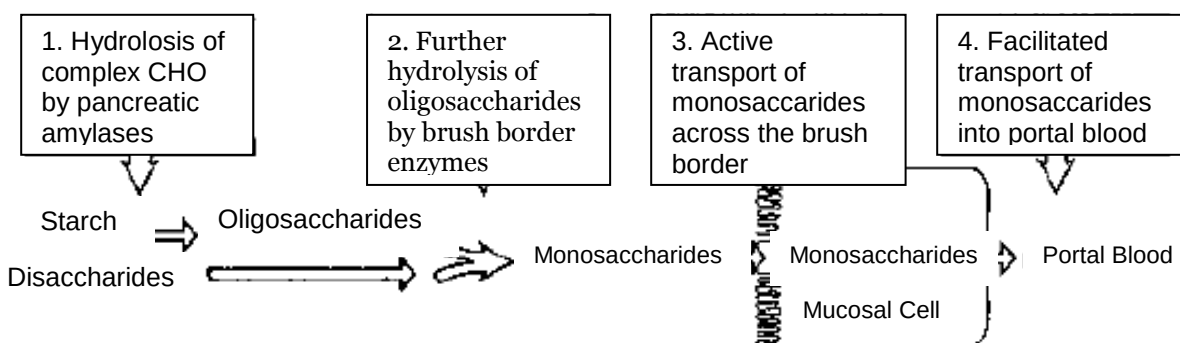


Figure 10. Major steps in the digestion and absorption of dietary carbohydrate.

Disaccharides $\longrightarrow$ Monosaccharides

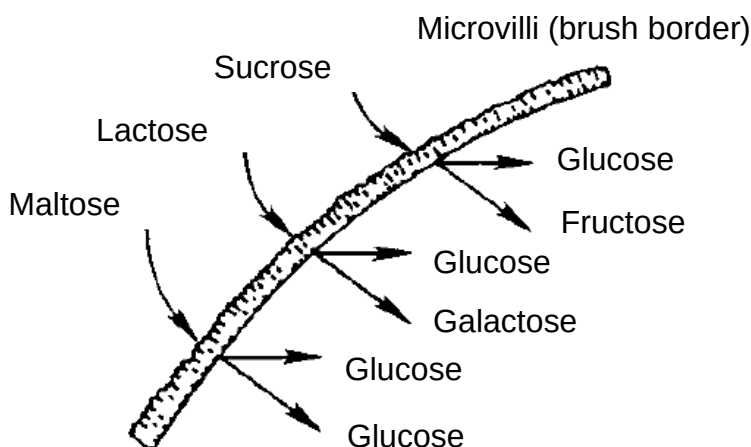


Figure 11. Disaccharides are split into monosaccharides at the brush border.

Sucrase-isomaltase is a hybrid molecule consisting of two enzymes – sucrase, hydrolyzing sucrose to glucose and fructose and the other, α -1,6 branch points of the α -limit dextrins. Isomaltase, which is the debrancher enzyme, hydrolyzing the 1,6-glycosidic linkage of α -limit dextrins. Both enzymes, acting as sucrase- α -dextrinase, act on α -limit dextrin's α -1,4 link at the nonreducing end, yielding glucose. The sucrase moiety thus breaks down sucrose into glucose and fructose.

We are born with a full complement of BBM disaccharidases (Table 4). Intake of large amounts of sucrose or starch increases sucrase activity. Starvation reduces SI protein and activity, which are rapidly restored by refeeding. In contrast, increasing the dietary load does not up-regulate manipulation can regulate the activities of



lactase or maltase. Disaccharidase enzymes are glycoproteins that are synthesized as proenzymes in the rough endoplasmic reticulum, then pass through the Golgi complex of the crypt and villus enterocytes for further processing. Lactase is completely processed when it is inserted into the BBM. Sucrase-isomaltase is inserted into the BBM, and is processed further by pancreatic proteases in the small intestinal lumen. In normal adult small intestine, these enzymes are expressed in the more well-differentiated villous cells compared to crypt cells and their activities are greater in the proximal compared to distal small intestine. Sucrase-isomaltase is encoded by a single gene located on chromosome 3 at locus 3q-25-26 while the lactase gene is located on the long arm of chromosome 2. Expression of SI depends upon steady-state levels of SI mRNA, as well as post-transcriptional and post-transcriptional regulation. Most regulation of LPH is by transcription.

Table 4. BBM carbohydrases

Enzyme	Substrate
➤ Lactase	• Lactose
➤ Maltase-glucoamylase	• α -1,4 linked oligosaccharides containing as many as 9 residues
➤ Trehalase	• Trehalose, α -limit dextrinase rapid hydrolysis of penta- and hexa- α -limit dextrans
➤ Sucrase-isomaltase (sucrase- α -dextrinase)	
- Sucrase	• Sucrose
- Isomaltase	• α -limit dextrin, α -1,6 link
- Both enzymes	• α -limit dextrin, α -1,6 link at nonreducing end

Once the disaccharides are broken down, the monosaccharides are absorbed. Glucose binds to the BBM carrier SGLT1, along with luminal Na^+ . The gene for SGLT1 is on chromosome 22. A single missense mutation in amino acid 28 (aspartate $\rightarrow$ asparaginase) is responsible for familial glucose-galactose malabsorption. Normally, intracellular Na^+ concentration is low because of BLM Na^+ , K^+ -ATPase pumping Na^+ out of the enterocyte. Two molecules of Na^+ that entered the enterocyte with one molecule of glucose moves down its concentration gradient, across the cytosol to the BLM, to be pumped out by Na^+ / K^+ -ATPase. The electrochemical gradient (PD) developed by Na^+ provides the driving force for glucose entry. This represents a secondary active transport process. Once the 2 Na^+ and 1 glucose molecule reach the cytosolic side of the BBM, glucose dissociates from the SGLT₁, then the 2 Na^+ come off the carrier. the ligand-free transporter changes its conformation, ready to again bind Na^+ and glucose in the intestinal lumen. This process is extremely rapid (turnover of SGLT₁ 1000 times a second at body temperature), and is responsible for the daily absorption of about 5 L of water (for every two Na^+ cations and two anions, plus one molecule of glucose, about 1100



molecules of water also cross the epithelium to maintain 150-osmolarity of the absorbate).

Fructose, released from the hydrolysis of sucrose, is transported by BBM GLUT5, a Na^+ -independent carrier. Small amounts of glucose (and other sugars) may be metabolized in the enterocyte. Glucose and fructose exit across the BLM and into the portal system by the non- Na^+ -dependent carrier, GLUT2.

In addition to SGLT₁ (high-glucose affinity Na^+ -dependent, phlorizin-sensitive transporter), there is a low affinity transporter. This may be SGLT₄, SGLT₆, or GLUT₂. GLUT₂ may quickly traffic to and be inserted into the BBM during a glucose-containing meal, to further facilitate glucose and fructose, especially when there is a meal resulting in large amounts of these sugars. Primary lactase deficiency is very common in certain ethnic groups, such as persons from South East Asia, and may limit the intake of milk in some adults. Secondary Deficiency of disaccharidases results from anatomic injury of the small intestine, as in celiac disease, tropical sprue and gastroenteritis. When disaccharidase levels are sufficiently low, the particular oligosaccharide or disaccharide remains unhydrolyzed within the intestinal lumen, and augments intraluminal fluid accumulation by virtue of its osmotic effect.

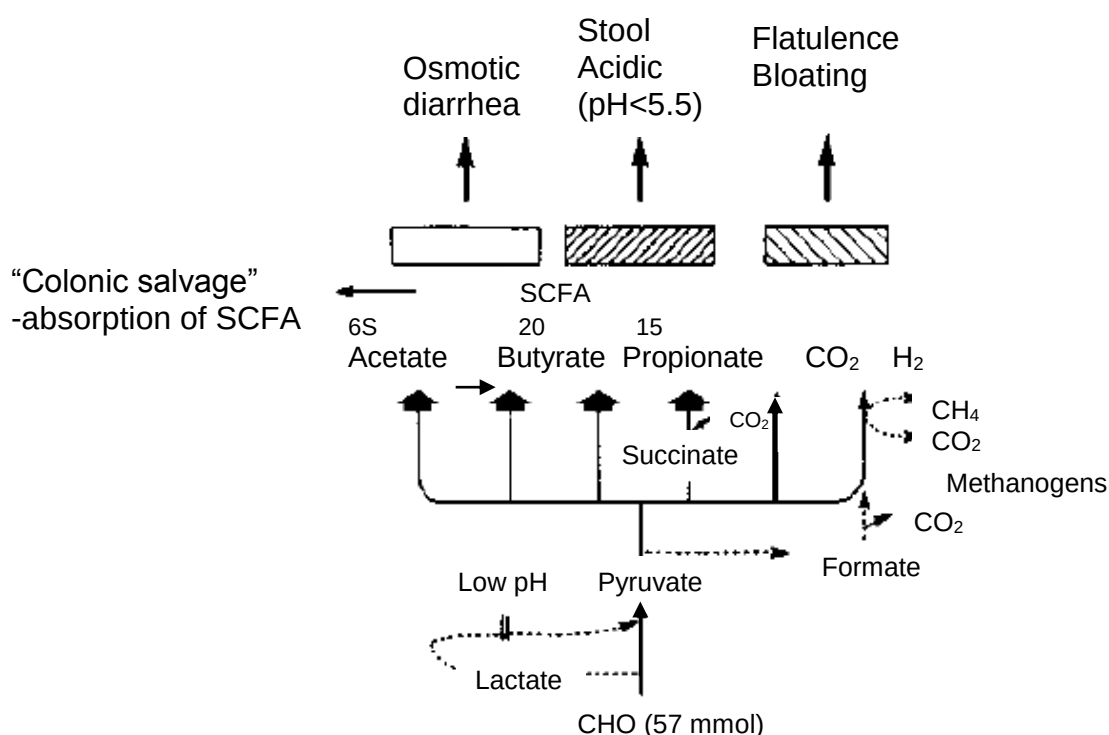


Figure 12. Intermediate and end products of anaerobic bacterial fermentation of carbohydrates. Minor pathways are depicted by dashed lines.

Source: Soergel KH. The role of the colon in case of inhibition of carbohydrate absorption. In: Creutzfeldt W, Fölsch UR (eds.), *Delaying absorption as a therapeutic principle in metabolic diseases*. Stuttgart and New York: Thieme Verlag, 1983:854.



Bacterial fermentation of disaccharides that reach the colon produces fatty acids, alcohols and gases (H_2 and CO_2) (Figure 12). The benefits of this bacterial fermentation to the host are twofold. First, reabsorption of fatty acids and alcohols in the colon “salvages” calories from malabsorbed carbohydrates. Second, this colonic “salvage” reduces the number of osmoles of the solutes in the lumen, and hence lessens the water lost in feces.

Although infants have a relative deficiency of amylase, starch is not fed for the first few months of life. In the adult, there is a great excess of pancreatic amylase secreted into the intestinal lumen, so that even in patients with severe fat malabsorption due to pancreatic exocrine insufficiency, residual salivary and pancreatic amylase output are usually sufficient to completely hydrolyze starch by the time a meal reaches the mid-jejunum. Hence, severe maldigestion of starch rarely occurs in humans.

3.4. Digestion and Absorption of Peptides and Amino Acids Derived from Protein

An average adult consumes about 70 g of protein daily. About half of the protein in the intestine is derived from endogenous sources, such as salivary, gastric and pancreatobiliary secretions, desquamated mucosal cells and exudated plasma proteins.

Protein digestion is initiated in the stomach. Pepsinogen release from gastric chief cells is stimulated by gastrin, histamine and acetylcholine. Pepsins are derived from precursor pepsinogens; autoactivation of secreted pepsinogens in the acidic pH with loss of a small basic peptide, producing pepsin. Pepsin hydrolysis of proteins results in a peptide mixture with a small amount of amino acids (AAs). This mixture is emptied into the duodenum. Pancreatic amylase is secreted in an active form, but pancreatic proteases are secreted as proenzymes that require luminal activation. Enterokinase released from the enterocyte BBM converts trypsinogen to trypsin, in the duodenal lumen. Trypsin, in turn, activates other proteases, and autocatalyzes its own further activation from trypsinogen. Proteases have been classified into endopeptidases (trypsin, chymotrypsin, elastase), which split internal peptide bonds, or exopeptidases (carboxypeptidases A and B), which remove single AAs from the carboxyl-terminal end of peptides (Figure 3). The final products of luminal protein digestion consist of neutral and basic AAs (about 30%), as well as oligopeptides of 2 to 6 amino acids (about 70%).



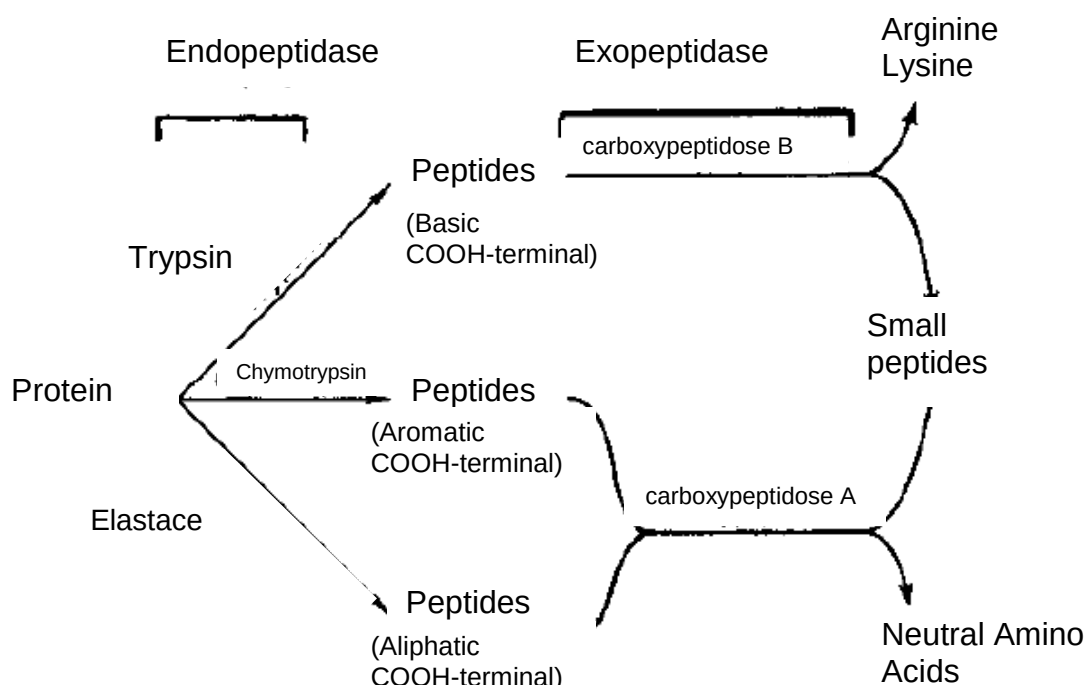


Figure 13. Sequence of events leading to hydrolysis of dietary protein by intraluminal proteases.

Source: Gray GM. Mechanisms of digestion and absorption of food. In: Sleisenger MH, Fordtran JS (eds.), *Gastrointestinal disease: pathophysiology, diagnosis, management*. 3d ed. Philadelphia: WB Saunders, 1983:854.

Peptidase activities are present in the enterocyte BBM and cytoplasm. Oligopeptides are hydrolyzed by BBM peptidases, but dipeptides and tripeptides are either hydrolyzed by the BBM or are absorbed intact and then hydrolyzed by the cytoplasmic peptidases. Most peptidases are aminopeptidases that remove an amino acid residue from the peptide amino terminus. Proline-specific carboxypeptidases and another dipeptidylaminopeptidase IV (DAP IV) have not been identified in the BBM and cytoplasm along with a cytoplasmic proline-specific enzyme. Most of the BBM peptidases are synthesized in the ER and Golgi complex, and are inserted in the BBM as glycoproteins.

Dipeptides, tripeptides and some tetrapeptides are absorbed intact into the enterocytes, AAs are more efficiently transported as peptides than as single amino acids, ie, there is a transport kinetic advantage of peptides over amino acids. Curiously, AAs in the duodenal lumen inhibits the hydrolysis of peptides (product inhibition), and the absorption of both amino acids and peptides is reduced by glucose and acid in the duodenal lumen. Because of this alternate small peptide pathway, patients with inherited basic or neutral aminoacidurias (e.g., cystinuria, Hartnup's disease) are able to absorb sufficient amino acids through intact peptide transport that protein deficiency states do not develop.



Adjacent to the BBM is an acid microclimate, which creates a BBM H^+ gradient. This is maintained by a BBM Na^+/H^+ - exchanger and the BLM Na^+/H^+ -ATPase. A single hydrogen ion is transported with peptide by a hydrogen-peptide cotransporter (hPepT₁). hPepT₁ transports neutral, anionic and cationic dipeptides. Note that hPepT₁ does not use a Na^+ electrochemical gradient, but rather the driving force achieved by a H^+ -gradient: in the enterocyte cytosol, the H^+ is released from the hPepT₁- H^+ complex, and diffuses back across the BBM and into the lumen. The peptides transported by hPepT₁ are hydrolyzed by cytoplasmic peptidases. AAs absorbed primarily, by active carrier-mediated processes in the BBM. The L-isomers of the AAs are preferentially absorbed. Transport of AAs and rarely some peptides occurs across the BLM into the portal circulation.

There are 20 AAs and at least seven BBM four for neutral AAs, the NBB system, the PHE system for phenylalanine and methionine, the imino system for imino acids, and a fourth system for beta AA. There is a separate BBM transporter for basic and one for acidic AA, four BLM AA transporters. A small amount may be absorbed by passive diffusion, but most AA absorption is mediated by a Na^+ -dependent gradient. SLC 36A₁, aka the human PAT₁ (human proton-coupled amino acid transporter 1) in the BBM transports the imino acids proline and hydroxyproline as well as glycine, proline, alanine, taurine PAT₁, also uses a H^+ electrochemical gradient.

4. Absorption of Salt and Water

4.1. Passive Permeation

The epithelium of the small intestine exhibits a high passive permeability to salt and water that is a consequence of the leakiness of the tight junctions between epithelial cells. The ileum is less permeable to ions than is the jejunum, and the colon is even less permeable with the reaction being “tighter” than the cecum. In the small intestine most water absorption occur as the result of carrier-mediated transport of solutes. Osmotic equilibration between plasma and lumen is rapid; as a result, large differences in ion concentration do not really develop. These intercellular junctions are more permeable to cations than anions, so that lumen-to- blood concentration differences for Na^+ and K^+ are generally smaller than those for Cl^- and HCO_3^- . One consequence of this lower passive ionic permeability (higher electrical resistance) is that electric potential differences across the colonic epithelium are an order of magnitude greater than those in the small intestine (remember Ohm’s law, $E = IR$, where E is electrical potential, I is electrical current, and R is electrical resistance). Active Na^+ absorption, which is the main transport activity of the distal colon, generates a serosapositional charge or potential difference (PD). Under the influence of aldosterone (i.e., salt depletion), this PD can be 60 mV or even higher. A 60 mV PD will thus sustain a 10-fold concentration difference for a monovalent ion such as K^+ . Most of the high K^+ concentration in the rectum is accounted for, therefore, by the PD.

Water and some small water-soluble solutes can pass across the mucosal barrier formed by the enterocytes. There are four types of structures in this paracellular pathway (Table 5).



Learning Points:

- Movement of an uncharged particle is determined by concentration gradients
- Movement of charged particles (ions) is determined by electrochemical gradients
- Permeability is higher and transepithelial resistance is lower in proximal versus distal intestine, and in the crypts versus than the villi
- The electrical potential inside the enterocyte is negative as compared with the outside, with the intracellular electronegativity creating a driving force more powerful than the chemical concentration gradient, e.g. Cl^- driven out of the cell by intracellular negativity, despite lower intracellular than extracellular concentration
- Water is absorbed largely in association with the carrier-mediated absorption such as SGLT1 in the BBM, possibly by aquaporin membrane proteins in the small and large intestine, and by solvent drag across the paracellular pathway



Table 5. Composition and Function of Components of the Paracellular Pathway

Components of paracellular pathway	Membrane Proteins	Scaffolding Proteins	Function
ZO	Claudins JAMs Occludins	-ZO-1, ZO-2, ZO-3 -MUPP1	-influence charge-selectivity of TJs -vesicular transport via GTPase of the Ras superfamily -activation of molecules regulating PAR-3/-6 and a PKC -modify paracellular permeability
ZA	Cadherins (mostly E-) Catenins	-Actin cytoskeleton molecules; α -actinin, radixin, vinculin -Rab, SRC, yes	-cell-to-cell adherence -maintain cell polarity -intracellular signaling -changes in cadherins-catenins -may influence carcinogens
DES	Cadherin-like proteins	-Intermediate filaments -dense plaque of intracellular anchor proteins	
GJ	Connexins		-exchange of small molecules from one neighboring cell to another through connexin hemichannel

Abbreviations:

ZA, zona adherens
 ZO, zona occludens (aka Tight Junctions [TJs])
 DES, desmosome
 GJ, gap junction
 JAMs, junctional adhesional molecules

ZO-1, -2, -3, zona occludens proteins
 GTPase, guanosine triphosphatase
 PAR-3/-6, partition defective protein
 aPKC, atypical protein kinase C



4.2. Nutrient Dependent

SGLT₁ is high affinity, low capacity, whereas the GLUT₂ recruited to the BBM by a glucose containing meal (SGLT₁ activation, protein kinase activation) is low-affinity, high-capacity. SGLT₁ may also be a type of water channel, transporting 210 molecules of water with each 2 of Na⁺ and 1 of glucose—the explanation for the effectiveness of ORS. Some water may also pass through the paracellular pathway: with transcellular glucose transport by SGLT₁, the actomyosin ring in the terminal web contracts, the transport of glucose across the BLM by GLUT₂ generates a small (3 mOsm) gradient, and water flows.

The BBM processes for nutrient absorption of glucose and neutral amino acids are Na⁺-dependent. The sodium pump (Na⁺/K⁺-ATPase), located in the BLM of the enterocyte, extrudes Na⁺ that has entered the enterocyte from the lumen, thereby maintaining a low intracellular Na⁺, a high intracellular K⁺, and a negative intracellular PD. This Na⁺/K⁺ pump provides the energy for uphill sugar and amino acid absorption across the BBM.

Glucose is cotransported with Na⁺ by way of the BBM Na⁺-dependant sugar transporter SGLT1 (Figure 14). Persons with intestinal secretory diseases such as cholera absorb glucose normally. Na⁺ (and thus water) are also absorbed with glucose, so that the secretory fluid losses incurred by these patients can be replaced by oral glucose-electrolyte solutions (e.g.; ORT, oral replacement therapy). Intravenous fluids may therefore not be needed unless the patient is semiconscious, or too nauseated to drink the necessary large volumes of ORT to correct the dehydration arising from the diarrhea.

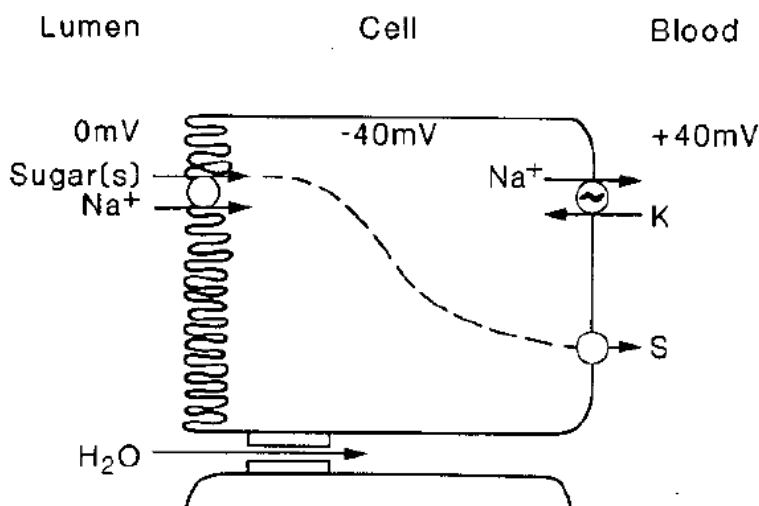


Figure 14. Na⁺-coupled sugar absorption in the small intestine. This model presents the mechanism for sodium-coupled absorption of sugar. In addition to sugar, many amino acids, certain B vitamins and bile salts are absorbed through this mechanism. Sodium is taken up across the membrane

in association with glucose (SGLT1) and exits by means of the basolateral sodium/potassium-ATPase. Glucose exits through a facilitated diffusion pathway in the basolateral membrane (GLUT2). Details of the model are described next.

4.3. Nutrient-Independent

Nutrient-independent active absorption of electrolytes and water by intestinal epithelial cells occurs through mechanisms located along the small and large intestine. All of these mechanisms have a requirement for luminal Na⁺ and for BLM



Na^+/K^+ -ATPase. In the distal colon (Figure 15), the BLM contains Na^+ channels. Na^+ entering through these channels is then extruded across the BLM by the Na^+/K^+ -ATPase pump. Aldosterone quickly increases the number of these BBM Na^+ channels, and more slowly increases the number of BLM Na^+/K^+ -ATPase pumps. As a result, Na^+ absorption is enhanced in the distal colon.

Chloride (Cl^-) is absorbed along with Na^+ , and traverses the epithelium by both cellular and paracellular routes. The transcellular route involves a $\text{Cl}^-/\text{HCO}_3^-$ exchanger in the BBM, and Cl^- channels in the BLM. Intracellular mediators such as cyclic AMP (cAMP) do not affect these Na^+ channels. Thus, patients with secretory diarrheas, who are salt-depleted and therefore have elevated blood levels of aldosterone, are able to reabsorb some of the secreted Na^+ and fluid.

In the more proximal colon and in the ileum, the luminal membrane contains Na^+/H^+ exchangers (NHE) that permit net Na^+ entry (Figure 16). The colon and the ileum (but not the jejunum) also have $\text{Cl}^-/\text{HCO}_3^-$ exchangers in their luminal membranes. The intracellular pH adjusts the relative rates of the anion and cation exchangers. Thus, H^+ extrusion by Na^+/H^+ exchange results in cell alkalinization, which then stimulates Cl^- entry and HCO_3^- extrusion by the $\text{Cl}^-/\text{HCO}_3^-$ exchange. The $\text{Cl}^-/\text{HCO}_3^-$ exchanger then increases intracellular H^+ , thereby sustaining further Na^+/H^+ exchange.

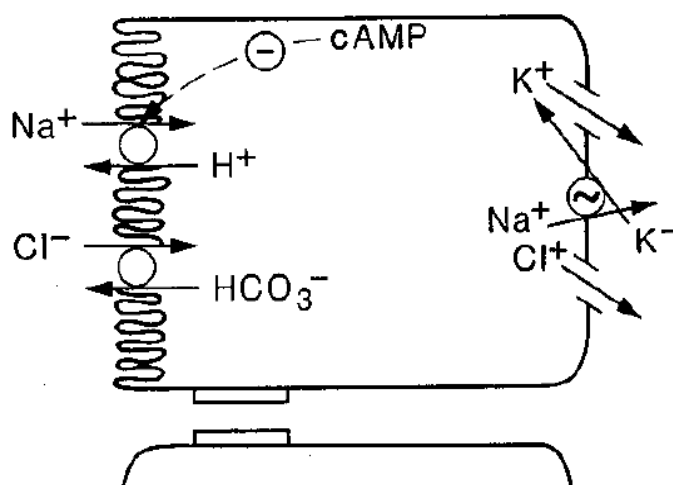


Figure 15. Electroneutral sodium chloride absorption in the small intestine and colon. Apical sodium chloride entry through sodium/hydrogen and chloride/bicarbonate permits sodium and chloride to enter the cell in an electroneutral fashion. Sodium exits the cell through the basolateral sodium/potassium-ATPase. The route of chloride efflux remains relatively speculative, but likely occurs through some basolateral channel.

Increases in cell concentrations of cAMP and free Ca^{2+} inhibit the Na^+/H^+ exchange. Cyclic AMP and its agonists thereby cause cell acidification, which in turn inhibits $\text{Cl}^-/\text{HCO}_3^-$ exchange. Electrolyte absorption in the small intestine and proximal colon are down-regulated by hormones, neurotransmitters and some luminal substances (e.g. bacterial enterotoxins, bile salts, hydroxylated fatty acids)



that increase cell concentrations of cAMP or free Ca^{2+} . For this reason, body fluid secreted in response to these stimuli cannot be effectively reabsorbed in the absence of amino acids and sugars, except in the distal colon. In the jejunum, where there is no $\text{Cl}^-/\text{HCO}_3^-$ exchange, Na^+/H^+ exchange can be well sustained by anaerobic glycolysis, which generates H^+ as well as some ATP.

4.4. Na^+ -channel

The entry of Na^+ through the Na^+ -specific channels (ENaCs) in the luminal membrane of the distal colon and rectum occurs down a Na^+ electrochemical gradient created by the Na^+/K^+ pump in the basal membrane. ENaCs are stimulated by increased synthesis by mineralocorticoids (aldosterone) and increased exocytosis by cAMP and vasopressin, and are inhibited by increases in the intracellular concentrations of calcium (iCa^{2+}). Aldosterone and cAMP also increase ENaCs by blocking the association of ENaCs with Nedd4-2, a ubiquitin protein ligase, which leads to the degradation of ENaCs: less Nedd4-2 association, less breakdown of ENaC, more remaining ENaC activity (Figure 16).

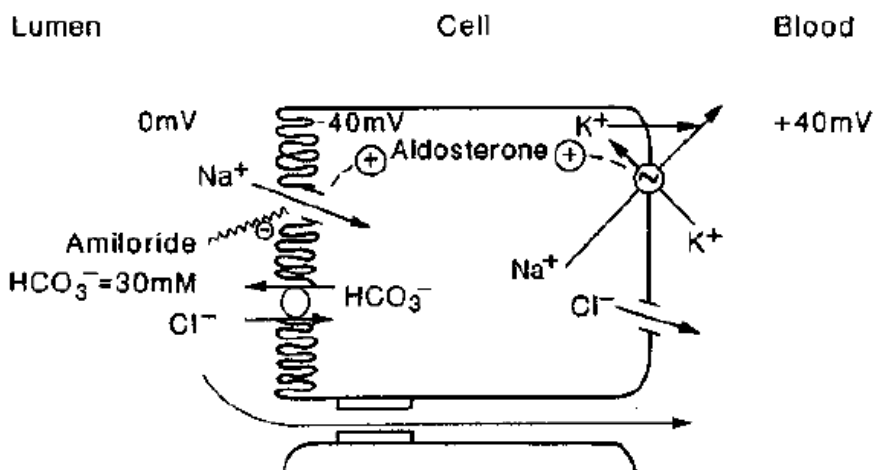


Figure 16. Electrogenic Na^+ absorption in the distal colon. Sodium enters the cell at the apical membrane through sodium channels and leaves the cell at the basolateral membrane through the sodium/potassium-ATPase. Details of the model are described in the text.

4.4.1. NHE, Na^+/H^+ exchangers

The modestly acidic intracellular environment (H^+ -gradient) and the Na^+ -gradient across the BBM created by the Na^+/K^+ -ATPase in the BLM pumping Na^+ out of the cell, creates the conditions for the functioning of the sodium-hydrogen exchangers (NHE). This electroneutral process (exchange of Na^+ into and H^+ out of the cell) is more active during fasting than feeding. The NHE-1 is uniformly present along the villus-crypt unit (Figure) is on the BLM of the enterocytes and regulates intracellular pH, cell volume and growth. NHE-3 and NHE-2 are on the apical membrane and mediate electroneutral Na^+ absorption in the small intestine, and NHE-2 is mainly in the proximal colon.



The 10 isoforms of NHE are modulated differently by endocrine, paracrine and neural stimulations and include NHERFs (NHE regulatory factors), kinases and phosphatases. For example, NHE-3 is upregulated by glucocorticoids acting through SGK₁, a serum and glucocorticoid inducible kinase. NHE-3 is down-regulated by cAMP, through activation of protein kinase A, NHERF₁ and NHERF₂, and ezrin, a cytoskeleton protein. cGMP is also inhibitory of NHE-3.

4.4.2. Electrochemical NaCl absorption

Electroneutral NaCl absorption in the ileum and proximal colon is achieved through the coupling of Na⁺ absorption to Cl⁻ absorption, through a Cl⁻/HCO₃⁻ exchanger, Cl⁻ moving into the cell (giving electroneutral NaCl absorption), and HCO₃⁻ moving HCO₃⁻ out of the cell, to combine with H⁺ to form H₂O. Cl⁻ also moves through the paracellular pathway in the jejunum, as the result of the transepithelial lumen PD-negative gradient.

4.4.3. Bicarbonate (HCO₃⁻) transport

HCO₃⁻ is formed from intracellular metabolism, and cytoplasmic HCO₃⁻ also arises from diffusion of CO₂ into the enterocyte or colonocyte, or from the BLM Na⁺/HCO₃⁻ cotransporter. HCO₃⁻ is secreted by electrogenic as well as by electroneutral processes. Electroneutral Cl⁻/HCO₃⁻ exchange is the major process of HCO₃⁻ absorption, achieved by apical Cl⁻/HCO₃⁻ exchangers. CFTR and other apical anion channels result in electrogenic secretion of HCO₃⁻.

4.4.4. Chloride secretion and absorption

Water secretion is achieved by way of chloride (Cl⁻) secretion (Figure 17). The BLM NKCC1 transports 2Cl⁻, 1Na⁺ and 1K⁺ into the secretory cell, such as the crypt enterocyte. The Na⁺ is pumped out of the cell by the BLM Na⁺ pump; the K⁺ leaves the cell through the BLM K⁺ channel. Na⁺ and H₂O cross through the paracellular pathway into the intestinal lumen, where the Cl⁻ channel combines with the paracellular pathway of Na⁺.

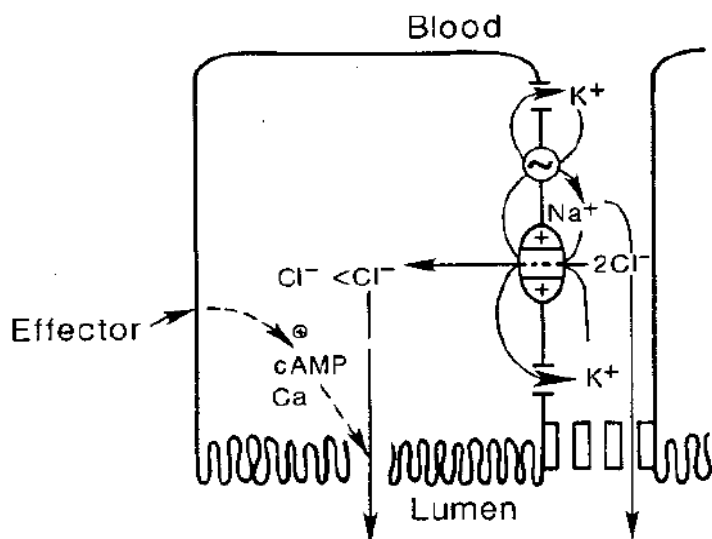


Figure 17. Electrogenic chloride secretion in both small and large intestine. A cyclic AMP-activated channel in the apical membrane permits hormone-stimulated chloride secretion. the chloride channel is coded by a gene (cystic fibrosis transmembrane conductance regulator [CFTR]) that is responsible for cystic fibrosis. Chloride enters the cell through a sodium/potassium transport along the basolateral surface. Details of this model are



discussed in the text.

There are at least three classes of classes of Cl^- channels, the best known of which is CFTR. CFTR belongs to the ABC (ATP binding cassette) protein family. CFTR activity is increased by protein kinase A (PKA) activation of the R domain of CFTR, increasing gating and activity of the Cl^- channel, as well as recruiting the insertion of CFTR into the apical membranes. In persons suffering from cholera, the organism *Vibrio cholerae* produces several toxins which stimulate BLM adenylyl cyclase, increase cytoplasmic cAMP, which stimulates secretion through the BBM Cl^- channel (CFTR), and reduces Na^+ absorption. Drugs are being developed to inhibit or to stimulate CFTR, for purposes of treating diarrhea or constipation, respectively.

The calcium-activated Cl^- (CLCA) channels are Cl^- channels involved in rotavirus-associated diarrhea. Cl^- secretion across the BLM of the enterocytes is accomplished through the K^+ channels, the cAMP-activated $\text{KCNE}_3/\text{KCNQ}_1$ channels and the Ca^{2+} -calmodulin-activated KCNN4 channels.

4.4.5. Potassium (K^+) transport

Despite the high fecal K^+ level, little K^+ is lost in the stool, since stool volume (about 200–300 mL per day) is normally so low. With high-volume diarrhea of small bowel origin, stool K^+ loss is because of the large volumes involved. In such states, the stool K^+ concentration is low (and the Na^+ concentration relatively high) because diarrheal fluid passes through the colon too rapidly to equilibrate across the colonic epithelium.

The lumen-negative PD in the small intestine provides the driving force for passive K^+ absorption. The H^+ , K^+ -ATPase pumps in the luminal membrane of the distal large intestinal colonocytes actively transports K^+ . Cl^- secretion across the BLM of the enterocytes is accomplished through the K^+ channels, the cAMP-activated $\text{KCNE}_3/\text{KCNQ}_1$ channels and the Ca^{2+} -calmodulin-activated KCNN4 channels.

4.5. Regulation of Electrolyte Absorption

Intestinal ion transport is regulated by luminal contents, autocrine factors, as well as by PINES, extracellular factors from Paracrine, Immunologic, Neural, and Endocrine Systems. There is integration of the ENS, GALT/MALT (Gut-Associated Lymphoid Tissue, and Mucosa-Associated Lymphoid Tissue), interneurons in the myenteric or submucosal plexuses, epithelial cells and blood vessels. There are agonists of electrolyte absorption (Table 6) and secretion (Table 7) and the balance between absorption and secretion determination the net absorption/ secretion.

Table 6. Agents that stimulate intestinal absorption of fluid and electrolytes

Endogenous Absorbagogues

- α -Adrenergic agonists
- Aldosterone
- Angiotensin
- Enkephalins

Pharmacologic agents

- Berberine
- Clonidine (α_2 -agonist)
- Cyclooxygenase inhibitors
- Glucocorticoids



- Glucocorticoids
- Growth hormone
- Neuropeptide Y
- Peptide YY
- Prolactin
- Short-chain fatty acids
- Somatostatin
- Lithium
- Mineralocorticoids
- Octreotide
- Opiates
- Propanolol
- Octreotide

Table 7. Endogenous agonists of intestinal secretion and their intracellular mediators

Intracellular Mediator	Agonist
➤ Ca^{2+}	○ Acetylcholine ○ Bombesin ○ Galanin ○ Gastrin ○ Histamine ○ Motilin ○ Neurotensin ○ Serotonin ○ Substance P
➤ cAMP	○ Adenosine ○ Arachidonic acid ○ Bradykinin ○ Peptic histidine isoleucine ○ Platelet activating factor ○ Prostaglandins ○ Reactive oxygen metabolites ○ Secretin ○ Vasoactive intestinal polypeptide
➤ cGMP	○ Atrial natriuretic peptide ○ Guanylin ○ Nitric oxide
➤ Miscellaneous	○ Calcitonin, calcitonin gene-related peptide ○ Gastric inhibitory polypeptide ○ Leukotrienes



Table 8. Cells secreting endogenous agonists of intestinal secretion

➤ ENS	○ Acetylcholine ○ Calcitonin, calcitonin gene-related peptide ○ Neurotensin ○ Peptic histidine isoleucine ○ Serotonin ○ Substance P ○ Vasoactive intestinal polypeptide
➤ Immune cells	○ Adenosine ○ Arachidonic acid ○ Bradykinin ○ Histamine ○ Leukotrienes ○ Motilin ○ Nitric oxide ○ Platelet activating factor ○ Prostaglandins ○ Reactive oxygen metabolites
➤ Endocrine cells	○ Gastrin ○ Motilin ○ Secretin
➤ Mesenchymal cells	○ Nitric oxide ○ Prostaglandins

Abbreviations: cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ENS, enteric nervous system.

Adapted from. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 99.2, page 1687, Ninth Edition, 2010.

4.6. Active Electrolyte Secretion Along the Intestine

In the secretory cell, the entry of Cl^- is coupled to that of Na^+ and probably also K^+ by a triple cotransporter with a stoichiometry of 1 Na^+ , 1 K^+ and 2 Cl^- . Na^+ entering in this fashion is then recycled to the contraluminal solution by the Na^+/K^+ exchange pump (Figure 17). K^+ , diffuses back through K^+ channels.

Because of the Na^+ gradient, Cl^- accumulates above the electrochemical equilibrium and can either 1) recycle back to the contraluminal side of the cell through the $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ cotransporter, or through BLM Cl^- channels, or 2) Cl^- may be secreted into the lumen through luminal membrane Cl^- channels. When Cl^- is secreted into the lumen it generates a serosa-positive PD, which provides the driving force for Na^+ secretion through the paracellular pathway between cells. In the resting



crypt secretory cell, the luminal Cl^- channels are closed. Secretion is stimulated by opening the Cl^- “gate” in the luminal membrane of the secretory cell.

There are numerous intracellular mediators of secretion such as cAMP, cGMP and Ca^{2+} (Tables 7 and 8). These arise from the blood, nerve endings, endocrine cells in the epithelium, mesenchymal elements (e.g. lymphocytes, plasma cells and mast cells), or the enterocytes themselves. Except for the cAMP agonists, lipoxygenase products and calcitonin, the actions of the other agonists are short-lived, desensitization develops rapidly, and they fine-tune electrolyte transport rather than invoking persistent secretion.

There are also agonists which inhibit secretion and/or stimulate absorption. These include adrenocorticosteroids, norepinephrine, somatostatin, enkephalins and dopamine. Glucocorticoids enhance electrolyte absorption throughout the intestinal tract, but the mechanisms involved are less well understood than for aldosterone. Steroids may act in part by inhibiting phospholipase A2 and therefore the arachidonic acid cascade. The adrenergic receptors on enterocytes are almost exclusively alpha 2 in type. The sympathetic nervous system in the intestinal mucosa releases norepinephrine (an alpha 2 antagonist) and so inhibits electrolyte secretion and stimulates absorption. Sympathectomy, whether chemical or surgical, leads to diarrhea. Diabetics with autonomic neuropathy sometimes develop persistent diarrhea that is associated with degeneration of adrenergic nerve fibers to the gut. An imbalance between the normal physiological levels of water and electrolyte absorption and secretion leads to diarrhea. This clinical topic is discussed in a later section.



Chapter 7: The Small Intestine Intestinal Digestion and Absorption in Disease

A.B.R. Thomson and H.J. Freeman



1. Malabsorption

1.1. Clinical Signs and Symptoms

There are numerous orders that cause malassimilation (Table 1). “Malabsorption” is the term that is usually used clinically to describe all processes that result in reduced delivery of nutrients to the portal circulation and/or lymphatics. “Malabsorption” in this context is strictly speaking not a correct term, since it may result from abnormal digestion or deranged enterocyte metabolism or delivery of nutrients is complex, so it is not surprising that many diseases may result in malabsorption. There are numerous signs and symptoms which may suggest the presence of malabsorption process or syndrome (Table 2), and this may lead to deficiencies of specific vitamins and minerals, leading to unique clinical manifestation (Table 3).

Table 1. Classification of malassimilation syndromes

Defective intraluminal digestion	Defective intramural absorption
○ Mixing disorders ○ Postgastrectomy ○ Pancreatic insufficiency ○ Primary ○ Cystic fibrosis ○ Secondary ○ Chronic pancreatitis ○ Pancreatic carcinoma ○ Pancreatic resection ○ Reduced intestinal bile salt concentration ○ Liver disease ○ Hepatocellular disease ○ Cholestasis (intrahepatic or extrahepatic) ○ Abnormal bacterial proliferation in the small bowel ○ Afferent loop stasis ○ Strictures ○ Fistulas ○ Blind loops ○ Multiple diverticula of the small bowel ○ Hypomotility states (diabetes, scleroderma, ○ intestinal pseudo-obstruction) ○ Interrupted enterohepatic circulation of bile salts ○ Ileal resection ○ Ileal inflammatory disease (regional ileitis)	○ Inadequate absorptive surface ○ Intestinal resection or bypass ○ Mesenteric vascular disease with massive intestinal resection ○ Regional enteritis with multiple bowel resections ○ Jejunioileal bypass ○ Mucosal absorptive defects ○ Biochemical or genetic abnormalities ○ Celiac disease ○ Disaccharidase deficiency ○ Hypogammaglobulinemia ○ Abetalipoproteinemia ○ Hartnup disease ○ Cystinuria ○ Monosaccharide malabsorption ○ Inflammatory or infiltrative disorders ○ Regional enteritis ○ Amyloidosis ○ Scleroderma ○ Lymphoma ○ Radiation enteritis ○ Eosinophilic enteritis ○ Tropical sprue ○ Infectious enteritis (e.g., salmonellosis) ○ Collagenous sprue ○ Nonspecific ulcerative jejunitis ○ Mastocytosis ○ Dermatologic disorders (e.g., dermatitis herpetiformis)



- Drugs (by sequestration or precipitation of bile salts)
 - Neomycin
 - Calcium carbonate
 - Cholestyramine
 - Lymphatic obstruction
 - Intestinal lymphangiectasia
 - Whipple's disease
 - Lymphoma
-

Table 2. Clinical signs and symptoms of malassimilation

➤ Clinical sign or symptom	Deficient nutrient
○ General Weight loss	– calories
○ Loss of appetite, amenorrhea	– protein, energy
○ Decreased libido	– general malnutrition
○ Skin Psoriasiform rash	– zinc
○ Eczematous scaling	
○ Pallor-Folate	– iron, vitamin B12
○ Follicular hyperkeratosis	– vitamin A
○ Perifollicular petechiae	– vitamin C
○ Flaking dermatitis	– protein, energy, niacin, riboflavin, zinc deficiency
○ Bruising	– vitamin K
○ Pigmentation changes	– niacin, protein, energy
○ Scrotal dermatosis	– riboflavin
○ Thickening and dryness of skin	– linoleic acid
○ Head Temporal muscle wasting	– protein, energy
○ Hair Sparse and thin:	dyspigmentation – protein
○ Night blindness	– vitamin A
○ Photophobia, blurring	– riboflavin, vitamin A
○ Corneal vascularization	– riboflavin
○ Xerosis, Bitot's spots	– vitamin A, keratomalacia
○ Mouth Glossitis	– riboflavin, niacin, folic acid
○ Bleeding gums	– vitamin C, riboflavin
○ Cheilosis	– riboflavin
○ Angular stomatitis	– riboflavin, iron
○ Hypogeusia	– zinc
○ Tongue fissuring	– niacin
○ Tongue atrophy	– riboflavin, niacin, iron
○ Scarlet and raw tongue	– niacin
○ Nasolabial seborrhea	– pyridoxine
○ Neck Goiter	– iodine
○ Parotid enlargement	– protein
○ Thorax Thoracic "rosary"	– vitamin D



➤ Clinical sign or symptom Deficient nutrient

○ Abdomen Diarrhea - niacin, folate, vitamin B12	○ Nails Flattening, brittleness, luster loss, spooning - iron
○ Distention – protein, energy	○ Transverse lines - protein
○ Hepatomegaly – protein, energy	○ Neurologic Tetany - calcium, magnesium
○ Extremities Edema - protein, thiamine	○ Paresthesias - thiamine, vitamin B12
○ Softening of bone - vitamin D, calcium, phosphorus	○ Loss of reflexes, wrist drop - thiamine, foot drop
○ Bone tenderness - vitamin D	○ Loss of vibratory and position, sense, ataxia - vitamin B12
○ Bone ache, joint pain - vitamin C	○ Dementia, disorientation - niacin
○ Muscle wasting and weakness - protein, energy	○ Blood Anemia - iron, vitamin B12, folate
○ Muscle tenderness, muscle pain - thiamine	○ Hemolysis - phosphorus
○ Hyporeflexia - thiamine	
-

Carbohydrate malassimilation may result in excess flatus and the associated symptom of borborygmi distention or bloating. Malabsorbed carbohydrates that enter the colon are fermented by colonic bacteria to gases (CO₂, H₂ and CH₄) and organic acids. These organic acids produce diarrhea by malassimilation. These gases produce flatulence, with associated borborygmi and abdominal distention. The presence of intraluminal H₂ gas, eventually absorbed into the circulation and exhaled, forms the basis of the hydrogen breath test to detect carbohydrate malabsorption acting directly on colonic epithelium to stimulate fluid secretion and by their osmotic effect, which further draws water into the lumen. The presence of organic acids in the stool reduces the pH below 6 and suggests carbohydrate malabsorption.

Physical examination may reveal a distended tympanitic abdomen with hyperactive bowel sounds. Stools float on the water because of their increased gas content with severe malassimilation of carbohydrate there will be decreased plasma insulin levels, increased plasma glucagon and cortisol levels, and decreased peripheral T₄-to-T₃ conversion. The body may enter a state of oxidative metabolism, with catabolism of fat and muscle. There may be signs of weight loss from both fat stores and lean body mass. The patient will be weak and will easily develop fatigue. Fat loss will generally be noted as sunken cheeks and flat buttocks, with wrinkled or loose, skin indicative of loss of subcutaneous fat stores. The loss of muscle mass is easily noted as a reduction in the thenar mass and sunken soft tissues between the extensor tendons on the dorsum of the hands. There may be direct evidence of a reduced metabolic rate secondary to decreased T₃ conversion. The patient may be mentally slowed.



Table 3. Specific vitamin and mineral deficiencies*Vitamin/mineral Clinical manifestation*

➤ Vitamin A - Night blindness ○ Xerosis (dry bulbar conjunctiva) ○ Bitot's spots (conjunctiva plaques) ○ Keratomalacia (corneal ulceration) ○ Skin Hyperkeratosis ➤ Vitamin B12 - Anemia ○ Nonreversible loss of vibratory and position sense ○ Paresthesia ○ Gastrointestinal – diarrhea ➤ Vitamin C Skin - perifollicular papules (brittle hair) ○ Perifollicular hemorrhages ○ Gum bleeding ○ Skin purpura, ecchymosis ➤ Vitamin D - bone pain and softening ○ Joint pain ○ Rickets ○ Proximal myopathy	➤ Vitamin K - bruising ○ Bleeding ➤ Vitamin B6 - seborrheic dermatitis ○ (Pyridoxine) Cheilosis ○ Glossitis ➤ Niacin - dermatitis ○ Diarrhea ○ Dementia ➤ Thiamine - congestive heart failure ○ Wernicke's encephalopathy ○ Wernicke-Korsakoff syndrome ➤ Zinc - acrodermatitis enteropathica ○ Alopecia ○ Taste Hypogeusia ➤ Folate - anemia ○ Reversible loss of position and vibratory sense

Abbreviations: CVS, cardiovascular system; CNS, central nervous system

Excessive loss of fat in the stool deprives the body of calories and contributes to weight loss and malnutrition. More specific is the action of unabsorbed long-chain fatty acids, which act on the colonic mucosa to stimulate cAMP and to cause secretory diarrhea. In addition, fatty acids bind calcium, which would normally be available to bind oxalate. In fat malabsorption, oxalate is not bound to calcium and remains free (undissociated) within the colonic lumen, where it is readily absorbed. This results in oxaluria and calcium oxalate kidney stones. Failure to absorb the fat-soluble vitamins A, D, E and K also results in a variety of symptoms. Vitamin K deficiency presents as subcutaneous, urinary, nasal, vaginal and gastrointestinal bleeding. Vitamin A deficiency results in follicular hyperkeratosis. Vitamin E deficiency leads to a progressive demyelination of the central nervous system. Malabsorption of vitamin D causes rickets and osteopenia.

Severe loss of body protein may occur before the development of any laboratory abnormalities, so that the patient at risk must be identified early. Impaired protein synthesis from liver diseases and excessive protein loss in renal diseases can further



aggravate protein deficiencies arising from malassimilation. Protein deficiency results in edema and diminished muscle mass. Since the immune system is dependent upon adequate proteins, protein deficiency can manifest as recurrent infections. Protein deficiency in children results in growth retardation, mental apathy and irritability, weakness and muscle atrophy, edema, hair loss, deformity of skeletal bone, anorexia, vomiting and diarrhea. Protein-calorie malnutrition is known as marasmus, whereas protein malnutrition by itself (with sufficient caloric intake) is known as kwashiorkor.

Hypochromic microcytic anemia characterizes iron deficiency. Since malassimilation may result in folate or B12 deficiency (producing megaloblastic red cells), the microcytosis of iron deficiency may be obscured with automated cell counters. A dimorphic picture may result from combined deficiencies. Rarely, these may be accompanied by pica and dysphagia. Pica originally referred to the eating of clay or soil; however, the commonest “pica” in North America is the eating of ice. Dysphagia may be due to the Plummer-Vinson (Paterson-Kelly) syndrome (with atrophic papillae of the tongue and postcricoid esophageal webs), and/or cheilosis (reddened lips with angular fissures, aka cheilitis or angular stomatitis). Pallor, weakness, fatigue, dyspnea and edema also can occur. Examination often reveals pallor, an atrophic tongue and koilonychia (brittle, flat or spoon-shaped fingernails).

The clinical picture of cobalamin (vitamin B12) and folic acid deficiency includes pallor, glossitis, megaloblastosis, and elevated serum lactate dehydrogenase (LDH). Subacute combined spinal cord degeneration occurs with severe cobalamin deficiency as well as dorsal column damage. Neurologic manifestations are not part of folic acid deficiency. Symmetrical paresthesias in the feet and fingers may occur with associated disturbances of vibration sense and proprioception, progressing to ataxia with subacute combined degeneration of the spinal cord.

Impaired absorption of calcium, magnesium and vitamin D lead to bone pain, fractures, paresthesias and tetany. In latent tetany, the neuromuscular instability can be brought out by provocative tests such as Chvostek’s and Trousseau’s sign. Osteomalacia resulting from vitamin D deficiency principally affects the spine, rib cage and long bones with or without fractures (Milkman’s fractures). A child with calcium or vitamin D malabsorption will present with classical rickets.

Hypomagnesemia may cause seizures and symptoms identical to those of hypocalcemia. In addition, hypomagnesemia may reduce the responsiveness of the parathyroids to calcium and impair parathyroid regulation of calcium homeostasis.

1.2. Diagnostic Approach to Malassimilation

A detailed history and physical examination (must always include DRE – digital rectal examination) may, in some instances, provide clue to the cause and further focus the clinical evaluation, for example the detection of dermatitis herpetiformis might suggest the closely linked disorder, celiac disease. Or, a history of repeated bouts of severe abdominal pain and weight loss in a chronic alcohol abuser might suggest chronic pancreatic insufficiency after repeated bouts of alcohol-induced pancreatitis.

Investigation includes blood, breath and stool tests, diagnostic imaging including upper and lower GI tract endoscopy with biopsies, as well as double balloon endoscopy, if available. Numerous imaging methods of the small bowel are available, including small bowel barium studies, CT or MRI enterography, and video capsule endoscopy.



A complete blood count may show a macrocytic or microcytic anemia. A peripheral blood smear may demonstrate microcytic cells (i.e., iron deficiency), changes suggestive of megaloblastosis with hypersegmented polymorphs (i.e., folate or vitamin B12 deficiency) or splenic hypofunction (i.e., Howell-Jolly bodies from hyposplenism in celiac disease). Serum calcium, phosphorus and alkaline phosphatase (from bone origin) may suggest osteomalacia. Serum albumin may provide an index of the nutritional state and protein stores. A reduced serum carotene, (vitamin A) vitamin D, and prolonged INR or (International Normalized Ratio, vitamin K) indirectly suggest fat assimilation and clotting status (before a small intestinal biopsy). Body iron stores may be assessed from the measurement of serum iron, total iron binding capacity (TIBC) % saturation and ferritin concentration. Serology for anti-transglutaminase is both sensitive and specific to detect celiac disease as long as person does not have IgA deficiency. Serology is positive a small intestinal biopsy should be done to confirm the serological suspicion of celiac disease before treatment with a gluten free diet. A fasting blood sugar and TSH measurement will help exclude diabetes or thyroid disease. Dual Energy X-ray Absorptiometry (DEXA) bone scanning is useful to detect osteopenic bone disease. Serum vitamin B12, an index of body stores of vitamin B12, may be reduced owing to reduced intake, deficient production of intrinsic factor, abnormal luminal pH, pancreatic insufficiency, small intestinal bacterial overgrowth (SIBO) or impaired ileal absorption. Hydrogen breath tests after an oral load of a sugar such as lactase, glucose, fructose or sucrose helps to establish the presence of SIBO. Fecal studies help to exclude infectious or parasitic condition. A 72 hour stool collection performed after a 3 day dietary fat intake of 100 gm/day is sometimes necessary, and should include stool weight (2200g/day), fat, bile acids, and depending on the circumstance, stool electrolytes, osmolality, and laxatives such as Mg²⁺ and phenolphthalein.

1.2.1. Site of defect therapy

The therapy for some specific maldigestion or malabsorption syndromes are detailed in Table 4 and representative doses of some nutritional therapies are noted in Table 4.

Table 4. Therapy of malassimilation syndromes.

Site of defect	Therapy
Pancreas	Enzyme supplements; insulin; dietary counseling; surgery for pancreatic duct obstruction or cancer
Hepatobiliary	Endoscopic therapy or surgery for obstruction of biliary tree
Site of defect	Therapy
Mucosa	Diet, such as gluten withdrawal or milk-free diet; nutrient supplements; 5-ASA compounds or steroids for Crohn disease; antibiotics for bacterial overgrowth or Whipple's disease
Lymphatics	Low-fat diet; medium-chain triglycerides (MCTs)



2. Diarrhea

The term *diarrhea* usually means a change in the frequency ($>3/\text{day}$ is considered to be abnormal). In physiological terms, diarrhea is the increased secretion or decreased absorption of electrolytes or water, with stool weights exceeding 200 g/day (higher unless are seen normally in persons consuming much more than the usual 30 g fibre/day). To the patient, diarrhea is a change in the frequency and fluidity of their stools. Note that persons with IBS may have frequent watery stools, but usually there is no abnormality in electrolyte or water absorption/secretion. “Overflow diarrhea” may occur in the person with severe constipation or fecal impaction or fluid-nature of the stools. Finally, disease of the distal colon or rectum can lead to loss of stool reservoir, with frequent and often painful passage of small stools, yet there may be little fecal water and no increase in stool weight.

If the diarrhea has lasted less than two weeks, the diarrhea is said to be “acute” probably has an infectious or toxic cause. When diarrhea lasts for longer than two weeks, other explanations need to be considered. In the absence of prior gastric surgery, the most common causes of chronic diarrhea in persons less than 50 years are the irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), chronic intake of diarrhea-causing drugs or alcohol, chronic intestinal infections such as giardiasis. In a person over the age of 50 years, and certainly if there is blood in the stools, colorectal cancer and fecal impaction with overflow diarrhea must always be appropriately excluded.

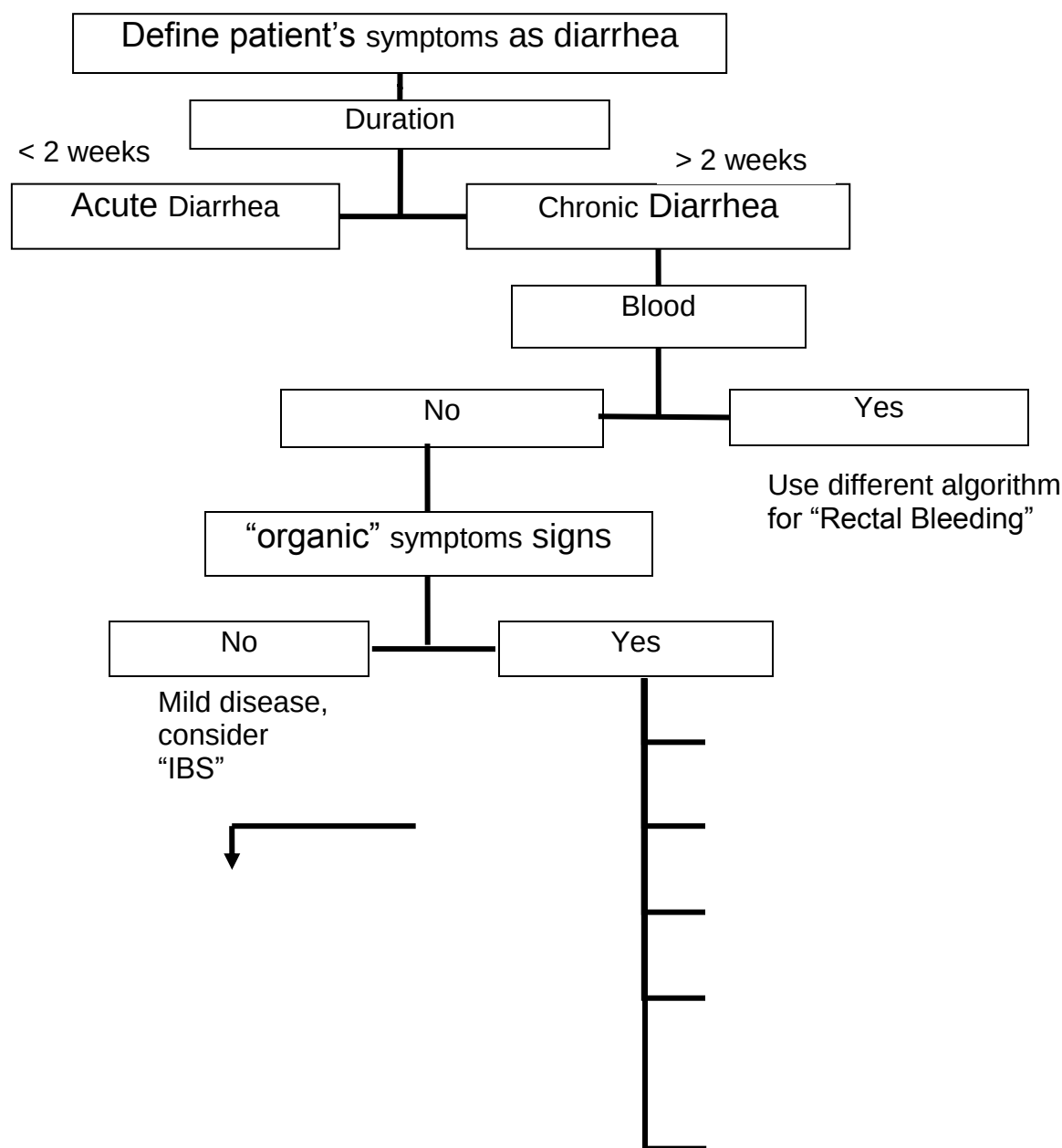
A sense of incomplete evacuation suggests involvement of the rectum or sigmoid colon. The passage of blood, pus and mucus suggests bowel inflammation, ischemic bowel disease or neoplastic diseases, including cancer. Malabsorption syndromes (discussed in the previous section) are suspect if there is passage of food and oil droplets, or if the patient develops symptoms suggestive of nutrient deficiency, particularly weight loss.

Understanding of the pathophysiology of diarrhea requires an appreciation of the normal balance between the processes of water and electrolyte absorption and secretion.

2.1. Investigation

For a patient with chronic diarrhea, a careful history and physical examination helps define the responsible site in the intestinal tract (Table 5). Although there is considerable symptom overlap, it may be possible to differentiate clinically a small intestinal cause of diarrhea from a colonic cause for diarrhea. Colorectal disease often is associated with small, frequent bloody motions accompanied by tenesmus and urgency. Small intestinal or pancreatic diseases often produce large volume, loose, pale and bulky stools that are uncommonly bloody or accompanied by urgency. Despite overlap, this “bedside” definition of the characteristics of the diarrhea may be helpful to avoid a less productive “shotgun” approach to the investigation.



Table 5. Simplified Clinical Approach to the Patient with Chronic Diarrhea

Because of the complexity of the mechanisms leading to chronic diarrhea, and the large number of causes, and often multiple interacting causes, it is useful to have a simple clinical approach to guide clinical thinking (Table 5 and 6) and investigations (Table 6). This may be a friendly way to approach the patient's problem, and then once a cause of chronic diarrhea is established (such as Crohn disease), then to apply your understanding of physiology to better understand the mechanisms causing diarrhea in that patient with that disorder.



Table 6. Simplified Approach to the Investigation of the Patient with Diarrhea

-
- Blood - CBC, ESR/CRP, lytes
 - Fe, FA, B₁₂, VA, VD, INR
 - Anti-tissue transglutaminase (tTG), IgA
 - Stool - C/S, O/P, FOB
 - 72 hr collection (weight, fat, bile acids, osmololity, electrolytes)
 - Laxatives
 - Breath - CHO : Lactose, Lactulose, Fructose, Sucrose
 - C 13/14 bile acid breath test
 - Diagnostic Imaging - endoscopy + biopsy : EGD/colonoscopy/capsule endoscopy
 - SB barium, enteroclysis
 - Air contrast barium enema
 - CT or MR enterography
-

Table 7. Representative doses for agents used in replacement therapy in patients with malassimilation syndromes

-
- Minerals*
- Calcium PO: requires at least 1,000 mg elemental calcium daily as:
 - Calcium gluconate (93 mg Ca²⁺/500 mg tablet)
 - Calcium carbonate (200 mg Ca²⁺/500 mg tablet)
 - IV: Calcium gluconate, 10 mL (9.3 mg Ca²⁺/mL) of 10% soln over 5 min
 - Magnesium PO: Magnesium gluconate (29 mg Mg²⁺/500 mg tablet), 2–6 g/day
 - IV: Magnesium sulfate (50% soln, 1 mL contains 2.03 mmol Mg²⁺)
 - Iron PO: Ferrous fumarate (65 mg elemental Fe/200 mg tablet), 200 mg tid
 - Ferrous gluconate (35 mg elemental Fe/300 mg tablet), 600 mg tid
 - Ferrous sulfate (60 mg elemental Fe/300 mg tablet), 300 mg tid
 - IM: Iron dextran 1 mL once daily (calculated from existing Hb)*
 - IV: Iron dextran approx. 30 mL (calculated from existing Hb)* in 500 cc
 - 5% D/W over 4 hrs, beginning with slow observed infusion
- *NOTE: IM/IV Fe for deficit replacement only
- Zinc PO: Zinc sulfate (89 mg elemental zinc/220 mg capsule), 220 mg tid
-



- Vitamins*
- Vitamin A Water-miscible vitamin A (25,000 IU/capsule), 25,000 IU daily
 - Vitamin B12 100 µg/IM monthly
 - Vitamin D2 (Ergocalciferol) (50,000 IU/capsule), 50,000 IU 3 times per week
 - Vitamin E Water-miscible vitamin E (100 IU/capsule), 400 IU daily
 - Vitamin K1 (Phytonadione) has caused fatal reactions, thus should be avoided
 - Vitamin K3 (Menadione) water-soluble
 - PO: 5–10 mg/day
 - IV: 5–10 mg/day
 - Folic acid PO: 1 mg/day
 - Other : water-soluble Multiple vitamin 1/day
-

Table 8. Representative doses for agents used in replacement therapy in patients with malassimilation syndromes (cont'd)

Pancreatic supplements

Enzyme activity (IU/unit)

Preparation Type Lipase Trypsin Proteolytic Amylase

Ku-Zyme HP® Capsule 2,330 3,082 6,090 594,048

Festal® Enteric-coated 2,073 ,488 1,800 219,200

Cotazym® Capsule 2,014 2,797 5,840 499,200

Viokase® Tablet 1,636 1,828 ,440 277,333

Pancrease® Microencapsulated

> 4,000 > 25,000

Usually taken as 4–8 capsules with each meal and half that number with snacks. Some patients will need higher doses or will need acid-lowering therapy with an H₂-receptor antagonist or a proton pump inhibitor to alkalize the fluid in the duodenum and achieve greater activity of the pancreatic enzymes.



➤ *Bile salt binding agents*

Cholestyramine 4 g (1 scoop), 3–6 times daily, according to response

Psyllium and aluminum hydroxide gel may also be effective

Colestipol 1 g 3–6 times daily, according to response

➤ *Caloric supplements*

Medium-chain triglyceride oil: (8 cal/mL), 60 mL/day po, 480 cal/day

Portagen®: medium-chain triglyceride + other oils: (1 cal/mL), 1 L/day

Enteral supplements:

Grams of Osmolality

Kcal/protein/ Na K mOsm/kg*

Product 1,000 mL 1,000 mL mg/L mg/L Water

Ensure® 1,060 37 740 1,270 450

Isocal® 1,040 34 530 1,320 300

Osmolite® 1,060 37 540 1,060 300

Precision

Isotonic Diet® ,960 29 800 ,960 300

Precision LR Diet® 1,110 26 700 ,810 525

Travasorb STD®

(unflavored) 1,000 45 920 1,170 450

Standard Vivonex®

(unflavored) 1,000 21 470 1,170 550

High-Nitrogen

Vivonex®

(unflavored) 1,000 44 530 1,170 810

Meritene Powder®

in milk 1,065 69 1,000 3,000 690

Compleat B® 1,000 40 1,200 1,300 390

Formula 2® 1,000 38 ,600 1,760 435–510

*When prepared in standard dilution

Parenteral supplements: Intralipid® 1 L/day IV (10 mL/kg/day)

Travasol® 2 L/day IV (mix as per patient's protein requirement)

2. Acute Diarrhea

2.2.1. Bacterial Diarrhea

Three major clinical syndromes caused by bacterial infections are 1) food poisoning, 2) infectious gastroenteritis and 3) traveler's diarrhea (Table 9).

In immunocompetent individuals, enteric infections are usually self-limiting and resolve in less than two weeks. Acute infections diarrheas are classified into *toxigenic types*, in which an enterotoxin is the pathogenic mechanism, and *invasive types*, in which the organism penetrates the enterocyte or colonocyte as primary event (although an enterotoxin may be produced as well). Enterotoxins are either *cytotoxic* (producing intestinal fluid secretion by activation of intracellular enzymes, without damage to the epithelial surface) or *cytotoxic* (causing injury to the enterocyte as well as inducing fluid secretion).

2.2.2. Food Poisoning

The food poisoning syndrome characteristically features the development of a brief but explosive diarrheal illness in persons following exposure to a common food such as a restaurant meal or family picnic is suggestive. Food source may be contaminated with bacteria or bacterial toxins; such as *Staphylococcus aureus*, or *Salmonella* species. The diagnosis of food poisoning is usually made by history. Except in special circumstances (e.g., botulism), isolation of the toxin is not cost-effective.



Table 9. Common causes of acute diarrhea

Drugs	Bacteria (toxin-mediated, cytotoxic)	Viruses
Laxatives	<i>Clostridium difficile</i>	Bacteria (toxin-mediated, cytotoxic)
Antacids	<i>Staphylococcus aureus</i>	Parvovirus (Norwalk agent)
Antibiotics	<i>Shigella dysenteriae</i>	Enterotoxigenic <i>Escherichia coli</i>
Cholinergic drugs	<i>Campylobacter jejuni</i>	Reovirus (rotavirus)
Lactose	<i>Yersinia enterocolitica</i>	(both heat-labile and heatstable toxins)
Guanethidine		Protozoa
Quinidine		<i>Vibrio cholerae</i>
Bacteria (invasive)		Cryptosporidia
Digitalis	<i>Salmonella</i>	<i>Vibrio parahaemolyticus</i>
Colchicine		<i>Giardia lamblia</i>
Enteroinvasive	<i>Escherichia coli</i>	<i>Clostridium perfringens</i>
Potassium supplements		<i>Entamoeba histolytica</i>
Lactulose	Bacteria (unknown mechanism)	<i>Bacillus cereus</i>
Enteropathogenic	<i>Escherichia coli</i>	Parasites
Enteroadherent	<i>Escherichia coli</i>	<i>Strongyloides</i>
		<i>Trichuris</i>

Salmonella food poisoning has been attributed to an enterotoxin similar to that of *Staphylococcus aureus*, but none has been clearly identified. Within 12 to 36 hours after ingestion of contaminated foods (usually poultry products), there is a sudden onset of headaches, chills and abdominal pain, with nausea, vomiting and diarrhea. These symptoms may persist for one to four days before subsiding. Antibiotic therapy of non-typhoidal *Salmonella* gastroenteritis fails to alter the rate of clinical recovery. In fact, antibiotic therapy will increase the duration of intestinal carriage of the *Salmonella*, and is contraindicated.

Certain conditions increase the risk of salmonellosis: hemolytic anemia, malignancy, immunosuppression, achlorhydria and ulcerative colitis. With uncomplicated *Salmonella* gastroenteritis, treatment is symptomatic. In fact, antibiotic therapy increases the duration of intestinal carriage of these organisms. Patients with complicated *Salmonella* gastroenteritis (e.g., those with predisposing conditions or sepsis, or who are very young or very old) should be treated with ampicillin or cotrimoxazole.

- *Campylobacter jejuni*–induced diarrhea is more common than diarrhea from either *Salmonella* or *Shigella*. Infection is from consumption of improperly cooked or contaminated foodstuffs. *Campylobacter* attaches to the mucosa and releases an enterotoxin that destroys the surrounding epithelia. Clinically, there is often a prodrome of constitutional symptoms along with headache and generalized malaise. A prolonged diarrheal illness follows – often with a biphasic character, with initial bloody diarrhea, slight improvement, then increasing severity. The illness usually lasts less than one week, although symptoms can persist for a longer period, and relapses occur in as many as 25% of patients. Erythromycin 500 mg q.i.d. for 7 days is optimal therapy.



- *Clostridium perfringens* and *Bacillus cereus* are responsible for 90% of these outbreaks.

Symptoms usually reside with 24 hours, antibiotic therapy is not recommended. Oral rehydration therapy is usually possible. *Staphylococcus aureus* produces a heat-stable, odorless and tasteless enterotoxin that is generated in poorly refrigerated desserts and seafoods. Ingestion of the preformed enterotoxin causes nausea, vomiting and profuse diarrhea within 4 to 8 hours. Spontaneous resolution occurs within 24 hours. No specific therapy is available or necessary. *Clostridium perfringens* produces a preformed toxin from spores that germinate in contaminated meats cooked at less than 50°C. Symptoms are diarrhea and crampy abdominal pain without vomiting, beginning 8 to 24 hours after the meal.

- *Bacillus cereus*

Bacillus cereus produces either a diarrheal syndrome or a vomiting syndrome, depending upon the enterotoxin. The vomiting syndrome is always associated with ingestion of rice and is caused by a preformed toxin that is elaborated when rice is left to cool unrefrigerated. Flash-frying later does not generate enough heat to destroy the toxin. The diarrheal syndrome occurs after ingestion of the organism itself.

2.2.3. Infectious Gastroenteritis

The organisms responsible for bacterial gastroenteritis exert their predominant effects by invading and destroying the intestinal epithelium or by producing various enterotoxins.

- *Toxin-mediated, cytotoxic bacterial gastroenteritis*

- *Vibrio cholerae* is the prototypic cause of toxigenic diarrhea. The *Vibrio cholerae* organisms elaborate a toxin that attaches to the inner cell membrane of the small intestinal BBM. Adenylate cyclase (aka “adenyl cyclase”) elevates cyclic AMP (cAMP) levels. Cyclic AMP then stimulates the enterocyte to secrete fluid and electrolytes while at the same time impairing their absorption. Stool output can exceed 1 L/hour. Treatment is based on restoring fluid and electrolyte balance and maintaining intravascular volume. Even though fluid and electrolyte transport is impaired, glucose transport is intact. Since glucose absorption carries Na⁺ (and thus water with it), an oral rehydration solution containing glucose, sodium and water will enhance water absorption during the profound dehydration stage of cholera. ORT (oral hydration therapy) is sufficient for many sufferers.

Several types of *Escherichia coli* (*E. coli*) are intestinal pathogens. Each exerts its effects through different mechanisms (Table 10). Invasive forms of *E. coli* may cause colitis that may resemble ischemia bowel disease. *Enterotoxigenic E. coli* (ETEC) colonizes the upper small intestine after passing through the acid in the stomach, and bind to the mucosal surface without penetrating into the cell. Two types of enterotoxins are produced by ETEC: the heat-labile toxin (also called “labile toxin” or LT) and the heat stable toxin (also called “stable toxin” or ST). ETEC can elaborate LT only, ST only, or both toxins. ST produces diarrhea by stimulating intestinal secretion through guanylate cyclase and subsequently cyclic GMP. LT produces diarrhea through adenylate cyclase and cyclic AMP. After a 24- to 48-hour incubation period, the disease



begins with upper abdominal pain followed by watery diarrhea. The infection can be mild or severe. Treatment is symptomatic. Antibiotic therapy is not used because it is ineffective, and also because the use of antibiotics may lead to the emergence of resistant ETEC strains.

Table 10. Types of *Escherichia coli* intestinal pathogens

○ Toxin	○ Mechanism
- Enteropathogenic Shiga-like toxin	- Adherence
- Enterotoxigenic Labile toxin (LT)	- Activates adenylate cyclase
- Stable toxin	- Activates guanylate cyclase
- Enteroinvasive Shiga-like toxin	- Penetrates epithelium
- Enteroadherent	- Adherence
- Enterohemorrhagic Shiga-like toxin (verotoxin)	- Unknown

- *Vibrio parahaemolyticus* causes acute diarrheal disease after consumption of seafood: raw fish or shellfish often without proper refrigeration. Explosive, watery diarrhea is the cardinal manifestation, along with abdominal cramps, nausea and vomiting. Fever and chills occur in 25% of cases. The duration of illness is short, with a median of three days. Treatment is symptomatic; there is no role for antimicrobial therapy.

After ingestion, *Shigella dysenteriae* organisms attack the colon, sparing the stomach and small bowel. Shigella organisms adhere to and then, penetrate the mucosal surface, multiply within the epithelial cells, moving laterally through the cytoplasm to adjacent cells by filopodium-like protrusions. Shigella organisms rarely penetrate below the intestinal mucosa, and almost never invade the bloodstream. Both attached and intracellular organisms elaborate toxic products. Even a small inoculum of 200 organisms (as contrasted with Salmonella, which requires greater than 10⁷ organisms) will lead to crampy abdominal pain, rectal burning, fever, multiple small-volume bloody mucoid bowel movements. Intestinal complications include perforation and severe protein loss. Extraintestinal complications include respiratory symptoms, meningismus, seizures, the hemolytic uremic syndrome, arthritis and rashes. The treatment of choice is Ampicillin 500 mg q.i.d. or co-trimoxazole 2 tablets b.i.d. for 5 days.

- *Yersinia enterocolitica* is transmitted to humans from pets or food sources. It has become more readily detected in fecal specimens because of the use of selective growth media and a cold enrichment technique. The organism invades epithelial cells and also produces an enterotoxin. The spectrum of illness ranges from simple gastroenteritis to invasive ileitis and colitis that must be distinguished from Crohn disease or ulcerative colitis.

- *Y. Enterocolitica* causes diarrheal illness in adults, including the elderly, and frequently in children, often less than 5 years of age. Children over 5 years of age



develop mesenteric adenitis and associated ileitis, which mimic acute appendicitis. *Yersinia* is less likely to cause disease in adults. If it does, *Yersinia* is an acute diarrheal episode followed two to three weeks later by joint symptoms and a rash (erythema nodosum). Treatment is symptomatic. There is no evidence that antibiotics alter the course of the gastrointestinal infection.

- *Clostridium difficile* causes antibiotic-associated colitis and is discussed later.

- Invasive bacterial gastroenteritis

Certain strains of *E. coli* are invasive, producing an illness indistinguishable from shigellosis. Isolates of *E. coli* 0157:H7 have been identified in the stools of patients with a diarrheal illness clinically designated as “hemorrhagic colitis.” Infection has been traced to contaminated hamburger meat obtained from a variety of sources, including large international restaurant chains. *E. coli* 0157:H7 infection may be complicated by thrombotic thrombocytopenic purpura (TTP), or by the hemolytic uremic syndrome (HUS), which sometimes leads to death. Ingestion of this organism results in severe crampy abdominal pain and fever, followed within 24 hours by bloody diarrhea that lasts five to seven days. Since the organism is shed in the stool for only a short period of time, early stool collections are critical for the diagnosis. Treatment is symptomatic, and antibiotics do not alter the disease course. In severe cases with possible toxic megacolon, systemic antibiotics may be in order.

Approximately 1,700 serotypes and variants of *Salmonella* are potential pathogens for humans. A dose of approximately 10²–10⁹ organisms is required to produce clinical illness. *Salmonella* organisms invade the mucosa of the small intestine and particularly the colon. This form of gastroenteritis produces nausea and vomiting followed by abdominal cramps and diarrhea that lasts three to four days and then gradually subsides. In 10% of cases bacteremia of the *Salmonella* organism occurs, and in approximately 5% there are disseminated infections to bones, joints and meninges.

- Bacterial gastroenteritis of unknown mechanism

- Enterohemorrhagic *E. coli*–induced diarrhea tends to occur in neonates and young children. Only occasionally does it affect older children and adults. The pathogenic mechanism of this diarrhea is unclear; adherence of the organism to the intestinal epithelial cell seems to cause intestinal damage. There is no indication for specific treatment except for neonates in a nursery epidemic when oral nonabsorbable aminoglycosides are used.

2.2.4. Traveler's Diarrhea

Traveler's diarrhea is a syndrome characterized by an increase in frequency of unformed bowel movements, typically four to five loose stools per day. Associated symptoms include abdominal cramps, nausea, bloating, urgency, fever and malaise. Traveler's diarrhea usually begins abruptly, during travel or soon after returning home, and is generally self-limiting, lasting three to four days. Ten percent of cases persist longer than one week, approximately 2% longer than one month, and very few beyond three months.



Traveler's diarrhea may be associated with past-infectious irritable bowel syndrome (IBS). *Enterotoxigenic E. coli* (ETEC) is the most common causative agent of traveler's diarrhea. These organisms adhere to the small intestine, where they multiply and produce an enterotoxin that causes fluid secretion and hence diarrhea. Salmonella gastroenteritis, Shigella dysentery, and viral enteric pathogens (rotavirus and Norwalk-like virus) are less common causes of traveler's diarrhea.

Since traveler's diarrhea is usually mild and self-limiting, with complete recovery even in the absence of therapy, therapy should be considered optional (Table 11). The value of prophylaxis for travelers is unclear. Bismuth preparations are helpful, but their use is limited by the large volumes necessary and by their taste. Antibiotic prophylaxis can reduce the likelihood of developing diarrhea, but carries its own risks.

Table 11. Traveler's diarrhea: recommendations for treatment

-
- General
 - Avoid ice cubes, raw vegetables and fruits, raw fish and shellfish, unrefrigerated food.
 - Drink canned pop and beer, boiled water.
 - Drink oral replacement solutions for acute attacks.
 - Avoid over-the-counter preparations sold locally for acute attacks.
 - Specific
 - To provide symptomatic relief of acute attack:
 - Diphenoxylate 1 tab, 2.5 mg, after each bowel movement to max 8 tab/day
 - Loperamide 1 cap, 2.0 mg, after each bowel movement to max 8 cap/day
 - Pepto-Bismol® 30 mL q 30 min ~ 8 doses
 - To decrease severity of acute attack:
 - Co-trimoxazole 1 tab bid po ~ 3 days
 - Doxycycline 100 mg bid po ~ 3 days
 - Prophylaxis:
 - Not recommended except for persons who are immunosuppressed or suffer chronic illness. If
 - indicated, then:
 - Co-trimoxazole 1 tab bid po ~ 3 days
 - Doxycycline 100 mg bid po ~ 3 days
 - Ciprofloxacin 500 mg bid po ~ 7 days
 - Immunization
-

- Viral Gastroenteritis

At least two groups of viruses are capable of producing an acute diarrheal illness.

 - *Norwalk Virus*



The Norwalk virus causes a self-limiting diarrhea and vomiting syndrome that affects children and adults, mainly in winter. Recently, several epidemics have been reported from cruise ship passengers. An incubation period of 24 to 48 hours is followed by a variable combination of fever, anorexia, nausea, vomiting, myalgia, abdominal pain and diarrhea. Spontaneous recovery occurs two to three days later. Immune electron microscopy of fecal filtrates demonstrates the characteristic 27 nm Norwalk virus. No specific treatment is available, except to ensure proper hydration. The vomiting represents delayed gastric emptying; there are no morphologic features of gastritis.

- *Rotaviruses*

Rotaviruses are the most common causes of acute nonbacterial gastroenteritis in infancy and childhood. Rotaviruses invade mucosal epithelial cells, more severe resulting in illness than that caused by the Norwalk virus. Rotavirus infection commonly requires hospital admission and intravenous fluids. Infection occurs mainly in children from 6 to 24 months old, and almost always in winter. Virus excretion is maximum three to four days after the onset of symptoms, and disappears after a further three to four days. The stability of the virus and the large number of viral particles excreted make environmental contamination inevitable, with a high risk of secondary infection in susceptible contacts. For example, 20% of the rotavirus infections diagnosed in paediatric hospitals are nosocomial-acquired in the hospital. Most older children and adults have antibodies to rotaviruses, so any subsequent infection is generally mild.

○ *Parasitic Enteritis*

The parasites that infect the intestine are divided into three broad groups. These include protozoa, roundworms and flatworms. The flatworms may be further divided into cestodes (tapeworms) and trematodes (flukes). We focus on only a few protozoa seen in immunocompetent Canadian residents.

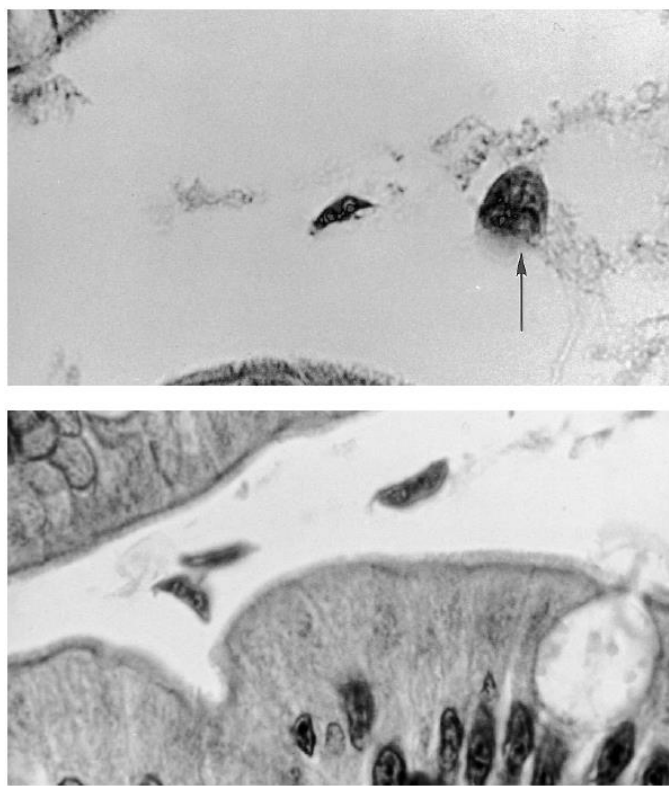


Figure 1A and B. Two high-power views of giardiasis show the typical appearance in cross-section. The crescentic shape and double nuclei are characteristic. One cut shows the organism in longitudinal section (arrow); the organism has the pear shape more familiar from smear preparations. Only one of the two nuclei is visible.

- *Giardia Lamblia*

Giardia lamblia is endemic in many areas of the world, including Canada. Some persons with giardiasis ("beaver fever") present with an abrupt, self-limiting illness that develops one to three weeks after infection, and lasts three to four days. Others may develop chronic and episodic diarrhea associated with bloating and, at times, steatorrhea and a malabsorption syndrome. Diagnosis is made by recovery of the organism. It may be detected in the stool of approximately 50% of patients and in 90% of histologically examined small bowel smear preparations (Figure 1A and B). The treatment of choice in both asymptomatic and symptomatic patients is metronidazole 250 mg t.i.d. for 7 days. Repeat therapy will occasionally be needed to totally eradicate the organism. Quinacrine 100 mg t.i.d. for 7 days also is effective. Some patients develop secondary lactase deficiency with lactose intolerance. This is usually completely reversible after eradication of the organism. Milk and dairy products should be avoided during the treatment phase and for a period of time after treatment so as not to confuse the persistence or recurrence of diarrhea with a persistent infection.

- *Amebiasis*

Amebiasis is an acute and chronic disease caused by the organism *Entamoeba histolytica*. Although there are numerous species of amoeba that inhabit the human intestinal tract, *E. histolytica* is the only variety that is pathogenic for humans. Its manifestations vary from the asymptomatic carrier state, to a severe fulminating illness with mucosal inflammation and ulceration. Asymptomatic carriers harbor cysts in their stools, have no evidence of tissue invasion, but since the cysts are resistant to the outside environment, the disease can be transmitted by these individuals who are unaware of their infective potential. This is in marked contrast to patients with acute or chronic invasive disease, who harbor a trophozoite that cannot survive outside the host.

The acute illness is characterized by diarrhea with the passage of blood and mucus, and by abdominal pain. In its most severe form amebiasis may mimic fulminating ulcerative colitis, and may progress to a toxic dilation (toxic megacolon) and perforation of the colon. During the acute illness, trophozoites may be recovered in the stool, from biopsies of shallow ulcers in the rectum, or from smears of rectal mucus. Chronic infectious features may develop many years after the patient has left an endemic area. Patients present with nonspecific bowel complaints and may show radiologic changes in the distal small bowel and colon that mimic ulcerative colitis, cancer or tuberculosis. Diagnosis necessitates recovering trophozoites from the stool. The indirect hemagglutination test can help detect patients with invasive disease.

Systemic dissemination of the amoeba may involve other organs, such as the brain, lung, pericardium and liver. Liver abscess is the most common extraintestinal infection by the amoeba.

Therapeutic agents used for the treatment of amebiasis act at selected sites: intraluminally, intramurally or systemically. Treatment must therefore be individualized to the location of the disease. Asymptomatic carriers are treated with iodoquinol 650 mg t.i.d. for 20 days; this agent acts against amebas located intraluminally. Acute or chronic intestinal disease is treated with metronidazole 750 mg t.i.d. for 10 days. However, because metronidazole is less effective against organisms within the bowel lumen, iodoquinol (650 mg t.i.d. for 20 days) must be added.



- *Cryptosporidia*

Cryptosporidia are a genus of protozoa classified within the subclass Coccidia. In immunocompetent persons, cryptosporidia infection presents as a transient, self-limiting diarrheal illness lasting from one to seven days. Adults are less commonly affected than young children. In most, the illness is mild and medical help is not sought. With immunological incompetence (e.g., HIV/AIDS, neoplasia, hypogammaglobulinemia or concurrent viral infection), a persistent chronic watery diarrhea may occur. Diagnosis is made by demonstrating Cryptosporidia oocysts in the stool or, better still, by mucosal biopsy and examination of the microvillus border for embedded Cryptosporidia oocysts (Figure 2). A successful treatment for Cryptosporidia has not yet been found.

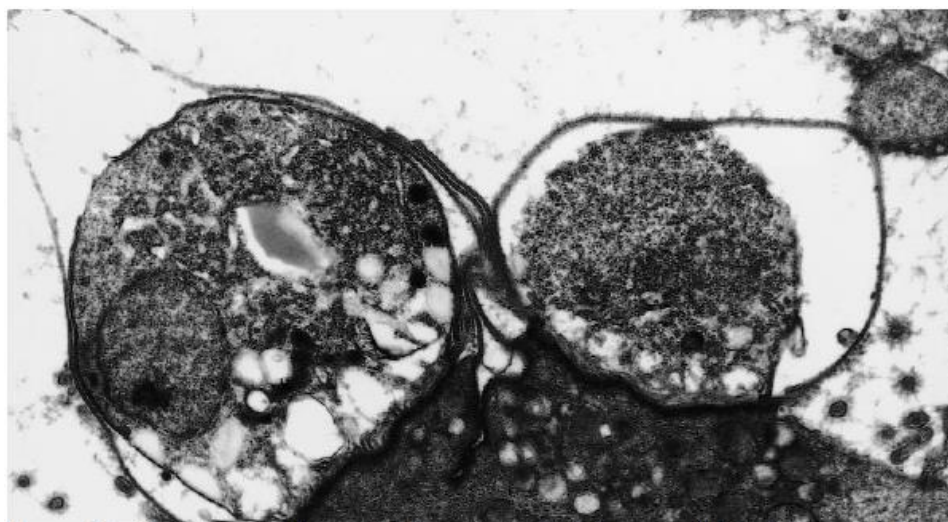


Figure 2. This electron micrograph of cryptosporidiosis in the small bowel shows the characteristics intracellular but extracytoplasmic location of the organisms.

2.3. Drugs and Chemicals

Since almost every drug can cause diarrhea, the first question to ask a patient is “What medications, both prescribed and over-the-counter, are you currently taking?” Discontinuing the drug is often the only therapeutic move required. Although many drugs can cause diarrhea, little is understood about the ways in which they do so. The common causes of drug-induced diarrhea with pathogenic mechanisms follow.

2.3.1. Antibiotics

Antibiotics are the most common cause of drug-induced diarrhea. Diarrhea occurring in association with the use of antibiotics is termed AAD, antibiotic-associated diarrhea. The condition is usually self-limiting. The development of pseudomembranous colitis (PMC) in association with antibiotics may be a serious and sometimes life-threatening condition. The increased incidence of PMC can follow the use of virtually any antibiotic. It may occur months after antibiotic exposure, and may occur without a



past history of antibiotic use. The frequency of diarrhea or colitis does not appear to be related to dose or route of administration of the antibiotic. Symptoms can occur while the patient is on the antibiotic, or within six weeks following its discontinuation.

Only increasing age is clearly identifiable as a risk factor. The diarrhea is usually loose with mucus. Frank bleeding is uncommon. The diarrhea can be devastating, with up to 30 bowel movements in a 24-hour period. The diarrhea may be associated with varying degrees of abdominal pain and low-grade fever. Depending on the severity of the diarrhea and the amount of fluid loss, hypotension, shock and even death have been reported. In many patients the problem is self-limiting and resolves spontaneously with discontinuation of the antibiotic.

PMC is an endoscopic and histological diagnosis. PMC is usually associated with the recent intake of antibiotics and is often associated with the demonstration of toxin in the stools produced by *Clostridium difficile*. Thus, AAD is not necessarily associated with PMC, and PMC is not always associated *C. difficile* infection not be treated but only if the toxin is produced. In recent years, a number of newly recognized and apparently more virulent strains of *C. difficile* have been reported.

An accurate history is usually sufficient to suggest the diagnosis of PMC, and a sigmoidoscopy may be all that is required for confirmation. The presence of copious amounts of mucus and typical raised white pseudomembrane plaques which are not washed away are characteristic features seen on sigmoidoscopy. Colonoscopy is recommended, because the plaques may be seen in the right colon beyond the reach of the sigmoidoscope, and the diagnosis would be otherwise missed. Biopsies help confirm the diagnosis (Figure 3A and B). Isolation of *C. difficile* toxin in the stools provides the diagnosis. If it is certain that there is no other likely cause for the diarrhea, treatment can be undertaken while awaiting assay results, although it is usually possible to quickly obtain a sigmoidoscopy to demonstrate the pseudomembranes. If symptoms are resolving with discontinuance of the antibiotic, no further therapy may be indicated. In mild cases, metronidazole 250 mg p.o. t.i.d. for 7–10 days is effective. In severe hospitalized cases the drug of choice is vancomycin 125 mg p.o. q.i.d. for 14 days. Vancomycin is poorly absorbed and central nervous system and renal toxic effects are uncommon. The high cost of this medication limits its use, even though the eradication rate of the *C. difficile* is high. It must be stressed that the vancomycin must be given orally, and not systemically. If oral therapy cannot be used, as with severe ileus or recent surgery, parenteral metronidazole is used. Some 20% of treated patients will have at least one recurrence of symptoms, PMC or *C. difficile*, usually within 4 to 21 days of stopping antibiotic treatment. In this case, another course of metronidazole or vancomycin should be given. If this fails, then pulse doses of vancomycin may be effective. Cholestyramine (Questran®) binds the toxin and can provide symptomatic relief even though it will not eliminate the microorganism. In extreme cases of fulminant non-responsive disease, colectomy, may be necessary.



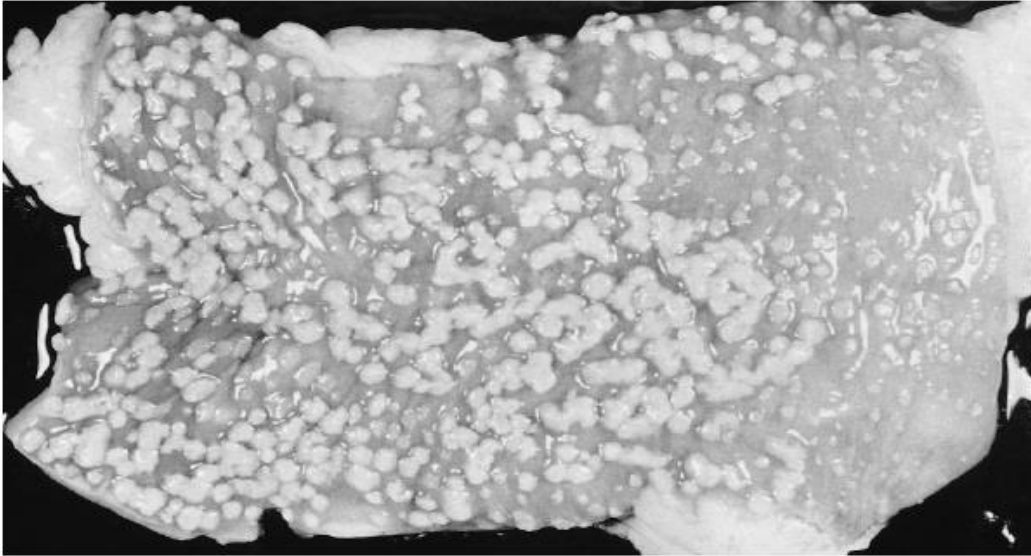


Figure 3A. Multiple, whitish plaques representing PMC (pseudomembranous colitis) from *C. difficile* infection of the colon.



Figure 3B. The confluent white patches of pseudomembranous colitis are typical. In Figure 3B the pseudomembrane is seen to arise like a volcano from a point of mucosal damage and is composed of an exudative fibrin and neutrophils.

2.3.2. Magnesium-Containing Antacids

The osmotically-induced diarrhea produced by Mg^{2+} is usually mild. A change to a magnesium-free, aluminum-containing antacid is all that is required to control the diarrhea. The use of magnesium-containing antacids is a common cause of diarrhea in



dyspeptic patients. Magnesium can be used to induce diarrhea by rare patient with the Münchausen syndrome who seek medical attention for self-induced problems.

2.3.3. Antiarrhythmic Drugs

The antiarrhythmic drugs most commonly associated with diarrhea include quinidine, procainamide and disopyramide. The mechanism involved is unknown. Changing the antiarrhythmic drug usually stops the diarrhea.

2.3.4. Other Medications

Colchicine, often administered for acute gout, produces diarrhea as a common side effect. It resolves with discontinuance of the medication. The mechanism of the diarrhea is unknown, but may relate to an intestinal cytotoxic effect of colchicine. Antimetabolites (e.g., methotrexate) often cause diarrhea as a result of damage to the small or large bowel mucosa. This type of diarrhea can be devastating and difficult to control. Except for rehydration and stopping the drug, little can be done. Diarrhea and cramps occur in at least 5% of persons taking misoprostol (an E2 prostaglandin) for gastro protection when concurrently consuming nonsteroidal anti-inflammatory drugs (NSAIDs). Proton pump inhibitors (PPIs) are commonly used to treat dyspepsia. Diarrhea occurs in 1-5% of persons taking a PPI, and may resolve by switching from one PPI to another, or from a PPI to an histamine-2 receptor antagonist. With lansoprazole, but not other PPI medications, well documented cases of microscopic colitis have been reported.

2.4. Chronic Diarrhea

There are at least four basic mechanisms that cause chronic diarrhea, including osmotic, secretory and exudative factors, and abnormal intestinal transit (Table 12). Often, diarrhea results from more than a single mechanism. If the diarrhea ceases when fasting, then an osmotic cause for the diarrhea is suspected. A significant osmotic gap in the stool water may be present but, under normal clinical circumstances, this is not measured. Examples include diarrhea after ingesting milk (and resulting from lactase deficiency), taking drugs such as magnesium-containing antacids, or the excessive use of artificial sweeteners (e.g., chewing gums) such as sorbitol and mannitol, which contain polycyclic alcohols. If the patient's diarrhea persists when fasting (such as may occur at nighttime when the diarrhea awakens the person from sleep), a secretory diarrhea is likely. Secretory diarrhea usually arises from infection or inflammation associated with toxigenic and invasive bacteria. Secretory diarrhea may also result from the spillage of excess bile acids into the colon (choleretic enteropathy) or from the cathartic effect of hydroxy fatty acids arising from the colonic bacterial action on malabsorbed fat (or fermented carbohydrate substrates). Very rarely, secretory diarrhea can arise from a tumor producing an intestinal secretagogue (e.g., pancreatic islet cell tumor producing vasoactive intestinal peptide or gastrin). Exudative diarrhea results from mucosal damage to the small or large bowel, which interferes with absorption of salt and water, and may be associated with the exudation of serum proteins, blood, and mucus and sloughed cells. This mechanism is seen in infectious, inflammatory and neoplastic disorders.



Table 12. Pathophysiologic mechanisms of chronic diarrhea

Major Disturbance	Probable Mechanisms	Examples/Associated Conditions
➤ Osmotic	○ Maldigestion ○ Malabsorption	- Antacids, laxatives - Pancreatic insufficiency, disaccharidase deficiency -Carbohydrate malabsorption, congenital chloridorrhea
➤ Disorders of intestinal transit	○ Slow transit (“blind loop syndrome”) – excessive contact time ○ Rapid transit – insufficient contact time	-Fistulas, strictures (such as in the patient with Crohn disease), diabetic neuropathy -Intestinal resection, hyperthyroidism, irritable bowel
➤ Secretory	○ Bacterial enterotoxins ○ Secretagogues	-<i>Vibrio cholerae</i>, enterotoxigenic <i>E. coli</i> -Bile acids, fatty acids, ethanol, prostaglandins, phenolphthalein, dioctyl sodium sulfosuccinate, VIP, gastrin, calcitonin
➤ Exudative	○ Increased passage of body fluids into lumen	-Ulcerative Colitis, Crohn disease

Disorders of intestinal transit may give rise to diarrhea secondary to abnormal intestinal motility in hyperthyroidism or diabetic neuropathy. Scleroderma leads to bacterial overgrowth and steatorrhea (as can the rapid transit in hyperthyroidism). The mechanism of diarrhea in these conditions relates to a combination of bacterial overgrowth, bile salt wastage and disorders of motility (slow or rapid intestinal transit).

2.4.1. Osmotic Diarrhea

Retention of solute molecules within the bowel lumen generates osmotic forces that retard the normal absorption of water and even act to draw water from the circulation into the intestinal lumen (Table 13).

Practical examples and may include poorly absorbed carbohydrates, or poorly absorbed divalent ions (e.g., phosphate, sulfate and magnesium) and are the laxative constituents of several common antacids and saline purges. Since the “pores” through which ions are absorbed are highly charged, these polyvalent ions tend to be absorbed



slowly. Thus, they accumulate within the intestinal lumen, raise the osmolality, and diarrhea results.

Some carbohydrates are poorly absorbed by everybody; for example, was developed to be a nonhydrolyzable, nonabsorbable disaccharide that would act as a cathartic. The action of lactulose mimics the effects of *primary lactase deficiency*. This common condition normally develops after weaning in the majority of African-, Caribbean- or Asian-Canadians, and also occurs in about a third of persons with southern European ancestry. The unabsorbed lactose acts osmotically to retain water in the small intestine. In fact, any disease that interferes with carbohydrate absorption (e.g., impaired intraluminal digestion due to pancreatic disease, primary disaccharidase deficiencies, and secondary disaccharidase deficiencies due to small bowel disease) will lead to osmotic diarrhea. Since carbohydrates are not inert in the colon, their metabolism leads to further osmotic forces. Once carbohydrate reaches the fecal flora, anaerobic fermentation occurs. Intermediary products are ethanol as well as formic, succinic and lactic acids. These products are further consumed to varying degrees. CO₂ and H₂ are rapidly absorbed, and in the breath exhaled air. Excess gas production causes borborygmi and flatus rich in H₂. Short-chain fatty acids (SCFAs) are also produced (acetic, propionic and butyric acids), and account for the acidic stool pH noted in diarrhea of carbohydrate malabsorption. In addition, the SCFAs may result in colonic secretion and worsen the diarrhea caused by the presence of osmotically active particles.

Table 13. Causes of osmotic diarrhea

➤ Carbohydrates	○ Specific disaccharidase deficiencies
○	○ Glucose-galactose malassimilation
	○ Mannitol, sorbitol ingestion (“chewing gum diarrhea”)
	○ Lactulose therapy
➤ Divalent ions	○ Magnesium sulfate (Epsom salts)
	○ Sodium sulfate
	○ Sodium phosphate
	○ Sodium citrate
	○ Magnesium-containing antacids

The caloric loss due to carbohydrate malabsorption is diminished to the extent that SCFAs are absorbed from the colon (where they may be used as nutrients by the colonocytes), thus “salvaging” some 75% of the malabsorbed carbohydrate energy that enters the colon. If there are large amounts of malabsorbed carbohydrate entering the colon, and the amount of SCFAs produced exceed the absorptive capacity of the colon, then the osmotically active SCFAs cause diarrhea. The excess SCFAs acidify the stool, less SCFAs are absorbed, and the osmotic diarrhea worsens. Osmotic diarrhea should stop when the patient stops ingesting the poorly absorbed solute.

As the extent of carbohydrate malabsorption increases, more short-chain fatty acids are formed than can be reabsorbed. This results in diarrhea due to the presence of osmotically active short-chain fatty acids. The stool pH consequently begins to fall,



which further decreases colonic salvage. In persons with osmotically-induced diarrhea, there will be a detectable positive osmotic gap – that is, stool osmolality minus stool Na^+ plus stool K^+ times 2 (multiplied by 2 to account for anions) is greater than 50, the size of the osmotic gap being approximately equivalent to the concentration of poorly absorbed solutes in fecal water.

2.4.2. Secretory Diarrhea

The small intestine normally secretes as well as absorbs fluid and electrolytes. Normally the secretion rate is lower than the absorption rate, and the net effect is absorption of fluid. For clinical purposes, it is best to consider inhibition of ion absorption and stimulation of ion secretion together (Table 14).

Table 14. Causes of secretory diarrhea

➤ Pathophysiologic mechanisms
○ Enterotoxins
○ Circulating secretagogues (VIP, calcitonin, prostaglandins, serotonin)
○ Increased hydrostatic pressure and tissue pressure
○ Gastric hypersecretion (Zollinger-Ellison Syndrome)
○ Pancreatic hypersecretion
○ Laxatives (ricinoleic acid, bisacodyl, phenolphthalein, oxyphenisatin, dioctyl sodium sulfosuccinate, aloe, senna, danthron)
○ Bile Salts
○ Fatty acids
➤ Clinical Syndromes
○ Acute secretory diarrhea
○ Chronic secretory diarrhea
– Surreptitious laxative ingestion
– Pancreatic cholera syndrome (VIP)
– Medullary carcinoma of the thyroid (calcitonin)
– Ganglioneuroma, ganglioneuroblastoma, neurofibroma
– Zollinger-Ellison syndrome (gastrin)
– Malignant carcinoid syndrome (serotonin)
– Idiopathic secretory diarrhea
– Congenital chloridorrhea (some cases)
– Secreting villous adenoma
– Total villous atrophy of small bowel mucosa
– Niacin deficiency
– Intestinal lymphoma
▪ Miscellaneous
– Intestinal Obstruction
▪ Intestinal distention/ileus

The first class of bacterial secretagogues comprises large (MW 84,000), heat-labile proteins (LT), of which cholera enterotoxin is the prototype (Table 12). The LT



stimulate secretion by activating mucosal adenylate cyclase and thus increasing cAMP levels in the mucosa. The intracellular “messenger” for secretion is less well defined; cyclic AMP is considered important, although there are additional steps that involve intracellular levels of Ca^{2+} and the calcium regulatory protein, calmodulin. The second class of secretagogues comprises smaller proteins that are heat-stable (ST). The ST of *E. coli*, stimulates secretion by activating mucosal guanylate cyclase, leading to higher levels of cyclic GMP in the mucosa.

Secretion is also stimulated experimentally by paracrine hormones, luminal factors (e.g., dihydroxy bile acids and fatty acids), neurotransmitters, prostaglandins and physical factors (e.g., distention). Putative secretagogues include vasoactive intestinal peptides (VIP) in the pancreatic cholera syndrome, calcitonin in medullary carcinoma of the thyroid, gastrin in the Zollinger-Ellison syndrome, serotonin in the malignant carcinoid syndrome, and glucagon in glucagonomas. Prostaglandins are also potent stimulators of intestinal secretion. Diarrhea secondary to prostaglandin-stimulated intestinal secretion is a common side effect of orally administered prostaglandin analogues (misoprostil).

The intestinal distention that occurs with obstruction or ileus also produces a local secretory state in the bowel proximal to the obstruction. The mechanism may be related to changes in permeability (as tight junctions are stretched and broken) and perhaps direct neural stimulation of secretory mechanisms. Secretory diarrhea maybe characterized clinically by 1) large volume, stools (often >1 L/day); 2) a stool osmolar gap of < 50 mOsm/L; and 3) diarrhea contains during fasting (between makes and overnight); there is a measured stool osmolar gap of < 50 mOsm/L; and 4) there is no excessive fat, blood or pus in their stools, but often develop depletion in fluid, Na^+ and K^+ .

Therapeutically, the offending agent must be removed. A variety of therapies that influence the secretory process (e.g., somatostatin, prostaglandin inhibitors, phenothiazines, calcium channel blockers, α -2-adrenergic agonists and lithium cholestyramine for bile acid – reduced diarrhea) may be effective. ORT is useful for maintenance of hydration, for bile acid-induced diarrhea, cholestyramine works well unless there has been a greater than 100 cm resection of the terminal ileum.

With more extensive resections (>100 cm) there will be both steatorrhea and bile salt wastage, and treatment must be focused on the steatorrhea as long as the loss of electrolytes and water doesn't lead to severe depletion, in which case intravenous fluid replacement may be necessary.

2.4.3. Exudative Diarrhea

Structural disruption of the intestinal wall by diffuse ulceration, inflammation, infiltrations and tumors will add cellular debris, mucus, serum proteins and blood to the intestinal lumen. The effects on stool volume will be most pronounced when the lesions also involve the colon, since there will be little opportunity for normal mechanisms of colonic fluid and electrolyte absorption to compensate for the increased volume of luminal contents common examples of exudative diarrhea would include inflammatory bowel disease (IBD), and colorectal cancer (CRC).

- Intestinal Transit and Diarrhea



The basal electrical rhythm of the small intestine alters the excitability of the muscle cells. The motility patterns of the small intestine consist of three essential patterns: 1) migrating motor complex (MMC), periodic bursts of contractile activity lasting at least 5 minutes that are succeeded by periods of quiescence and appear to migrate down the small intestine at a slow rate of less than 5 cm/min; 2) minute rhythm, regular groups of between 3 and 10 contractions that occur at intervals of 1 to 2 minutes, separated by periods of quiescence, and appear to migrate down the small intestine at a rapid rate of 60–120 cm/min; and 3) migrating action potential complex, a single ring contraction or single burst of spike potentials that migrates down the intestine at a rate exceeding 90 cm/min. These forms of small intestinal motility control the rate at which material travels along the intestine, and hence arrives at the anus. Gastrointestinal motor activity also determines the time and degree of contact between food, the digestive enzymes, and the absorptive epithelium. Accelerated transit of material through the gut produces diarrhea by limiting the time available for digestion and absorption.

The ileocecal valve is important to gut function. It extends over a 4 cm length of distal small intestine, and produces a high pressure zone of about 20 mm/Hg. Distention of the ileum results in a decrease in the ileocecal sphincter pressure, whereas distention of the colon results in an increased pressure in this area. The ileocecal valve slows down intestinal transit (ileal “break”), and also prevents backwash or regurgitation of contents from the colon. Surgical removal of the ileocecal valve results in rapid intestinal transit as well as the potential for bacterial overgrowth from colonic fecal “backwash.” Lastly, premature evacuation of the colon because of an abnormality of its contents or because of intrinsic colonic “irritability” or inflammation results in reduced contact between luminal contents and colonic mucosa, and therefore diarrhea.

2.4.4. Specific Disease Causing Malabsorption and/or Chronic Diarrhea

The three common causes of chronic diarrhea (Celiac disease, Crohn disease, and Ulcerative colitis, and Irritable bowel syndrome (IBS)) are considered in separate sections.

- Disaccharidase Intolerance

Disaccharide intolerance is a characteristic symptom complex resulting from the ingestion of ordinary dietary quantities of disaccharides, which produces a symptomatic diarrhea. The cause is a deficiency of one or more disaccharidases, but not all people with such a deficiency will experience symptoms, possibly because of a low dietary load, or slow emptying from the stomach. Dietary carbohydrates are presented to the surface of the jejunal mucosa in the form of isomaltose, maltotriose and three major disaccharides – maltose, sucrose and lactose. Trehalose, a disaccharide contained in young mushrooms and in certain insects, is a minor component of modern Western diets.



Deficiencies of disaccharidases may be *primary* (hereditary) or *secondary* (acquired) deficiencies. Characteristically in primary deficiencies, which are rare, only one enzyme is involved; the deficiency is present at birth (with the exception of the common adult-onset form of lactase deficiency), not associated with intestinal disease, and is irreversible because primary lactase deficiency is uncommon in Canadians with northern European ancestors. Secondary deficiencies usually involve all the disaccharidases, may occur at any age, are associated with a disorder of the small intestinal mucosa, and may be reversed if the intestinal disorder (e.g., celiac disease, small intestinal bacterial overgrowth (SIBO) or acute enteritis) resolve.

Table 15. Anatomic approach to the causes of chronic diarrhea

-
- Gastric
 - Excessive use of antacids*
 - Hypergastrinemia/Zollinger-Ellison syndrome
 - Postoperative unmasked celiac disease, lactase deficiency or pancreatic insufficiency
 - Postoperative dumping syndrome
 - *
 - Small intestine
 - Celiac disease*
 - Crohn disease*
 - Bacterial, viral or parasitic infection*
 - Whipple's disease
 - Lymphoma
 - Intestinal infiltration: scleroderma, amyloidosis, diabetes
 - Large bowel
 - Colon neoplasia*
 - Irritable bowel syndrome*
 - Inflammatory bowel disease*: ulcerative colitis, Crohn disease
 - Drugs
 - Antacids*
 - Antibiotics*
 - Alcohol*
 - Antimetabolites
 - Laxatives
 - Digitalis
 - Colchicine
 - Metabolic
 - Diabetes*
 - Hyper-and hypothyroidism



- Addison's disease
- Carcinoid syndrome
- VIPoma syndrome

*Common causes

The clinical manifestations of disaccharidase deficiency (disaccharide intolerance) result from osmotic diarrhea following ingestion of the disaccharide which cannot be digested into absorbable monosaccharides. The affected individual develops, abdominal distress, bloating, borborygmi flatus and diarrhea. The severity of the diarrhea varies with the disaccharide load, the degree of deficiency of enzyme activity and any associated/ causal intestinal disease. Although often unnecessary, the clinical diagnosis can be confirmed by direct enzyme activity or assay of jejunal mucosal biopsies or by indirect methods for detecting disaccharide malabsorption (e.g., the hydrogen breath test after an oral load of appropriate disaccharide). For children and adolescents (who have high nutritional requirements) and for adults who enjoy milk, low-lactose milk is available. It can also be prepared by adding yeast lactase (available in commercial form, Lactaid®) to milk and refrigerating it for 24 hours.

Delayed-onset (adult-onset) hereditary lactase deficiency is extremely common and probably "normal" for humans. Beginning as early as age two years and as late as adolescence in others, the activity of lactase in the majority of the world's populations drop sharply. This is the result of the genetically controlled "switching off" of lactase synthesis by intestinal cells. Individuals of northern European ancestry normally maintain intestinal lactase activity throughout adulthood, so that if they develop lactase intolerance, an underlying cause such as celiac disease must be identified.

- Short Bowel Syndrome

The severity of symptoms following resections of large segments of the small bowel relates to the extent of the resection, to the specific level of the resected small bowel, whether the colon is still in place, to the reason for which the resection was undertaken. A reduction in the dietary intake of long-chain fats will reduce the severity of diarrhea in >100 cm resection with steatorrhea, whereas a sequestrant of bile acids such as cholestyramine, colestipol or aluminum hydroxide is needed for therapy of the bile acid diarrhea arising from a resection of <100 cm.

The short bowel syndrome may also be complicated by hyperoxaluria and nephrolithiasis. Normally dietary oxalate is excreted in the feces, bound to calcium as an insoluble complex. In persons with steatorrhea, fatty acids in the intestinal lumen preferentially bind to calcium, leaving the oxalate soluble and available for absorption in the colon. The short bowel syndrome may also give rise to cholelithiasis; with extensive bile acid malabsorption lithogenic bile will be produced, predisposing to gallstone formation.

If less than 100 cm of the distal ileum is resected (for example, for Crohn disease), diarrhea will result from the moderate loss of the active reabsorptive pathway for bile acids, and the spillage of these malabsorbed bile acids into the colon, where a secretory diarrhea results. If greater than 100 cm of the distal ileum is lost, bile acid



malabsorption will be severe, the ability of the liver to synthesize adequate amounts of bile acids from cholesterol will be exceeded, insufficient bile acids are secreted into the intestinal lumen (less than the critical micellar concentration), and lipids are not solubilized and are malabsorbed. The result is steatorrhea.

- Postgastrectomy Maldigestion and Malabsorption

Postgastrectomy malabsorption frequently follows gastric surgery performed for the treatment of massive obesity, complicated ulcer disease, or gastric cancer. The small size of the gastric remnant causes inadequate mixing of food with digestive juices, particularly after a gastroenterostomy. With the loss of the pylorus, there may be rapid gastric emptying ("dumping"), poor mixing of bile and pancreatic secretions (especially if there is a Billroth II partial gastrectomy with a Roux-en-Y anastomosis), by passing the site of maximal absorption of iron, calcium, and food-stimulated release of secretion and cholecystokinin (CCK) from mucosal endocrine cells and rapid transit down the small intestine. Incoordinated secretion and poor mixing of bile and pancreatic juice leads to fat maldigestion. Small bowel intestinal overgrowth (in a blind loop or following vagotomy) results in maldigestion of fat, carbohydrate, protein, vitamins and minerals. Gastric surgery that allows food to enter into the upper small intestine without dilution and with minimal digestion may "unmask" clinically occult celiac disease, lactase deficiency or pancreatic insufficiency.



Chapter 8: Celiac Disease

H. J. Freeman, N. Gujral and A. B. R. Thomson



1. Definition

Celiac disease, also known as celiac sprue or gluten-sensitive enteropathy, is a life-long disorder characterized by malabsorption of macronutrients and micronutrients along with mucosal inflammatory changes in the proximal small intestine (duodenum), sometimes extending more distally into the jejunum. These appear to be precipitated by ingestion of gluten peptides found in wheat rye and barley. As a result, many celiac patients have intestinal or extra-intestinal symptoms, while others may be entirely asymptomatic. Little is known about the initial events that lead to celiac disease. By definition, however, clinical and histological improvement results from a strict gluten-free diet, and relapse occurs with re-introduction of dietary gluten.

2. History

Clinical GEM

Celiac Disease occurs in about one percent of the Canadian population. Learn to suspect and test for it in persons with typical gastrointestinal symptoms, as well as knowing when to screen for celiac disease in persons with associated disorders. such as autoimmune conditions.

Celiac disease may have been described as early as the first century AD. However, the link with gluten was only first established during World War II when it was noticed that some Dutch children improved with wartime food shortages and became worse with re-introduction of cereals. This association soon led to the definition of gluten sensitive enteropathy. Although early autopsy descriptions for celiac disease are available, an evolution in technology for procurement of small intestinal biopsies led to earlier clinical diagnosis, and an explosion of information on many disorders of the small intestine, besides celiac disease. In recent years, the extended recognition of clinical features and protean presentations of celiac disease has resulted in markedly improved awareness. Finally, development of improved screening methods in the laboratory has resulted in appreciation that celiac disease is common, particularly in Europe and North America, with rates of about 1 in every 100 persons.

Definition of celiac disease in adults depends on two sequential criteria: **first**, demonstration of the typical biopsy changes of untreated celiac disease; and **second**, improvement with absolute dietary gluten restriction. Most often, resolution of diarrhea and evidence of weight gain is sufficient to establish “improvement”. In others, especially in children, a second set of intestinal biopsies after a prolonged period of dietary gluten restriction may be needed to document this improvement.

3. Epidemiology

3.1. High Risk Populations

The true prevalence of celiac disease has not been defined, in part, because many are now recognized for the first time with “atypical”, few or no symptoms. Some have suggested that screening measures have especially increased recognition of celiac disease, at least in comparison to those known to have already established disease.



This has resulted in the conceptual notion of the so-called “celiac iceberg”: clinically evident disease may form only a minority of the overall disease burden that is largely sub-clinical and lies “below the surface”, often initially diagnosed only later in life (Figure 1).

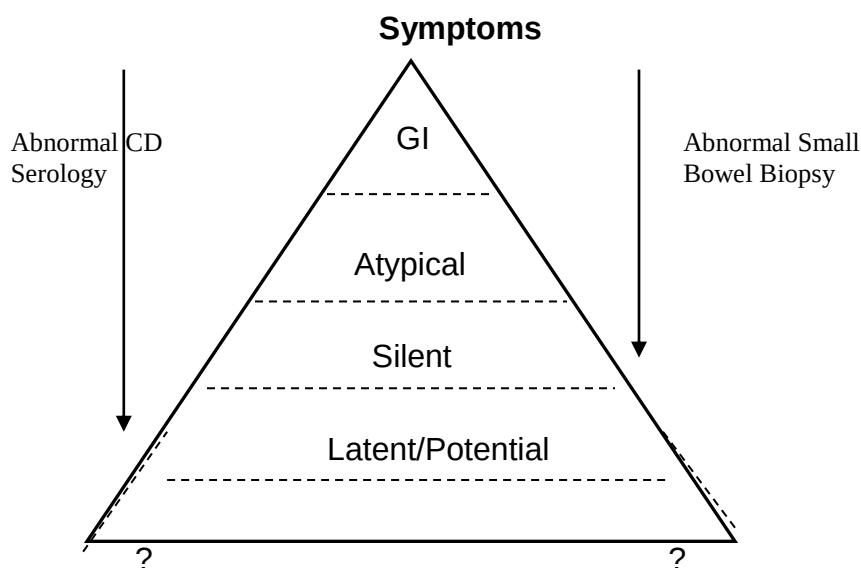


Figure 1. Schematic representation of the celiac iceberg phenomenon.

In North Americans, the reported general population prevalence is approximately 1:100 (1%) with a range of 1:80 to 1:140 (1.25% to 0.71%). A study in Swedish youth (<20 years old) diagnosed with Type 1 Diabetes confirmed the low prevalence (0.7%) of diagnosed symptomatic CD at initial onset of clinical diagnosis, but document by screening an increasing prevalence of silent CD during a 5-year follow-up to reached an overall prevalence of 10% (Larsson 2008). Thus, the prevalence of an association with CD in high risk groups may increase over time. High-risk groups that exceed this general population prevalence are listed in Table 1.

Table 1. High Risk Populations for Celiac Disease

- Relatives, especially first-degree
- Iron or folate deficiency anemia
- Osteomalacia or osteopenic bone disease
- Insulin-dependent diabetes (type1), especially children
- Liver disease, especially AIH and PBC*
- Genetic disorders, including Down and Turner’s syndrome
- Autoimmune thyroid disease
- Skin disorders, particularly dermatitis herpetiformis
- Reproductive disorders, including unexplained infertility
- Neurological disorders, including ataxia, epilepsy and MG*
- Other disorders, including Addison’s, IgA nephropathy.

Abbreviations: AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; MG, myasthenia gravis.



The prevalence of CD in dyspeptics is similar to that in the community at large (Giangreco et al. 2008). About 34% of persons with CD are diagnosed in persons over the age of 60 years (Johnson et al. 2008). While they may be present with the usual gastrointestinal symptoms, their presentation may be subtle, and they are more likely to present with iron deficiency, autoimmune thyroiditis, osteoporosis and bone fractures, as well as non-Hodgkin lymphoma (Freeman 2008). Most often, in adults, the disease is diagnosed in females, compared to males. However, for unknown reasons this female sex preponderance disappears with increased aging. In the elderly, the prevalence rates in females and males are similar.

Table 2. Differences between children and adults with CD

	Children	Adults
○ Female/male ratio	1.6:1	5.7:1
○ Typical symptoms	63%	31%
○ Average months to diagnosis	8	90
○ Mucosal atrophy	86%	52%

Even within a country the size and population of Sweden, there is considerable variation in the risk of developing CD (Olsson et al. 2009). This raises once again that there might be an environmental factor(s) that trigger the onset of symptoms with a genetic risk of CD and who are exposed to gluten. These may include perinatal infections, or viral infections such as Adenovirus 12 and Hepatitis C virus (Plot and Amital, 2009). Further suggestions for a perinatal virus infection triggering CD come from the observations that “girls with the diagnosis of CD and patients of both sexes with a family history of CD have a different pattern of seasonality of birth from the general population (Lewy et al. 2009).

3.2. Age at Diagnosis

In the past, CD was largely diagnosed in children, who were classically described as having symptoms and signs becoming clinically evident from the ages of 4 to 24 months. The timing was possibly owing to the time of introduction of cereal grains into their diet. At the other end of the age spectrum, there are numerous differences between children and adults with CD (Vivas et al. 2008) (Table 2). Anti-tTG IgA levels were higher in children, and correlated with the degree of villous atrophy.

Now, however, it is appreciated that most clinically evident celiac disease is usually first detected between ages 25 and 40 years, not during childhood. Furthermore, in recent years the initial definition of celiac disease in the elderly has become increasingly appreciated, with some studies recording that about 20% of celiacs are older than age 60 years.



Clinical Gem

While the peak age of diagnosis of persons with celiac disease is 25-40 years of age, initial diagnosis of celiac disease may be established at any age, including the elderly.

3.3. Geographic Distribution

The geographical distribution of CD seems to have followed the spread of wheat consumption and the migratory flows of mankind. The highest reported prevalence of celiac disease is from western European countries, North America, particularly Canada and the United States, and Australia. These are all areas where Europeans emigrated. Celiac disease also occurs in the Indian subcontinent, particularly in the Punjab region of northwest India as well as in Indian emigrants to the United Kingdom and Canada. Sprue is probably underdiagnosed in Central and South America. Celiac disease also occurs in the Middle East, Africa, (especially in North Africa), and Asia, although it appears to be very rare in blacks and orientals. Celiac disease has also been described in First Nations persons living on the west coast of Canada; these persons sometimes also have other concomitant immune-mediated disorders.

4. Pathogenesis

Celiac disease results from the interaction between dietary gluten and specific immune, genetic and environmental factors. The current pathogenesis can be summarized as follows: in genetically-primed individuals, an inappropriate T-cell mediated immune response occurs against ingested dietary gluten, the major storage protein of wheat and related grains. This response leads to inflammation mostly in the proximal small intestine, loss or shortening of intestinal villi, and both intestinal as well as extra-intestinal symptoms. When gluten is withdrawn from the diet, these abnormalities improve, or disappear.

4.1. Immune Factors

Gluten generally refers to the entire protein content of wheat, rich in glutamine and proline. Most proteins or peptides that arrive in the proximal small intestine can be digested by luminal and brush border hydrolytic enzymes into amino acids and peptides. Gluten and other proline-rich proteins are poorly digested in the normal human small intestine, because of an apparent deficiency of prolyl-endopeptidases. A number of gluten peptides that may be up to 50 amino acids long can result from this hydrolytic process. For example, undigested gliadin (the alcohol-soluble fraction of gluten) molecules include the 33-mer (composed of 33 amino acids) and 19-mer (composed of 19 amino acids) alpha-gliadin fractions. This is resistant to enzyme digestion, and most of this gliadin remains in the intestinal lumen after gluten is ingested. Gliadin may directly damage the surface epithelium, causing increased IL-15 expression. In addition, gliadin may cause the activation of cytotoxic intra-epithelial lymphocytes that destroy specific epithelial cells with MICA on the surface.



Gliadin peptides may also permeate the epithelial barrier, likely during intestinal infections, or if there is increased permeability (possibly genetically-based, or after surgery), gliadins indirectly cause damage through interaction with lamina propria antigen-presenting cells. Gliadin (high in glutamine) entering the lamina propria may also be deamidated by the enzyme, tissue transglutaminase. This causes conversion of glutamine in these peptides to negatively-charged glutamic acid residues.

The resultant peptides contain sequences that are able to uniquely bind to HLA class II molecules DQ2 or DQ8 on antigen-presenting cells. This permits interaction with the T-cell receptor on gliadin-reactive CD4⁺ T-cells causing release of tissue-damaging mediators, including proinflammatory cytokines (eg., interferon-gamma). As a result, villous atrophy and crypt hyperplasia develop along with activation and expansion of B-cells which produce antibodies. A humoral or B-cell immune response also appears to be directed towards the exogenous antigen, gluten (19-mer alpha gliadin fraction), and the autoantigen, tissue transglutaminase.

The toxic peptides, such as the 19-mer, trigger an innate immune response (Maiuri et al. 2003), characterized by the production of IL-15 by epithelial cells and lamina propria dendritic cells (Di Sabatino et al. 2006). There is some evidence that this response is a generalized response in all individuals, but is amplified in CD patients (possibly due to a lower threshold to IL-15) who only get disease as a result of adaptive immune system involvement (D. Bernardo, 2008). IL-15 affects the epithelial barrier, both by increasing the permeability through disruption of the tight junctions (Clemente et al. 2003; Matysiak-Budnik et al. 2003) and acting on intraepithelial lymphocytes (IELs) promoting IFN- γ production as well as a potent cytotoxic activity particularly by NKG2D⁺ cells (Hue et al. 2004; Meresse et al. 2004). Therefore, immunoadaptive peptides, like the 33-mer, can now reach the lamina propria, where they are presented by dendritic cells to gluten-specific T cells (Nilsen et al. 1995; Rossi et al. 2005).

Regulatory T-cells (Tregs) may show impaired suppressor in CD (Granzotto et al. 2009), raising the possibility that defects in immune tolerance may be part of the pathogenesis of CD. In CD, small intestinal gluten-reactive CD4 (+) T cells bind to the immunodominant gliadin epitopes. The binding to DQ2 is enhanced by the extracellular deamidation of specific glutamine residues by endogenous tissue glutaminases in the lamina propria (Skovbjerg et al. 2008).

TG2 can be both deamidate and transdeamidate peptides, and this propensity is dependent both on substrate affinity and reaction conditions (Stamnaes et al. 2008). The ability of TG2 to hydrolyze the iso-peptide bonds between two peptide substrates represents a novel route for the generation of deamidated T cell epitopes in CD.

tTG2 is on the cell surface, intracellularly, as well as in the extracellular matrix. Anti-tTG antibody inhibits intestinal epithelial cell differentiation and induces proliferation, increases BBM permeability, activates monocytes, and disturbs angiogenesis (Caputo et al. 2009). The authors suggest that these multiple functions suggest that the presence of antibodies to tTG does not simply reflect an epiphenomenon. Other authors have suggested that anti-EMA antibodies are merely bystanders, not related to pathogenic mechanisms (Cianci et al. 2008). After a GFD has been initiated, anti-tTG antibody deposits disappear from the serum after they first disappear from tissue (Caputo et al. 2009).



There are eight Ca^{2+} -dependent transglutaminases that catalyze the cross-linking or deamidation of proteins, thereby playing a role in CD, IBD and cirrhosis. After dietary gluten peptides have been deamidated by the enzyme transglutaminase 2 (TG2), the T-cells are recognized and an inappropriate immune response results. There are large variations in the amount of deamidation between different peptides, and between individual glutamine residues within each peptide (Dørum et al. 2009). The authors suggest that "...the rate of deamidation by TG2 appears to be a factor of importance for the T-cell response to gluten in celiac disease".

A two-dimensional gel proteome reference map using MALDI-TOF ms analysis has been developed (Simula et al. 2009), and will be useful for future research on CD, including "...to identify the variability in protein expression levels, in isoforms expression, or in post-translational modifications associated to pathology or to a therapy".

NMR (nuclear magnetic resonance) has been performed on blood and urine of persons with untreated CD (Bertini et al. 2009). The elevated urine levels of indoxyl sulfate, meta-[hydroxyphenyl]propionic acid and phenyl acetylglycine suggest that there are alterations in the gut microbiota. Since these abnormalities returned to normal in 95% of the persons when treated with a gluten-free diet for a year, these alterations were likely the result of the gluten-associated small intestinal inflammation. In contrast, the reductions in total Bifidobacterium and B. longum population in the feces as well as from duodenal biopsies of both treated and untreated CD patients raises the possibility of this being a pathophysiological abnormality which may have a therapeutic implication (Collado et al. 2008).

A serological response to commensal bacteria occurs in persons with untreated CD (positive seroreactivity to ASCA [anti-Saccharomyces cerevisiae], 49; OmpW [a Bacteroides caccae T-on-B-linked outer membrane protein], 60%; and I2 [Pseudomonas fluorescens-associated sequence], 86%) (Ashorn et al. 2009). Serum levels of ASCA, anti-I2 and anti-OmpW antibodies decreased upon withdrawal of gluten-free diet.

Dendritic cells show increased secretion of IL-6, IL-8 and IL-12 from autologous T cells in response to gliadin in persons with or insilent CD, although the response is higher in CD (Rakhimova et al. 2009). IL-12 induced IFN gamma is the main proinflammatory signal in CD, but IL-17 producing T cells have also been identified (Castellanos-Rubio et al. 2009). Wheat gliadin induces significantly greater production of IL-1 beta, TNF-alpha and IL-23 from PBMC in CD than do non-CD PBMC (Harris et al. 2008). IL-1 beta itself triggers IL-23 secretion and regulated its production. The IL-6 promoter variant -174C increases the risk of developing CD in females (Dema et al. 2009).

IL-15R induces a more intense immunological response in CD than in non-CD persons, and leads to a secondary response of production of nitrites and IFN γ (Bernardo et al. 2008). The higher IL-15R α and lower IL-15 response threshold lead to a magnified effect and intestinal damage. IL-15 and cytosolic phospholipase A2 are included in the NKG2D-mediated cytotoxic T lymphocytes (Tang et al. 2009). This observation of the importance of NKG2D may help to open the way for new therapies in CD. The production of anti-tTG IgA is directly correlated to the production of anti-DGP (anti-deamidated gliadin peptide) IgA and IgG (Marietta et al. 2009).



These authors speculate that "...in well-established celiac patients, anti-tTG IgA is produced by a set of B cells that are reacting against the complex of tTG-DGP in the absence of tTG-specific T cell" (the hampton-carrier theory).

In children with normal duodenal villous architecture and normal or abnormal serology (latent CD), or with increased gammadelta IELs, 85% and 66% showed subepithelial anti-TG2 intestinal deposits (Tosco et al. 2008). This may prove to be a way to assess the likelihood of a genetically IgA predisposed (based in HLA alleles to develop CD).

In active (untreated) CD, there is lower phosphorylated ERK (extracellular response kinase) and higher JNK (c-Jun amino terminal kinase) in peripheral blood mononuclear cells (Broide et al. 2008). This reflects aberrant regulation of the p21/mitogen-activated proteins (MAP) kinase pathway.

After six months of a GFD, these altered values of the ERK and JNK returned towards normal, suggesting that this aberrant kinase response was the result of the active small intestinal inflammation.

The immunogenetics of CD have been renewed, and stress the importance of T cell-mediated immune responses to the pathogenesis of CD, and the use of a genome wide association study which implicated multiple new risk variants, implicating genes involved in the immune system (Dubois and van Heel 2008).

4.2. Genetic Factors

Celiac disease occurs in about 10 to 20% of first-degree relatives of the index patient. HLA genes encoding for HLA-DQ2 and HLA-DQ8 proteins are needed to develop celiac disease. However, their presence may occur in many without celiac disease, since 30% of the Caucasian populations carry HLA-DQ2, but only 1 in 100 will develop CD (Heap and van Heel 2009). While HLA-DQ2 and DQ8 are necessary for the development of CD, certain HLA DQ/DR combinations have a higher relative risk for the development of CD, and the HLA-DQ gene-dose effect influences the strength of the gluten-specific T-cell response (Vermeulen et al. 2009). There are shared as well as distinct HLA alleles in T1DM and CD (Smyth et al. 2008), suggesting that there may be common biological mechanisms in both diseases.

The DQB1*02 allele influences tTG antibody titers and the clinical and histological expression of CD (Nenna et al. 2008). The tTG antibody titers are HLA-DQB1*02 dose dependent, with higher levels in homozygous individuals, and greater clinicopathological expressivity of CD in those with at least one allele.

Genes within the HLA-DQ locus contribute about only 40% of the genetic influence in CD. Using microarray analysis on homogenates from epithelial cells from duodenal biopsies from persons with CD as well as healthy controls, 102 genes were found to have altered expression (Bracken et al. 2008). Validation of significantly altered genes was performed by RT-PCR and immunohistochemistry. This profile of the molecular changes from the epithelial cells in CD provides a focus for the study of novel candidate genes.

In sisters, brothers and parents with CD, high-risk HLA types were found in 57%, 71% and 58%, respectively, but CD was found in only 29%, 15% and 6%, respectively (Megiorni et al. 2009).



There is an association between the interleukin-23 receptor and CD in populations from Finland (Einarsdottir et al. 2009), as there also is such an association for Crohn disease and ulcerative colitis patients in Sweden. The dietary (gluten) and genetic (HLA DQ2 and 8) components of CD may have been in place for years (latent or silent) disease before CD becomes triggered to become symptomatic. Suggested triggers include viral infection, stress, surgery, pregnancy, and childbirth.

During assembly of the HLA class II molecules, they became associated with an invariant chain peptide called CLIP (class-II-associated invariant chain peptide). In CD, there is an alternate CLIP sequence associated with HLA-DQ2 and 8 which has superior binding properties in the peptide binding groove of these HLA molecules (Wiesner et al. 2009). This superior binding arising from the alternate CLIP sequence may contribute to the pathogenesis of CD.

This indicates that these genes are necessary but not sufficient alone to cause the disease. Non-HLA genes may also be important, as genome wide association studies have identified some other genes that may increase risk of celiac disease.

Clinical GEM

HLA-DQ2 and DQ8 are necessary but not sufficient by themselves to cause celiac disease.

4.3. Environmental Factors

A number of environmental factors may play a role in pathogenesis of celiac disease. . Studies have shown that childhood exposure to wheat, barley, and rye in the first 3 months or in month 7 onward significantly increased their risk for developing CD-associated autoantibodies, compared with exposure at 4 to 6 months (Ivarsson 2005; Norris et al. 2005). Breast feeding may be protective and introduction of dietary gluten prior to 3 months of age may increase the risk of disease development. Some viral infections (adenovirus, rotavirus) have also been implicated in earlier studies. Identifying these environmental triggers will be important to explain why some genetically at-risk persons who have consumed gluten for many years may first develop symptoms at an older age.

5. Clinical Features

The clinical features of CD are summarized in Table 3, which lists some of the more common and less common clinical features in children and adults. Most clinicians assume that childhood celiac disease and adult celiac disease are similar, but differences, particularly in their pathogenesis and clinical features, do occur. Indeed, some, but not all physicians believe that disease first detected in adults reflects long-standing sub-clinical disease in children that only becomes clinically evident as adults. Others believe that the disease may be much more heterogeneous, and may become initially activated in a genetically-predisposed person much later in life.



Table 3. Common and Less Common Clinical Features of Celiac Disease in Adults and Children

➤ Common	
○ Children:	- diarrhea & failure to thrive
○ Adults:	- diarrhea, weight loss & anemia with iron or folate deficiency
➤ Less Common	
○ Children:	- short stature & delayed puberty
○ Adults:	- osteopenia, dental enamel hypoplasia, hypertransaminemia, hyposplenism, polyneuropathy, ataxia, infertility, alopecia

5.1. Childhood Celiac Disease

Most children with celiac disease become clinically apparent after age 4 months, but often before 2 years. Historically, this was believed to be related to the introduction of dietary cereal grains as well as weaning from breast feeding. Diarrhea is commonly recorded, but occasionally, constipation may be present. Most often, in childhood, the disease is insidious with slowing of growth prior to the onset of weight loss. In some, vomiting and severe abdominal distension may occur. With clinically-evident disease, short stature, delay of puberty, pallor and anemia associated with iron and/or folic acid deficiency may develop. Irritability and behavioral disorders, including depression and poor school performance may occur. Rickets was reported in earlier historical experiences, but is not so evident now. Seizure disorder (epilepsy) with cerebral calcifications has been recorded.

The initial detection of celiac disease in older children and adolescents is less common. However, in children on a gluten free diet for previously diagnosed celiac disease, symptoms may re-develop in this age group, as compliance to a gluten-free diet in older children and adolescents may be less. Some children also have less typical presentations suggesting other disorders including: recurrent and episodic abdominal pain, often with hyperamylasemia (i.e., pancreatitis), and abnormal liver chemistry tests with a hepatocellular injury pattern (i.e., hepatitis). Recurrent aphthous ulcers and dental caries may also be noted.

5.2. Adult celiac disease

There are now recognized to be severe “types” of celiac disease occurring within a spectrum (Table 4). In *classical celiac disease*, diarrhea, weight loss and significant malabsorption of a range of macronutrients and micronutrients may occur. Severe histopathological changes appear in the proximal small bowel mucosa. Changes also develop along the length of the small bowel. Indeed, the extent and severity of these histological changes, the so-called “proximal-to-distal gradient”, correlate best with clinical features. With clinically significant malabsorption, for example, histological changes may be severe and extend well beyond the proximal jejunum.



Table 4. Spectrum of Celiac Disease

Types of Celiac Disease (adapted from Setty et al. 2008)

	HLA DQ2/DQ8	Anti-tTG2	Abnormal histology	GI/non-GI symptoms
○ Classical	+	+	+	+
○ Silent and Occult	+	+	+	-
○ Latent	+	+/-	-	-

Further along the small intestine, into the ileum, the morphological changes are less severe and may be patchy in distribution. This may simply reflect exposure in the most proximal small bowel to normally higher concentrations of ingested gluten peptides, since studies have shown that the distal small bowel is in fact very sensitive to gluten peptides if they are infused through long intestinal tubes. With more extensive disease and malabsorption, diarrhea and weight loss occur.

After removal of dietary gluten, clinical improvement occurs with resolution of diarrhea and weight gain. This is usually accompanied by at least partial resolution of abnormal histological changes, first from the most distal portions of the small bowel, and later from more proximal small bowel (i.e., “distal-to-proximal gradient”).

Clinical GEM

In addition, to the classical form of celiac disease, in which the patient with intestinal symptoms or with symptoms and signs of malnutrition or nutrient deficiencies, some persons will have clinically silent (occult) celiac disease, and be suspected as having celiac disease because of their having an associated (often autoimmune) condition. Latent celiac disease is a form of sprue in which the person has at one point in time both normal serology and intestinal morphology, but at a later time the intestinal biopsy becomes abnormal.

In some, clinically silent or **occult celiac disease** may be present. Few or no intestinal symptoms may be evident. These persons are often suspected from conditions associated with celiac disease (Table 5). In these, only limited histological changes are detected in the most proximal small bowel and only isolated nutrients absorbed primarily at this site may become deficient (eg., iron deficiency anemia). More than enough normal small intestine is present more distally to permit absorption of other nutrients so that diarrhea and weight loss are not seen. Another clinically silent form is **latent celiac disease**. This was initially reported in persons with dermatitis herpetiformis. In this entity, the small intestine appears to be histologically normal, and serology for celiac disease is initially normal.



Table 5. Intestinal and extraintestinal conditions associated with Celiac Disease

➤ Intestinal

- Esophagus – squamous cell Ca, adenocarcinoma
- Stomach – lymphocytic gastritis; pernicious anemia
 - celiac disease (classical, occult, latent)
 - ulcerative ileojejunitis
 - tropical sprue
 - collagenous sprue
 - diffuse small intestinal lymphoma
 - early aberrant T-cell lymphoma (EATL)
 - refractory sprue, types 1 and 2
 - unclassified sprue (sprue-like intestinal disease)
- Small Bowel
- Colon – microscopic colitis, IBS
- Liver – AIH, AIC, PBC, PSC, idiopathic transaminitis
- Pancreas – 2° pan-insufficiency, severe insufficiency, diabetes, autoimmune pancreatitis
- Nutritional abnormalities - short stature, osteopenic bone disease, iron and vitamin deficiencies, unexplained weight loss

➤ Extra-intestinal

- Neuropsychiatric and CNS
 - Chronic fatigue syndrome
 - Irritability
 - Depression
 - Peripheral neuropathy
 - Epilepsy with intracranial calcifications
 - Gluten ataxia syndrome (gait and limb ataxia) Paresthesias
 - Night blindness
 - Autism
- Teeth – dental enamel defects
- Lung – fibrosing alveolitis
 - Bird fancier's lung
- Hematopoietic – iron deficiency anemia, hemorrhage
 - Thrombocytosis
 - Howell-Jolly bodies
 - IgA deficiency
- Musculoskeletal – atrophy, tetany, weakness, myalgias
 - autoimmune connective tissue disorders: Sjogren's syndrome, RA, lupus
 - osteoporosis
- Endocrine - secondary hyperparathyroidism, insulin-dependent DM, autoimmune thyroid disease, autoimmune adrenal disease; delayed



- puberty
- Integument - Follicular hyperkeratosis and dermatitis
 - petechiae, ecchymoses
 - edema
 - dermatitis herpetiformis
 - acrodermatitis enterohepatica
- Obstetrical - infertility, obstetrical complications (miscarriage), amenorrhea
- Renal – IgA nephropathy
- Miscellaneous - Downs syndrome, Turners syndrome
- Delayed puberty, slow growth

Abbreviations: AIC, autoimmune cholangitis; AIH, autoimmune hepatitis; CD, celiac disease; DM, diabetes mellitus; IBS, irritable bowel syndrome; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis.

Adapted from: Green PHR, Rostami K, Marsh MN. *Best Practice & Research Clinical Gastroenterology* 2005;19(3): pg 39.; and Crowe SE. *2007 AGA Institute Postgraduate Course*: page 25.

5.3. Associations

Neurological disorders occur in about 10% of persons with CD. Anti-tTG2 is associated with intestinal disease, whereas anti-tTG 6 IgA and IgG has been reported to be independent of intestinal involvement (Hadjivassiliou et al. 2008). Temporal lobe epilepsy with hippocampal sclerosis has been described in association with CD (Peltola et al. 2009).

The prevalence of CD is about 3-fold increase in those with idiopathic epilepsy (Emami et al. 2008). The cerebellar syndrome and small fiber neuropathy may complicate CD, but often do not respond to a gluten-free diet. In a small group of such individuals, intravenous immunoglobulin was therapeutically effective (Souayah et al. 2008). Other neurological disorders associated with CD include dementia and subacute combined degeneration from associated vitamin B12 deficiency (Freeman 2008).

While osteoporosis (intestinal osteopathy) is more common in persons with CD, there is no need to routinely screen all postmenopausal women for CD (Kavuncu et al. 2009), as, in addition, there does not appear to be an excess risk of CD in adult patients with osteoporosis (Legroux-Gérot et al. 2009). However, children may benefit from bone mineral density screening at the time they are diagnosed with CD, especially in those with low body mass index, or with severe mucosal changes on mucosal biopsy (Jatla et al. 2009).

Autoimmune thyroid disease is associated with CD, with the increased susceptibility of each being possibly related through cytotoxic T-lymphocyte-associated protein 4 (CTLA4) (Tolone et al. 2009).

While it is widely recognized that T1DM and CD may occur together, especially in children, the CD is often clinically silent, and even the person's height, body weight, and



haemoglobin concentration may be normal (Jatla et al. 2009). A high index of suspicion and appropriate screening for CD in T1DM is necessary.

It is not clear if the observation that anti-tTG from pregnant CD mothers directly binds to the syncytiotrophoblasts on the surface of the placenta, inhibiting the placental activity of tTG (Anjum et al. 2009), compromising placental function and lead to a poor outcome of the pregnancy. It remains controversial if all pregnant mothers should be screened for CD (Pope and Sheiner 2009).

Oxalate renal calculi are more prevalent in CD, and this is not due to the CD-associated diarrhea or malabsorption, but rather to unexplained hyperoxaluria (Ciacci et al. 2008). Placing the CD oxalate excretors on a GFD returned the hyperoxaluria to normal.

The prevalence of CD in children with Down syndrome is 5.2%, 10-times higher than the general Dutch population (Wouters et al. 2009).

The anemia which occurs in 34% of persons recently diagnosed with CD may be from deficiencies of iron and vitamins, as well as from the inflammation-associated increase in IFN γ , reduction in serum levels of erythropoietin, and thereby anemia of chronic disease (Bergamaschi et al. 2008).

There is a higher than expected rate of eating disorders, (especially bulimia nervosa) in CD, and non-compliance with a GFD is higher in this group (Karwautz et al. 2008).

For children with clinical manifestations suggestive of CD, BMI SDS (Body Mass Index Standard Deviation Score) is more sensitive than height or weight to be used as an indicator of the need to screen for CD (van Dommelen et al. 2008). In children with CD, there is an increased frequency of enamel defects, particularly in deciduous teeth (Ortega Paez et al. 2008). In children with T1DM, 11% were positive for CD-specific antibodies, and 15% had positive thyroid antibodies (Fröhlich-Reiterer et al. 2008). Some persons with CD are hyposplenic, and this may contribute to the increased rate ratio (1.61) of pneumococcal infection in England in celiac patients (Thomas et al. 2008). CD is associated with thyroid disease. In Sweden, the hazard ratio is 4.4 for hypothyroidism, 3.6 for thyroiditis and 2.4 for hyperthyroidism (Elfström et al. 2008). CD also occurs in IgA-deficient persons, so one must be aware that the presence of the relatively common IgA deficiency will cause false negative IgA CD serological tests (Cianci et al. 2008).

CD is associated with hyperhomocysteinemia, which is itself associated with an increased risk of cardiovascular disease (particularly stroke), recurrent miscarriage and osteoporotic fractures. The elevated levels of homocysteine in CD normalize on a GFD (Dickey et al. 2008). Supplementation of CD patients who were already on a GFD had an improvement in their psychological well-being, and especially anxiety and depression, when given a daily supplement of B vitamins (Hallert et al. 2009).

Over half of 54 untreated CD children (mean age of 7 years) had reduced serum calcium and vitamin D3 concentrations plus elevated PTN levels, with the hyperparathyroidism returning to normal when a GFD was introduced (Zanchi et al. 2008).

Untreated persons with CD may have an inadequate response to hepatitis B immunization: as compared with CD treated with a GFD where the response rate was



96%, those not on a GFD have an immunization response of only 51%, and the poor response correlated with the degree of nonadherence to the GFD (Nemes et al. 2008).

Dermatitis herpetiformis (DH) is associated with CD. Patients with DH suffer from a papulovesicular eruption which contains IgA deposits in the dermal papillae. The epidermal transglutaminase, TG3, is distinct from the TG produced by the small intestine, TG2. Patients with DH and adults with CD have elevated serum levels of antibodies to TG3, as well as to TG2 (Hull et al. 2008).

Clinical GEM

Definition of celiac disease in adults depends on two sequential criteria: **first**, demonstration of the compatible biopsy changes of untreated celiac disease; and **second**, improvement with absolute dietary gluten restriction. But the definition is challenging, with the recognition of non HLA genotypes, and biopsy-negative latent/potential disease, and the fact that many patients have few or no typical GI symptoms

Approximately 3% of CD patients will have primary biliary cirrhosis, primary sclerosing cholangitis, or autoimmune hepatitis. These do not respond to a GFD. In contrast, about half of CD patients will have transaminitis associated with a nonspecific hepatitis, both of which normalize on a GFD (Volta, 2009). Rarely, cryptogenic chronic hepatitis or cirrhosis will be found histologically, and this may partially respond to a GFD.

5.4. Refractory Celiac Disease

In some persons with well-defined and treated celiac disease, diarrhea or malabsorption may recur and appear to be refractory to continued dietary gluten withdrawal. Often, these recurrent clinical features are associated with the return of severe histological changes which are typically seen in untreated celiac disease. In most, poor compliance with a strict gluten-free diet is evident as the cause of the recurrence of symptoms and histological signs. Sometimes, the actual source of gluten is ubiquitous, such as pill capsules or communion wafers.

Other causes of refractory symptoms may need to be considered. A second cause of symptoms (i.e., diarrhea and weight loss) may be present, such as an infectious diarrhea. Also, histologic changes in the small bowel due to other related causes (eg., folate deficiency, zinc deficiency) may occur. In these, treatment of the specific infection or the deficient nutrient may be sufficient for the patient to improve.

In others, a concomitant cause for malabsorption may be present. For example, pancreatic exocrine insufficiency with pancreatic calcification may occur, particularly in celiac patients with long-standing malnutrition. On occasion, re-evaluation of the original diagnosis is needed to ensure that a different diagnosis was not initially missed. Finally, diarrhea may be due to a disorder associated with celiac disease, (eg., lymphocytic or



collagenous colitis), or a serious complication (eg., lymphoma). An unusual and rare disorder, collagenous sprue, sometimes may occur in celiac disease. In most persons with collagenous sprue severe malabsorption with diarrhea, weight loss and marked nutritional and electrolyte disturbance may develop.

In a small number of persons with refractory celiac disease, no specific cause can be identified. Some have a rare syndrome with small bowel histologic changes of variable severity, splenic hypofunction and cavitation of mesenteric lymph nodes. Some eventually develop or have a concomitant intestinal lymphoma.

CD subjects have high levels of TCR gamma delta+ IELs in the small intestinal mucosa, but these elevated levels fall in about half of refractory CD (RCD) type II patients who develop enteropathy-associated T-cell lymphoma (EATL) (Verbeek et al. 2008), with these being a negative correlation between the number of TCR gamma delta+ IELs and aberrant IELs. Intracellular CD3 epsilon is present in IELs and lymphoma cells in CD, but the cell surface lacks the T-cell receptor (TCR) – CD3 complex due to either impaired synthesis or defective association of the TCR chains (Tjon et al. 2008). This results in the premalignant transformation in RCD II.

There is a positive pathogenetic relationship between CD and lymphocytic gastritis (presence of ≥ 25 lymphocytes per 100 epithelial cells) (Prasad et al. 2008). In contrast, while there is a 80% prevalence of antroduodeno-jejunal fasting and fed motility abnormalities observed in untreated CD, which decline on a gluten-free diet (GFD) (Bassotti et al. 2008). Their occasional persistence on a GFD raises the possibility that these motor abnormalities may explain persistent symptoms in some persons with CD who are on a GFD.

Lymphocytic duodenitis is not part of the histological spectrum of CD (Vande Voort et al. 2009). Intestinal T-cell lymphoma are tumors which differ in their association with “enteropathy, intraepithelial or nonepithelial origin, primary or secondary inducement, and T-cell or natural killer-like T-cell immunophenotypic” (Muram-Zborovski et al. 2009). It is suggested that “...a large monoclonal antibody panel [be used] for the differential diagnosis of this heterogeneous group of T-cell lymphoma”.

Enteropathy-associated T-cell lymphomas (EATL) are T-cell non-Hodgkin lymphomas of the small bowel occurring in persons with CD. The incidence in the Netherlands is 1/105 inhabitants per year, is usually in the jejunum, more often in males, peak incidence in the 7th decade, with the diagnosis usually made by surgical resection (Verbeek et al. 2008).

5.5. Unclassified Sprue or Sprue-like Intestinal Disease

Occasionally, some adults may have diarrhea and weight loss. Severe intestinal mucosal biopsy changes are present, similar to those in untreated celiac disease, but these fail to respond to a gluten-free diet. This may represent a heterogeneous group, with no specific cause identified. Some could have a “clinically-resistant” form of celiac disease, whereas others may eventually prove to have a “difficult-to-diagnose” lymphoma. Most remain severely symptomatic with malabsorption and profound wasting despite a gluten-free diet. In some, an abnormal subset of intra-epithelial lymphocytes may be detected with morphologically normal, but phenotypically abnormal lymphocytes (based on immunochemical staining). Most of these persons unfortunately die with uncontrolled malabsorption despite steroid therapy and parenteral nutrition.



This suggests that immunohistochemical changes represent a marker of poor prognosis.

6. Malignant Complications

Some of the malignant complications are listed in Table 6. The overall cancer risk in celiac disease is approximately double the rate in the general population. The two main malignancies in persons with celiac disease include adenocarcinoma or lymphoma of the small intestine. Some reports suggest that other sites in the gastrointestinal tract may have an increased rate of malignancy. In particular, hypopharyngeal cancer may occur, possibly in association with iron deficiency anemia. The risk of colon cancer is not thought to be increased.

Table 6. Complications of Celiac Disease

-
- Enteropathy-associated T-cell lymphoma (and B-cell lymphoma)
 - Carcinoma of hypopharynx
 - Carcinoma of esophagus
 - Carcinoma of small intestine
 - Refractory sprue
 - Collagenous sprue
-

Clinical GEM

In the celiac patient who was previously well on a gluten-free diet, and who then has a recurrence of GI symptoms, assess for possible dietary non-compliance, intestinal lymphoma or adenocarcinoma, development of collagenous sprue or microscopic colitis, intercurrent infections.

Small intestinal adenocarcinoma is an unusual malignancy, but, this cancer is markedly increased in adult celiac disease. These are usually located in the jejunum, although localization in the duodenum may occur. Like adenocarcinoma that occurs in the colon, an adenoma-to-carcinoma sequence has been proposed. Most often, however, adenocarcinoma occurring in the patient with celiac disease presents late in the clinical course, sometimes with symptoms of a small bowel obstruction. Rarely, this malignancy is the presenting feature of celiac disease. Surgical resection of the carcinoma has the greatest potential for cure, although adenomas and carcinomas may be multifocal and occur elsewhere in the small intestine, thereby presenting a surgical care.

Small bowel lymphoma may also occur in persons with celiac disease. Most are T-cell in type, the so-called enteropathy-associated T-cell lymphoma. However, B-cell lymphomas also may occur. These also occur in the jejunum, but duodenal lymphoma may also be seen. Most often, these lymphomas present as ulcerating or



obstructing tumors. Although splenic atrophy is usually seen in adults, the development of splenomegaly may be a clinical clue to the development of an occult lymphoma. Rarely, the lymphoma may also develop in an extra-intestinal site or may be multifocal.

Involvement of lungs or pleura, and thyroid with T-cell lymphoma in celiac disease has been described, possibly reflecting their common embryonic origins from the intestinal tract. Hepatosplenic T-cell lymphoma, an exceedingly rare entity, has also been reported in celiac disease without evidence of small bowel involvement with lymphoma.

Often, surgical treatment is required for complications, particularly intestinal obstruction. Radiation and chemotherapy have also been used. A lymphoma may be the first presentation of underlying celiac disease. Finally, there is some evidence, primarily from long-term studies in the United Kingdom, suggesting that the continued use of a gluten-free diet may be protective for the development of lymphoma in the person with celiac disease.

7. Diagnosis

7.1. Serology and urine testing

There are a number of clinical indicators for CD (Table 7). A number of serological tests have been developed that may be helpful for screening for celiac disease. If celiac disease is suspected, a serologically-positive test may confirm suspicion of celiac disease, but a biopsy should be done to determine if changes of untreated celiac disease are present prior to initiating a gluten-free diet.

Most commonly used serological tests for celiac disease are IgA antibodies to endomysium (EMA) and tissue transglutaminase (tTG). The former is semi-quantitative whereas the latter is quantitative and may be automated. While both serological tests are highly sensitive, false-positive assays may occur in the absence of celiac disease (Table 8).



Table 7. Clinical indications for serological testing for CD

-
- Autoimmune endocrine disorders
 - Insulin-dependent diabetes mellitus
 - Autoimmune thyroid disease
 - Autoimmune adrenal disease
 - Autoimmune connective tissue disorders
 - Sjogren's syndrome
 - Rheumatoid arthritis
 - Systemic lupus erythematosus
 - Hepatobiliary conditions
 - Primary sclerosing cholangitis
 - Primary biliary cirrhosis
 - Autoimmune cholangitis
 - Elevated transaminases
 - Other gastrointestinal disorders
 - Lymphocytic gastritis
 - Microscopic colitisMiscellaneous conditions
 - IgA deficiency
 - IgA nephropathy
 - Down's syndrome
 - Turner's syndrome
-

Printed with permission: Crowe SE. 2007 AGA Institute Postgraduate Course: page 25.

Table 8. Performance Characteristics of Tests for Celiac Disease

	Sensitivity (%)	Specificity (%)
○ Lactulose/mannitol ratio in urine	85	46
○ Saccharose in urine	60	53
○ AGA – IgA	15	100
○ AGA – IgG	20	100
○ EMA	50	78
○ TGA – IgA	77	100
○ TGA – IgA and EMA	98	100

Abbreviations: AGA, anti-gliadin antibody; EMA, endomyceal antibody; anti-tissue transglutaminase



The tests may also be positive if there is co-existent chronic liver disease. In addition, the tests are not as helpful if selective IgA deficiency is present, as is the case in about 5% of the general population. This is why it is often recommended to perform a quantitative test for IgA when performing the IgA-anti tTg test.

The anti tTg test is about 95% sensitive and specific to diagnose CD, with false positives or false negatives (Table 9).

Table 9. Clinical indications which are associated with false positive or false negative, serologic testing for CD

-
- False negative
 - True false negative
 - IgA deficiency
 - Children < 2 years
 - Recent gluten free diet
 - TPN
 - Recent steroids, immunosuppressives, anti-TNFs
 - Hematopoietic stem cell transplantation
 - False positive
 - Congestive heart failure
 - Autoimmune diseases (may be associated with CD which is in a latent phase)
 - Liver diseases
 - Inflammatory bowel disease
 - Silent (potential), potential (latent) celiac disease
-

Adapted from: Green PHR, Rostami K, Marsh MN. *Best Practice & Research Clinical Gastroenterology* 2005; 19(3): pg 391.

Standardized measurement of transglutaminase antibodies is necessary, because of the very wide range of laboratory sensitivities (69% to 93%) and specificities (96% to 100%) of this important assay (Li et al. 2009). A standardized method of analysis is also needed to determine quantitatively to gluten content of food and to be certain that “gluten-free” truly represents an accepted low level of gluten (Thompson and Mendez 2008). An electrochemical sensor has been developed to detect gluten in foods, and it performs well compared to the ELISA (Nassef et al. 2008).

In children, IgA antibody testing to tissue transglutaminase (tTG) had the best operating characteristics, with a sensitivity of 93%, specificity of 98%, PPV of 98% and NPV of 92% (Basso et al. 2009). In children with IgA deficiency, AGA IgG II testing was positive. In children over 2 years and without IgA deficiency, tTG IgA and AGA IgG II were equivalent in performance. These serum markers fell towards normal within a year of a gluten-free diet.

Whole blood tests have been developed for the diagnosis of CD, and while the sensitivity is a little lower (91%) than the standard serum-based ELISA tests, their specificity is comparable (98%) (Raivio et al. 2008).



A cost-effective, point-of-care electrochemical immunosensing method has been developed for the detection of serum antibodies to tTG (Pividori et al. 2009), and may provide a means for population screening in a primary care setting.

In children, the tTG may be less reliable than in adults, with a sensitivity of 93% and specificity of 90% (Leach et al. 2008).

Screening for CD using serology may need to be performed several times over an extended time interval. For example, it is accepted that T1DM is associated with CD. The cumulative frequency of positive CD serology in children and adolescents with T1DM rises from approximately 4% to 10% over a 5 year interval (Larsson et al. 2008).

Intestinal permeability tests from urine samples can screen for a wide range of small intestinal diseases, including CD and enteric infections. Monosaccharides (mannitol) and disaccharides (lactulose, saccharose) molecules have been used to investigate intestinal permeability. The use of hyperosmolar lactulose and mannitol test solutions is found to increase the sensitivity of the test in detecting CD. Intestinal permeability is characteristically elevated in untreated CD, with a sensitivity of up to 85% (Table 8). The reason being for this is an increase in the absorption of lactulose (through the paracellular route) due to "leakiness" of the intestine and a reduction in the absorption of mannitol (through the transcellular route) due to a reduction in surface area as a result of villous atrophy

7.2. HLA Genotyping

Genotyping methods for HLA risk factors are laborious, complicated and costly. An approach which "...exploits linkage disequilibrium between single nucleotide polymorphism (SNPs) and the CD-associated HLA risk factors DQ2, 5 and 8..." shares that only six SNPs are needed to predict the risk types carried by greater than 95% of CD patients, with a sensitivity greater than 99%, a specificity of 99.6%, and a predictive value of 94.8% (Monsuur et al. 2008). This method would appear to be excellent for population screening for CD.

Negative testing for HLA-DQ2 and DQ8 could eliminate the need to perform serological tests in persons thought to be otherwise at risk of developing CD, and it is possible that this approach could prove to be cost-effective (Chang and Green 2009). CD-associated HLA allele typing would provide a high negative predictive value to exclude CD in high-risk groups (Donat et al. 2009).

Population screening for CD is not yet advocated, but certainly in high risk groups and possibly on an index basis, a novel HLA genotype method using six HLA-tagging single nucleotide polymorphisms suitable for high-throughput approaches gives sensitivities and specificities of 95% to 100% in European persons (Koskinen et al. 2009), and may prove to be cost-effective and lead to widening of the indications for screening.

7.3. Endoscopy and Diagnostic Imaging

There are a number of endoscopic features which are thought to be associated with CD. About two-thirds of CD patients will have a mosaic pattern, nodular mucosa, scalloping of folds, and reduction/loss of folds. If there were more than one of these endoscopic markers present, 84% of these persons had CD. The positive predictive



value (PPV) was about two-thirds overall for these endoscopic findings (Piazzini et al. 2008).

Endoscopic changes in the upper small intestine by EGD (esophagogastroduodenoscopy) may also be seen with video capsule endoscopy (CE). While the mucosa changes in CD are often in the proximal intestine and are readily within the reach of EGD, CE does not allow detection of subtle endoscopic changes further along the intestine. CE showed a 78% concordance with histology to diagnose CD in those who had failed to respond to a GFD (Maiden et al. 2009). Patchy involvement is unusual, and the typical features (villous atrophy, scalloping, fissuring, mosaic pattern) gradually decreased along the length of the small intestine (Ersoy et al. 2008).

MDCT enteroclysis may prove to be useful to raise the possible diagnosis and its complications of CD (Soyer et al. 2008).

Extending the use of endoscopy to raise the suspicion of CD, optical band imaging enhances the contrast of the mucosal surface without the use of dyes, and provides excellent sensitivity, specificity, PPV and NPV in the evaluation of the villous patterns and optimizing the diagnostic accuracy in celiac disease (Cammara et al. 2008).

7.4. Histology

Clinical GEM

At present, the “gold standard” for the diagnosis of celiac disease remains the small intestinal mucosal biopsy

Although the diagnosis of CD can be suspected on clinical or laboratory grounds, or as a result of serological tests, histology of the small intestinal mucosa is still the diagnostic gold standard and must always be performed. Histopathological analysis of small intestinal biopsy samples of individuals with CD is characterized by typical architectural abnormalities. Marsh (Marsh, 1992) has pioneered the theory of a sequence of progression of the CD lesion in the small intestinal mucosa.

The characteristic histopathological findings for untreated celiac disease include crypt hyperplasia and villous atrophy causing a “flattened” mucosal appearance (Figures 2 to 5). Intraepithelial lymphocytosis also occurs, and the lamina propria region shows increased cellularity largely from plasma cells and lymphocytes. Some experts have termed this biopsy appearance as: crypt hyperplastic villous atrophy (severe “flat” lesion, Marsh 3 lesion). Over time, the clinical and histological changes revert to normal on a strict gluten-free diet. Most newly diagnosed sprue patients will notice clinical improvement within a few weeks. Histological evidence of improved architecture in the most proximal small intestine may take many months, even years, especially in adults.

Less severe histopathological changes may occur in adult celiac disease and the changes may be patchy rather than diffuse. In children, CD-related histological changes are always present in the duodenal bulb, and sometimes this is the only site to be histologically abnormal (Bonamico et al. 2008). These authors suggest that for the



diagnosis of CD, 2 biopsies be taken from the duodenal bulb and 2 from the distal duodenum.

Minimal intestinal lesions are at the very mild end of the spectrum of histological changes in CD. In a three year follow-up study of 209 persons performed in Italy, when CD serology was initially negative and duodenal biopsy showed a minimal lesion, three years later, only one person was on a GFD because of gluten-sensitive symptoms, and was DQ2 and 8 positive (Biagi et al. 2008). This strongly suggests that a minimal lesion plus initially negative endomysial antibodies is unlikely to be CD.

In Sweden, IBD occurred in 0.3% of small intestinal mucosal biopsies showing villous atrophy (VA) (Ludvigsson et al. 2009). Thus, comorbidity other than CD in the biopsy showing VA is rare, and the specificity of CD is high in villous atrophy. The same type of validation needs to be performed in other geographical regions.

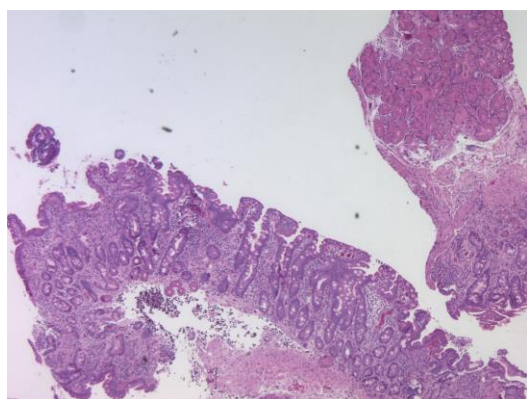


Figure 2.

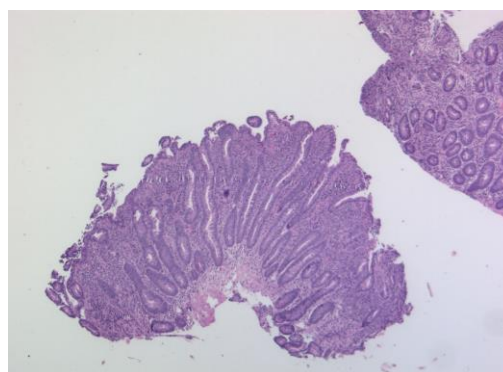


Figure 3.

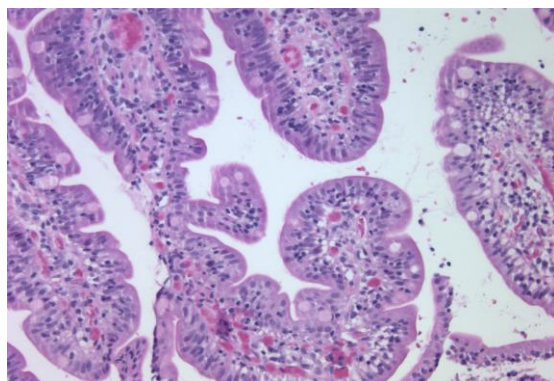


Figure 4.

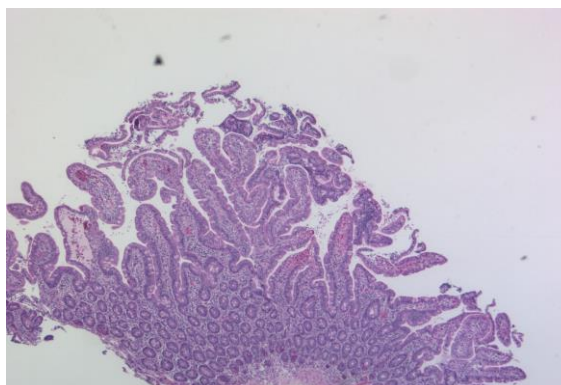


Figure 5.



There are many small bowel disorders which may mimic CD (Table 10) (Figure 6).

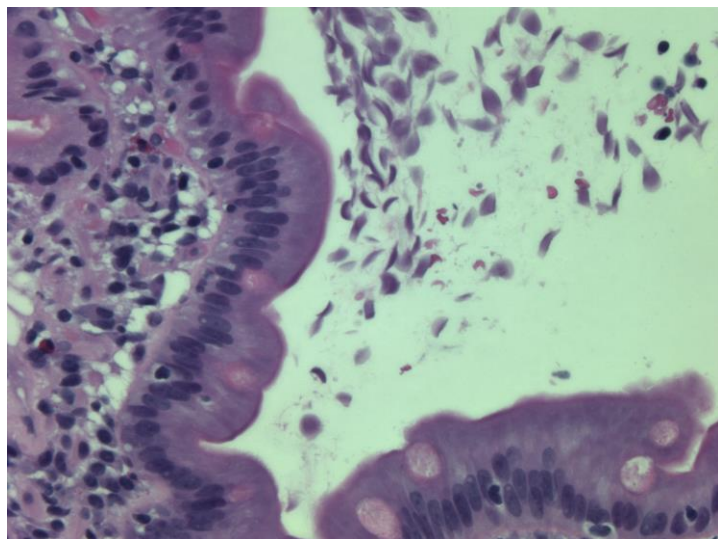


Figure 6

Table 10. Differential diagnoses of a “sprue-like” small bowel biopsy in a patient suspected of having CD

-
- Celiac disease and its variants
 - Infection
 - post viral gastroenteritis
 - giardiasis
 - small intestinal bacterial overgrowth (stasis syndrome)
 - HIV (immunodeficiency syndromes)
 - MAC (Mycobacterium-avium complex infection)
 - cryptococcus, giardia lamblia, strongyloides
 - tropical sprue (infections agent suspected)
 - Whipple’s disease
 - Crohn disease
 - Amyloidosis
 - Mastocytosis
 - Histoplasmosis
 - Eosinophilic enteritis
 - Waldenstroms macroglobulinemia
 - Infiltration
 - Benign
 - Malignant immunoproliferative small intestinal disease (IPSID, ie alpha chain disease), lymphoma
 - Immune
 - graft-versus-host disease
 - hypogammaglobulinemia



➤ Food

- food protein hypersensitivity (rye, barley, egg, fish, rice, poultry, cow's milk, soy, other proteins)
- oats-induced villous atrophy
- folate, cobalamin, zinc deficiency
- protein-calorie malnutrition

➤ Drugs, radiation

- NSAIDs, colchicines, neomycin, chemotherapy
- Radiation

➤ Miscellaneous

- Zollinger-Ellison syndrome
- mesenteric lymph node cavitation syndrome
- α - β -Lipoproteinemia
- lymphangiectasia
- microvillus inclusion disease (children)
- Waldenstrom's macroglobulinemia

Abbreviations: CD, celiac disease; IPSID, immunoproliferative small intestinal disease

Adapted from: Freeman HJ. *Canadian Journal of Gastroenterology* 2008;22(3): pg 277.

The combination of the presence or absence of villus shortening with or without increased intraepithelial lymphocytes (IELs) may be a helpful distinguishing factor (Table 11).

Table 11. Conditions other than CD, where there may be an increased density of small intestinal intraepithelial lymphocytes (IELs)

No villous shortening, ↑ IELs	Villous shortening, ↑ IELs	Villous Shortening, Normal IELs
○ Celiac disease ○ Tropical sprue ○ Autoimmune diseases/ conditions ○ Nonsteroidal anti-inflammatory drugs ○ Crohn's colitis ○ Microscopic colitis ○ Bacterial overgrowth syndrome	○ Celiac disease ○ Tropical sprue ○ Collagenous sprue ○ Protein intolerance (cow's or soya milk) ○ Post-infectious diarrhea	○ Tuberculosis (including atypical) ○ HIV/AIDS ○ Common variable immunodeficiency syndrome ○ Whipple's disease ○ Radiation enteritis ○ Immunoproliferative small intestinal disease ○ Crohn disease ○ Eosinophilic gastroenteritis ○ Autoimmune enteropathy ○ TPN



Abbreviations: CD, celiac disease; IELs, intestinal intraepithelial lymphocytes; TPN, total parental nutrition

Printed with permission: Collins P, Wahab PJ, Murray JA. *Best Practice & Research Clinical Gastroenterology* 2005;19(3): pg 344; and Daum S, Cellier C, Mulder CJJM. *Best Practice & Research Clinical Gastroenterology* 2005;19(3):pg. 415.

When there is not villus shortening and only an increase in IELs, subtle considerations may be helpful (Table 12).

Table 12. Factors which support the diagnosis of CD in patients with an increased density of intraepithelial lymphocytes (IELs) but no villous shortening

○ Family history of celiac disease ○ Concomitant autoimmune conditions ○ Increased density of $\gamma\delta$ + IELs ○ Increased density of villous tip IELs ○ HLA DQ2 or DQ8 ○ Gluten dependence	○ 15% of first-degree relatives are affected ○ Risk of celiac disease approximately 5-fold ○ Sensitivity 0.84, specificity 0.91 ○ Sensitivity 0.84, specificity 0.95 ○ High sensitivity, low specificity high. Negative predictive value ○ Should be ascertained by gluten challenge or gluten-free diet

Printed with permission: Collins P, Wahab PJ, Murray JA. *Best Practice & Research Clinical Gastroenterology* 2005; 19(3): pg 347.

In some instances special stains may give a clue to the diagnosis of the small bowel condition (Table 13).

Table 13. Histological features which may be used to distinguish the conditions from celiac disease

Cause of malabsorption	Cause of malabsorption
○ Collagenous sprue ○ Mycobacterium-avium complex ○ Infection (MAC) ○ Amyloidosis ○ Crohn disease ○ Eosinophilic gastroenteritis ○ Lymphangiectasia ○ Lymphoma ○ Mastocytosis	○ Collagenous band below atrophic epithelium ○ Acid-fast bacilli, foam cells, PAS positive macrophages ○ Congo red-stained deposits with apple-green birefringence in polarized light ○ Epithelioid granulomas and characteristic focal inflammation ○ Eosinophilic infiltration ○ Ectatic lymph vessels ○ Clonal expansion of lymphocytes ○ Diffuse infiltration with mast cells



- Infection
- Whipples
- Parasites may be seen on histological examination (eg. *guardia lamblia*, *strongyloides*), TB, HIV
- Acid-fast bacilli, foam cells, PAS positive, diastase resistant staining in macrophages
- α_1 antitrypsin deficiency
- Whipples disease (diastase resistant)
- MAC (Mycobacterium-avium complex infection)

Abbreviation: MAC, mycobacterium-avium complex infection

Adapted from: Freeman HJ. *Canadian Journal of Gastroenterology* 2008; 22(3): pg 277.

In the patient with diarrhea and or flat malabsorption a novel small bowel biopsy will help to exclude several conditions (Table 13).

Table 13. Conditions causing malabsorption that are usually excluded by a normal small bowel biopsy

- Sprue (actually, not always – patchy, treated, immunosuppression, potential – ATG positive, but small bowel biopsy normal)
- Hypogammaglobulinemia
- α - β -Lipoproteinemia
- Whipples (except in very rare circumstances with CNS Whipples)

A *mild* lesion may occur with no significant alteration in villus structure but with increased intra-epithelial lymphocytes. A *moderate* lesion (partial villus atrophy) with less severe change in villus architecture may also occur. Often, these less severe changes are associated with other diseases, rather than celiac disease. However, if detected, further studies should be done to exclude other causes (eg., giardiasis).

A number of small bowel disorders may cause histological changes that appear like untreated celiac disease, but do not respond to a gluten-free diet. Some of these are listed in Table 13. Only the biopsy changes of untreated celiac disease respond to a gluten-free diet.

Table 14. Causes of Severe Biopsy Lesions often confused with Celiac Disease

- Sprue Syndromes
 - Celiac disease (classic, occult, latent forms)
 - Refractory sprue (refractory celiac disease)
 - Collagenous sprue
 - Mesenteric lymph node cavitation syndrome
 - Other protein injury (soy protein, milk, other)
 - Unclassified sprue or sprue-like intestinal disease



-
- Infectious Causes
 - Infectious gastroenteritis (childhood)
 - Infections (protozoans, parasites, viral, fungal, mycobacterial)
 - Tropical sprue
 - Stasis syndrome (contaminated small bowe syndrome)
 - Whipple's disease
 - Deficiency Syndromes
 - Nutrient deficiency syndromes (zinc, vitamin B12, folate)
 - Kwashiorkor
 - Immunodeficiency syndromes (common variable, AIDS)
 - Intestinal lymphangiectasia
 - Others
 - Crohn disease
 - Graft-versus-host disease
 - Immunoproliferative diseases (lymphoma)
 - Zollinger-Ellison syndrome
 - Autoimmune enteropathy (?)
 - Drugs (sulindac, busulfan, methotrexate)
-

8. Treatment

The essential element of management is strict and lifelong removal of gluten from the diet.

8.1. Gluten Free Diet

The essential element of management is strict and lifelong removal of gluten from the diet. Gluten is found in wheat, rye and barley. Oats may be tolerated by some patients, theoretically permitting consumption of an increased variety of different foods.

Unfortunately, commercially available oats products are often contaminated with gluten-containing grains during growing, transportation and milling processes. Grains that appear to be safe include rice, buckwheat, corn, millet and sorghum.

Minerals and vitamins should be measured and replaced, if deficient. However, since most celiac patients that respond to a gluten-free diet absorption will improve so that these minerals and vitamins usually normalize without the need for specific supplements. Screening and monitoring for osteopenic bone disease with a bone mineral density test (DEXA scan) is recommended. Growth and development in children also requires monitoring after a gluten-free diet has been initiated. A skilled dietitian is helpful to review the diet initially and to serve as an information source. Patient support groups and online information and other literature may be available, such as, to locate sources of gluten-free products. These gluten free products maybe costly and in some developing countries, they may also be difficult to access.

Treatment compliance is important as a gluten-free diet is protective against the development of lymphoma. Treatment of symptomatic disease may improve nutritional



parameters, including bone mineral density measurements. Treatment may eventually result in increased body weight, body mass index, fat mass, bone mass, triceps skin fold thickness, and nutritional as well as biochemical status, including iron absorption parameters.

The patient and their family must be educated in the disease, and accept the need to be on a gluten free diet for life. Any associated nutrient deficiencies must be corrected. Many patients benefit from belonging to the Canadian Celiac Society (<http://www.celiac.ca/>).

Persons with gastrointestinal symptoms may choose to place themselves on a gluten-free diet, prior to proper investigation and establishment of the diagnosis. This practice must be strongly discouraged, since the PPV for clinical improvement after gluten withdrawal is only 36%, and only 28% PPV for clinical exacerbation after gluten reintroduction (Campanella et al. 2008).

Patients with CD on a GFD who have persistent symptoms tend to have more persisting histological abnormalities than those CD/GFD patients without symptoms, a higher intraepithelial lymphocyte count, and the symptoms that do persist are often different and may be unrelated to those at the time of diagnosis such as symptoms of gastroesophageal reflux disease, abdominal pain or constipation (Carroccio et al. 2008).

Assessing Quality of Life (using the Short Form-36 health survey, the Gastrointestinal Symptoms Rating Scale, and the Beck Depression Inventory) before and after a GFD demonstrated that within three months, there was a clinically and statistically significant improvement in classical and atypical but not in asymptomatic CD patients (Nachman et al. 2009).

A high throughput, immune-based assay using monoclonal antibodies specific for immunotoxic peptides has facilitated their detection in food (Morón et al. 2008). This may eventually prove to be useful for the establishment of gluten-free foods, as well as providing a means to monitor the action of TG2 on gluten peptides.

8.2. Follow-up

While it may be common to repeat duodenal mucosal biopsies in children after a suitable parent on a GFD, this is generally not recommended in adults, particularly if symptomatic improvement results with resolution of diarrhea and weight gain. In some, with no or few symptoms, and no or minimal changes in blood tests, another biopsy may be needed to show a GFD response (Vécsei et al. 2009).

8.3. Unproven Experimental Therapies

The only treatment currently available for CD is the life-long withdrawal of gluten from the diet. This gluten-free diet (GFD) is expensive, the GFD is not always palatable, and may contribute to the reduced quality of life reported by some persons with CD. Noncompliance with a GFD is often reported in adolescents with CD. Based on the young person's degree of adherence to a GFD (compliers, occasional noncompliers and noncompliers), different strategies may be used (Olsson et al. 2008). It should be noted though that histological changes improve initially in the more distal small bowel, so repeated biopsies from proximal duodenum may show little initial improvement (Jadrosin et al. 2008).



The IFN γ released from gluten-activated T cells enhances intestinal permeability, enhancing even further the transepithelial flux of gluten peptide in T84 cultured epithelial cell monolayers (Bethune et al. 2009). This raises the intriguing possibility of using anti-IFN γ therapy to break this “vicious cycle”.

The proposed new Codex Alimentarius Standard for naturally gluten-free foods is a maximum of 20 ppm. Surface-associated proteins on wheat starch may be removed, leaving a product which is sufficiently low in gluten (7 ppm) to be used by persons with CD (Kasarda et al. 2008).

Prolyl endopeptidases (PEPs) may be given to cleave the immunotoxic gluten peptides from cereal proteins (wheat, rye, barley) (Ehren et al. 2008). Using a combination of sequence and structure-based approaches with machine learning algorithms may provide the protein engineering means to develop new food products for use by CD persons.

AT-1001 is the antagonist for zonulin, which is an endogenous signaling protein that transiently and reversibly opens the tight junctions between the cells of epithelial and endothelial tissues such as the intestinal mucosa, blood brain barrier and pulmonary epithelia. The release of zonulin may restore the increased intestinal permeability which results from or may even contribute to the development of CD (Baldassarre et al. 2008). The use of AT-1001 will inhibit zonulin will prevent the opening of the tight junction, blocking the paracellular route of gliadin absorption. R-spondin 1 is a recombinant, secreted protein which may also have a therapeutic role in CD.

Analysis of gliadin T-cell epitopes has been developed from durum wheat to down-regulate the abnormal T-cell immune response in CD (Silano et al. 2008). These antagonist peptides may prove to represent a useful therapeutic strategy in CD.

Strains of sourdough lactic acid bacteria (*Lactobacillus sanfranciscensis* LS40 and LS41, and *Lactobacillus plantarum* CF1) have been used to reduce gluten in bread down to 20 ppm, qualifying this as being “gluten-free”, as well as enhancing the free amino acid concentration, thereby providing enhanced nutritional properties (Di Cagno et al. 2008).

8.4. Non-Dietary Treatments

The topic of novel non-dietary therapeutic strategies for CD has been reviewed (Sanz 2009). Gliadin may be neutralized by complexing it with a polymeric binder, and thereby preventing the toxic effects of gliadin on the intestine (Pinier et al. 2009).

Wheats may be genetically engineered to avoid the CD – immunogenic domains, such as by pre-screening for differentiated expression from the homologous alpha-gliadin genes at various genomic loci (Salentijn et al. 2009).

Selected enterococci and *Rhizopus oryzae* proteases may be used effectively to hydrolyse wheat proteins responsible for CD (M'hiri et al. 2009). Combinations of bacterial and fungal proteases when fermented with gluten may decrease gluten concentration by more than 98%.

A reliable extraction protocol has been developed to remove immune responsive gluten proteins in wheat, rye and barley (van den Broeck et al. 2009), which may prove to be useful in the development of foods free of gluten yet still containing non-toxic cereal proteins.



Chapter 9: Crohn Disease

A. B. R. Thomson, Q. Li, M.T. Clandinin, and H. J. Freeman



1. Definition

Crohn disease (CD) may be defined in a number of ways. Simply, “CD is a chronic [life-long], transmural [patchy] inflammatory disorder that may involve any part of the gastrointestinal tract from mouth to anus, mostly found in the ileum, the c[a]ecum and the colon. Characteristic symptoms of this idiopathic inflammatory bowel disease (IBD) are chronic or nocturnal diarrh[o]ea, abdominal pain, weight loss, fever and rectal bleeding” (Shao et al., 2009). It is likely caused by a multifactorial complex interplay among genetic, environmental, microbial, and immune factors in a genetically predisposed host (Mizoguchi and Mizoguchi 2008; Podolsky 2002), with uncontrolled inflammation affecting the mucosa as well as other layers of small intestine and/or colon (Fretland et al. 1990).

There may be a mild or a disabling clinical course with unpredictable relapses, perianal and extraintestinal complications, as well as frequent medical encounters including hospitalization, unpleasant therapies, and surgery. These all contribute to the sufferer's sense of hopelessness, depression, anxiety, sexual disturbances, unemployment, disability or need for sick leave from this debilitating disease (Caprilli et al. 2008).

While Crohn disease (CD) involves primarily the small intestine and more specifically the ileum, ulcerative colitis (UC) is a disease localized to the colon alone (2). Crohn's can affect any area of the gastrointestinal (GI) tract, from the mouth to anus, CD and UC are two separate conditions with distinguishing clinical, endoscopic, and pathological findings, but they do have some overlapping features and may even represent several different diseases with similar characteristics (Hanauer 2006).

Useful Practice Points:

What does the Primary Care Physician (PCP) Need to/Want to Know about IBD?

- Typical patient presentation & profile
- Major differential
- PCP-based investigations
- First line therapy for new IBD
- Identify and treat a recurrence
- When to refer

2. Demography

Modern management has improved IBD patient survival (Loftus et al., 2007). Because the mortality rate in CD is only slightly higher than in the healthy population, the prevalence of CD has been increasing over time. In most parts of the world, the incidence and prevalence of CD are higher than those for UC. In Canada, the incidence of UC and CD are approximately 5 and 10/10⁵, respectively, and the prevalence is at least 100 to 200/10⁵ (Panes et al., 2007; Loftus 2004; Vind et al., 2006).

Inflammatory bowel disease (IBD) affects approximately 1.5 million people in the United States and more than 2 million in Europe (Ruthruff 2007). In Canada, it has been estimated that nearly 200,000 Canadian men and women suffer from IBD. In the last generation, the incidence of CD has been increasing throughout most of the world



(Economou 2008), although in some countries, the rates are beginning to stabilize (Baumgart 2007). The incidence of CD is highest in North America and Europe. The peak incidence is 16-25 years of age (Vind 2006). In adults, there are slightly more women than men with CD (Jacobsen 2006; Loftus 2002), with the reverse seen in paediatric ages (Hait 2005, Panes 2007). Other differences between CD in children versus adults are given in Table 1.

Useful Learning Points

- CD is slightly more frequent in women than men
- 10-15% of CD patients are diagnosed before adulthood
- the peak incidence of CD is 16-25 years, with no secondary peak
- Differences between paediatric-onset vs adult-onset CD
- Disease onset may be influenced by different genetic loci
- Different inflammatory mediators may influence disease course
- Proximal and extensive disease is more common in paediatric-onset disease

Table 1. Differences in the child versus the adult with CD

- Age of diagnosis – more severe clinical course in those who are diagnosed at a young age (see below).
- Site
 - ileum: higher probability of activity
 - ileocolonic: earlier need for surgery and repeat surgery
- Slightly higher rate in males than females
- More proximal and more extensive disease
- More severe clinical course
- Different genetic loci influence disease onset
- Different inflammatory mediators (Panes et al.2007)

Useful Practice Points:

Why does the Primary Care Physician (PCP) Need to Know About IBD?

- Number of patients 300/105
- Number of PCPs 1/103
- Every PCP will have 2 to 3 IBD patients
- Number of PCP/GI in Canada 35,000 vs 500

CD is more common in Jewish than in non-Jewish persons, and in Caucasians more than African Americans (Ruthruff 2007). Familial distributions of IBD involved first-degree relatives (parent, child or siblings) more often than second-degree or third degree relatives (aunts, uncles, nieces and nephews). Among first-degree relatives, siblings (most often, female siblings) are most often affected with Crohn disease,



compared to parents or children (Freeman, 2002). This is in accord with polygenic inheritance (Kirsner 2001). CD has a higher incidence among smokers than nonsmokers (Ruthruff 2007). Cigarette smoking is detrimental in CD: it leads to an earlier age at diagnosis, and a higher likelihood of requiring immunomodulator therapy or surgery. Individuals who smoke and have a diagnosis of CD are at higher risk of a complicated clinical course and increased frequency of exacerbations. Conversely, smoking leads to a later diagnosis of UC, with a better overall clinical course.

3. Pathogenesis

While pathogenesis of Crohn disease is unknown, a current popular working model is that CD is the result of 1) either an exaggerated host immune response, an inappropriate chronic activation of the innate and adaptive mucosal immune systems in a genetically susceptible host (Bouma and Strober 2003) against the intestinal mucosal surface microbiotics, through either the activation of T cells and initial overexpression of inflammatory type 1 helper T-cell(Th1) cytokines (such as tumor necrosis factor-alpha [TNF- α], interleukin [IL] -1, -2, -12, -18, and interferon gamma) (Podolsky, 2002; Ardizzone et al.2005), or 2) a defect in down-regulating the immune response, leading to chronic inflammation in a genetically predisposed person (Shao et al.2009; Shanahan et al.). Various environmental and host factors (e.g. genetic-, epithelial-, immune and non-immune) play a major role in the pathogenesis of IBD (Lakatos et al. 2006). The role of abnormally increased intestinal mucosal permeability in CD is not clear, but will be discussed later.

➤ Familial and Genetic Considerations

CD has a familial inheritance pattern that does not follow simple Mendelian models. A positive family history is found in 5–20% of patients with CD and first degree family members of IBD patients are at a 10- to 15-fold increased risk to develop IBD themselves (either CD or UC), somewhat more in CD than in UC (Noomen et al. 2009).

The transmission of IBD from parent to child is low; with one parent with IBD; transmission risk is 7%. If both parents have IBD, there is a 37% risk of transmission (Yang H, et al. *Gut* 1993:517-24). The risk of transmission is higher in members of the Jewish faith (Table 2).

Table 2.

	CD	UC
Jewish	7.8%	4.5%
Non-Jewish	5.2%	1.6%

The most convincing evidence for genetic predisposition comes from twin studies, which show increased concordance rates for both UC and CD in monozygotic twins, as compared to non-identical twins. The concordance for CD in monozygotic twins is 35% compared with 7% in dizygotics, with the equivalent in UC being 11 versus 3% (Noomen 2009). The markedly increased concordance rates in identical twins can only be explained by an underlying genetic component.



With the completion of the human genome sequence, it became possible to perform 'genome-wide association studies', providing systematic assessment of the contribution of common variation to disease pathogenesis. This approach has had an unprecedented impact on our knowledge of the genetics of many autoimmune diseases. These studies have resulted in the identification of many novel loci for CD as well as UC, have highlighted the importance of the innate immune system, and have implicated new pathogenic pathways such as autophagy (Noomen 2009).

IBD has been classified as a complex disease complex diseases resulting from the interaction of multiple genetic and non-genetic factors (Goyette et al. 2007). The role of host genetic regulation of the innate immune response in the pathogenesis of CD has been brought to sharp focus by the identification of the NOD2 (CARD15) mutations (Lakatos 2006).

The NOD2 gene on chromosome 16 q (IBD1) was the first susceptibility gene identified for CD (Hugot 2001; Ogura 2001b) (Table 3). The product of this gene is expressed in many cells, including monocytes, dendritic cells, Paneth cells and intestinal epithelial cells. NOD2 contains an apoptosis-related CARD domain. Further understanding of regulatory elements within non-coding genomic regions and gene–gene interactions will lead to a better understanding of the underlying mechanisms that cause disease (Xavier 2007).

Table 3. The NOD2 gene

-
- 3 independent mutations of the nucleotide-binding oligomerisation domain2 (NOD2) gene
 - NOD2 gene encodes the NOD2/caspase recruitment domain (CARD) protein
 - CARD15 protein increases susceptibility to CD in Caucasians (18,19)
 - NOD2/CARD15 activate the NF-κB signalling pathway to stimulate the secretion of defensins (cryptins) (21)
 - There is a gene-dosage effect of NOD2/CARD15 variations (24): the risk of developing CD is 2.4 (95% CI 1.2-2.9) for a simple heterozygote, versus 17.1 (95% CI 10.7-27.2) for persons with two mutant chromosomes, simple homozygotes, or compound heterozygotes
-

NOD proteins (NOD 1 and 2) recognise peptidoglycan (PGN), a component of bacterial cell walls derived from Gram positive bacteria (Strober 2006), and are expressed predominantly by antigen-presenting cells and epithelial cells (Inohara 2003). PGN is also broken down in endosomes, and is thus a source of MDP (muramyl dipeptide), a substance that is sensed by and activates NOD2. Such activation initiates a mechanism of inhibition of PGN-mediated NF-κB activation and thus causes downmodulation of TLR-induced cytokine production (Strober 2007). Polymorphisms in NOD1 and 2 (also known as CARD4 and CARD15), result in a susceptibility to develop IBD, particularly Crohn disease in the case of NOD2 (Geier 2007). Homozygous mutation in NOD2/CARD15 has been shown to account for 10–15% of patients with CD, and this mutation leads to a decrease in NFκB activation upon stimulation.

There are three independent mutations of the nucleotide-binding oligomerisation domain 2 (NOD2) gene, which encode the NOD2/caspase recruitment domain (CARD)



15 protein, and increase CD susceptibility, but curiously only in Caucasians (Aberu 2005, Cho 2003, Ogura, 2001, Aldhous 2003). NOD2/CARD is involved in the recognition of bacterial peptidoglycan-derived muramyl dipeptides. The NOD2 gene codes for the NOD2 protein, which is a pattern recognition receptor that senses intestinal luminal bacterial breakdown products of peptidoglycans muramyl dipeptide (MDP) (Braus 2009). These activate the nuclear factor- κ B (NF- κ B) signalling pathway, and stimulate secretion of the antimicrobial α -defensins (cryptins) (Rosetiel 2006). In CD persons who are simple heterozygotes with one mutant chromosome in NOD2/CARD 15, the relative risk for their developing CD is 2.4 (95% CI 2-2.9). In contrast, persons who are simple homozygotes or compound heterozygotes with two mutant chromosomes have a relative risk of developing CD of 17.1 (95% CI 10.7, 27.2) (Economou 2004).

Interestingly, NOD 2 / CARD 15 variants are linked to CD phenotype: ileal disease, strictures (of ileum), and non-perianal fistulas (Brant et al. 2003). NOD2/CARD15 mutations may be associated with younger age of diagnosis, ileal or fibrostenotic disease (Ahmad 2002, Economou 2004); and higher intestinal permeability to sugars in relatives of CD patients (Sachar 2005). There are numerous other CD susceptibility genes. The OCTN genes (organic cation transporters) are linked to perianal CD (Vermeire 2005). The IBD 5 locus (IBD5 region on chromosome 5q 31-33) is linked to susceptibility to develop CD (Rioux 2001). The IL23R gene on chromosome 1p31 encodes A-subunit of the IL-23 receptor (Duerr 2006), and is associated with the development of CD. Other less well-studied CD susceptibility genes include DLG5, NOD1, TLR-4 and -9 (Vermeire 2005).

➤ Environmental Associations

There are numerous environmental associations with CD which may either initiate or continue the inflammatory response (Table 4).

Table 4. Environmental Associations of CD

-
- Higher economics development of country
 - Higher personal socioeconomic status (30)
 - Smoking cigarettes (31, 39)
 - Use of NSAIDs
 - Use of Antibiotics
 - C. Difficile infection
 - Upper respiratory tract and enteric infections
 - Psychological Stress
 - Pollution, diet
-

Adapted from Ardizzone and Bianchi Porro 2005

➤ Immune Function



The innate immune system is the first line of defense against resident luminal microflora and invading pathogens, and can respond to a wide variety of microorganisms. The innate immune system has evolved to monitor the resident microflora and relay danger signals in response to infection by invasive organisms. This response is mediated through the recognition by specific pathogen recognition receptors (PRR) of microbial components, known as pathogen-associated molecular patterns (PAMPs). The PRRs include the members of the Toll-like receptor (TLR) family, which are predominantly cell surface receptors, and the cytosolic Caterpillar-(CARD)/NOD intracellular receptors (Werts 2006). The binding of PAMP ligands to specific PRRs leads to the activation of several intracellular signaling pathways, which include the nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways for TLRs and predominantly the NF κ B pathway for CARD/NOD receptors.

These pathways in turn lead to the activation of transcriptional programs resulting in the broad-spectrum non-specific killing mechanisms of innate immunity. These mechanisms include synthesis of reactive oxygen species, activation of the complement protein system, secretion of chemokine and cytokines for chemotaxis of phagocytotic macrophages, and secretion of antimicrobial proteins by Paneth cells (Goyette 2007). Paneth cells are specialized epithelial cells located at the base of small intestinal crypts, which monitor the intestinal lumen and are considered important mediators of mucosal innate immune defense. They contribute to host defense and maintenance of the gastrointestinal barrier through the luminal secretion of a number of antibacterial peptides (defensins, lysozyme and secretory phospholipase A2), which protect nearby intestinal stem cells and control microbial density.

The intestinal lamina propria contains a complex population of immune cells that balance the requirement for immune tolerance to the normal luminal microbiota, but also with the need to defend against pathogens, the excessive entry of luminal microbiota, or both (Abraham 2009). The hallmark of active inflammatory bowel disease is a pronounced infiltration into the lamina propria of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells), as well as adaptive immune cells (B cells and T cells). Increased numbers and activation of these cells in the intestinal mucosa elevate local levels of tumor necrosis factor α (TNF- α), interleukin-1 β , interferon- γ , and cytokines of the interleukin-23–Th17 pathway (Abraham 2009, Izcue 2008). There is dysregulation of intestinal CD4+ T cells: In CD, for example, there is increased production in the intestinal mucosa of the Th17 cytokine interleukin-17 and the Th1 cytokines interferon- γ and TNF- α . Interleukin-23, secreted by macrophages and dendritic cells, may contribute to Th17 proliferation, survival, or both (McGeachy and Cua 2008). Levels of interleukin-23 and Th17 cytokines are elevated in the colonic mucosa in both Crohn disease and ulcerative colitis (Abraham 2009).

Studies of IBD in mice and humans implicate dysregulation of intestinal CD4+ T-cell subgroups in their pathogenesis. The defective T-cell mediated regulation is associated with a disruptive interaction between the immune system and gut luminal factors. Animal studies have identified a CD4+ CD25+ cell population which expresses the FOXP3 transcription factor (Hori 2003). This regulatory T cell population (Tregs) is thought to suppress the activation of effector T cells at the level of the antigen-presenting cell, and produce IL10 and transforming growth factor (TGF) β . In addition to this 'naturally occurring' Tregs, there are also 'adaptive' Tregs, the so-called Tr1 and



Th3 cells (Huibregtse 2007). Regulatory T cells appear to be key players of immune regulation, and they have important functions in suppressing unwanted inflammatory responses towards self-antigens, and the antigens of endogenous intestinal bacteria.

The role of B cells in IBD has not been as extensively studied as that of T cells. Intestinal B cells produce IgA antibodies, which contribute to immune protection without provoking inflammation. In animal models of colitis, both anti-inflammatory and proinflammatory roles of B cells have been described.

The proposed mechanism for the development of IBD involves the deregulation of the adaptive immune system stemming from an imbalance between regulatory and effector-cell immune responses to luminal antigens or other antigen (e.g. self-antigens). In contrast to innate immunity, adaptive immunity generates a slow and more targeted response involving antigen-specific recognition and immune memory. The GALT represents the largest part of the body's immune system, and given the large surface area of the mucosal epithelium, the immune system encounters more antigens in the gut than any other location in the body. In addition, since most of the antigens encountered by the mucosal immune system are derived from food proteins and commensal bacteria, the immune system must remain relatively unresponsive to avoid responses to harmless antigens and maintain epithelial integrity. It has been proposed that tolerance to these luminal antigens, also known as oral tolerance, occurs through a state of active cellular suppression or clonal anergy of immune reactive cells induced by specialized regulatory T cells (Mowat 2004). The proposed role of adaptive immunity in IBD is derived from genetic studies indicating a central role of the MHC in the development of IBD and also from in vivo observations in IBD patients of abnormal patterns of cytokine production and immune cell responses (excessive Th1 response in CD and Th2 response in UC), of modulations in regulatory T and B cell functions, and of antibodies to luminal antigens (Mizoguchi 2006).

➤ Intestinal Permeability

The integrity of the epithelium is maintained mostly through a combination of intercellular adhesion structures and specialized junctions, which also define cellular polarity. In addition, the presence of mucins and trefoil peptides, the rapid turnover of epithelial cells, and the peristaltic movement of the GI tract all help to protect against colonization and invasion of the intestinal mucosa by pathogens (Lievin-Le 2006). The role of increased epithelial permeability across the gut epithelial barrier (leaky gut) has gained increasing support in IBD pathogenesis, particularly as this epithelium represents an interface for genetic and environmental influences (Goyette 2007).

A compromised intestinal barrier may play a crucial role in the development of CD, by allowing the entry of luminal antigens and microorganisms into the mucosa and initiating overwhelming inflammatory responses (MacDonald 2005). A common feature of gut inflammation is increased epithelial permeability, both paracellular (i.e., the pathway between adjacent cells) and transcellular (i.e., material crosses through the apical and basolateral membranes) (Nazli 2006). One of the distinct features of CD is impaired intestinal epithelial function, characterized by increased permeability (altered barrier function) and ion secretion, often resulting in a lumenally-directed driving force for water movement causing diarrhea. Interestingly, in otherwise clinically asymptomatic CD patients, increased intestinal epithelial permeability preceding clinical relapse has been



observed, suggesting that a barrier defect may be an early event in disease reoccurrence.

Since first degree relatives of CD patients, without evidence of disease, also show abnormal intestinal permeability, it has been proposed that increased intestinal permeability may be a primary etiologic factor in IBD (Soderholm 2002). However, the inflammatory process itself leads to increased intestinal permeability (Bruewer 2003). Thus, it is not clear if these changes in the intestinal barrier integrity involved in the early events of IBD pathogenesis, or are simply a secondary phenomenon (Cobrin 2005, Targan 2005).

➤ **Intestinal microbiotics:** Interaction between genetics, immune function, permeability

Evidence supporting the hypothesis that in humans intestinal bacteria play a role in the pathogenesis of IBD includes 1) the observation that inflammation and lesions generally occur in intestinal regions with the highest bacterial concentrations (i.e. the terminal ileum and colon) (Thompson-Chagoyán 2005); 2) that IBD patients typically have greater numbers of adherent bacteria compared to normal subjects (Swidsinski 2002); and 3) diversion of the fecal stream can prevent intestinal inflammation whilst re-establishment of the flow will lead to recurrence (Fichera 2005).

There is likely an interaction between the intestinal microbiotics, and genetics, immune function and intestinal permeability. The microbiota then provides a constant stimulus for the host immune system (Shanahan 2004, Tannock 2005). Another hypothesis is that IBD develops due to an altered response to commensal bacteria, and not a pathogenic strain (Geier 2007). The associated lesions and the immunologic changes indicate a breakdown of mechanisms that maintain oral tolerance to components of the microflora and/or foodstuffs (Canny and McCormick 2008). The findings supporting the presence of an altered immune status include an exaggerated mucosal antibody response against intestinal bacteria.

In UC, particularly members of the genus *Bacteroides* are thought to play an important role in the development of intestinal inflammation: the rectal mucosa-associated bacterial flora in UC shows that both the highest bacterial counts and the highest isolation frequency were observed for *B. vulgatus*, *Bacteroides fragilis*, and *Bacteroides ovatus*, in that order (Poxton 1997).

Toll-like receptors (TLRs) are responsible for microbial recognition, induction of anti-microbial genes and control of the adaptive immune response (Cario 2005). There are a number of mechanisms to ensure tolerance, including a decreased surface receptor expression to limit recognition, and ligand-induced activation of peroxisome proliferators activated receptor- γ (PPAR γ) which uncouple NF κ B-dependent target genes (O'Neill 2006). TLR4 expression has been shown to be up-regulated in patients with IBD (Cario 2005).

The antibacterial peptides known as “ α -defensins” are produced by Paneth cells at the base of crypts in the terminal ileum (Strober et al. 2007). CD patients with impaired NOD2 function manifest reduced α -defensin production, in part because NOD2 in Paneth cells is an inducer of α -defensin production. Thus, it is possible that impaired NOD2 function also leads to increased bacterial density in the crypts of the terminal



ileum, and thereby greater stimulation of a mucosal immune system which is already set at a higher level of function.

4. Clinical Presentation

The course of CD is chronic, with recurrent episodes of inflammation, but not always associated with symptoms, complications, the need for hospitalization and possible surgery. The Vienna (Gashe 2000) and more recently the Montreal classifications are used to categorize the disease phenotype of CD and UC in a manner that has prognostic and therapeutic implications (Veloso 2001) (Tables 5, 6, and 7). The Vienna classification, and later, the Montreal classification, have both already been applied to Crohn disease populations in Canada but not for ulcerative colitis (Freeman 2001, Freeman, 2007).

Table 5. Summary of revised ‘Montreal classification’ of Crohn disease (Silverberg 2005)

○ Age at Diagnosis (A)		
- A1 16 years or younger		
- A2 17-40 years		
- A3 Over 40 years		
○ Location (L)	○ Upper GI modifier (L4)	
- L1 Terminal Ileum	- L1 + L4	- Terminal ileum + Upper GI
- L2 Colon	- L2 + L4	- Colon + Upper GI
- L3 Ileocolon	- L3 + L4	- Ileocolon + Upper GI
- L4 Upper GI		
○ Behaviour (B)	○ Perianal disease modifier (p)	
- B1* Nonstricturing, nonpenetrating	- B1p	- Nonstricturing, nonpenetrating + perianal
- B2 Stricturing	- B2p	- Stricturing + perianal
- B3 Penetrating	- B3p	- Penetrating + perianal

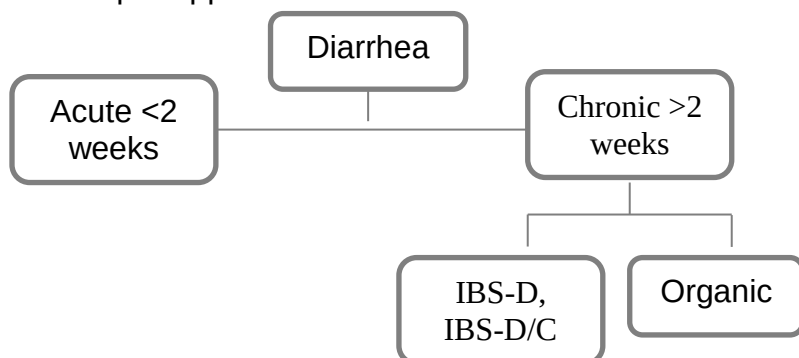
*B1 category should be considered ‘interim’ until a prespecified time has elapsed from the time of diagnosis. Such a time period may vary from study to study (eg. 5-10 years is suggested) but should be defined in order for B1 behaviour to be considered ‘definitive’.

Abbreviation: GI, Gastrointestinal.



Useful Practice Points:

A Simple Approach to Diarrhea



Note: IBS-D, IBS diarrhea predominant; IBS-D/C, IBD-diarrhea alternating with constipation; IBS-C, IBS-constipation predominant

- Organic Causes of Chronic Diarrhea
 - Stomach- ZES, Rx, resection
 - Hepatobiliary-Jaundice, pruritus (cholestasis)
 - Pancreatic-alcohol, trauma, CF
 - SB-LV, “F’s” foul, flush, fat, food, flatus
 - LB-SV, tenesmus, incontinence
- Intestinal Causes of Chronic Diarrhea – The “I’s”
 - Infection
 - Inflammation
 - Irritability
 - Ischemic
 - Infiltrative
 - Iatrogenic
 - Metabol-I-c
- Diarrhea: IBD vs IBS: “Alarms”
 - Blood
 - Nocturnal
 - Weight Loss
 - Fever
 - Mouth, joints, skin, liver, kidney
 - Abdominal Mass
 - Perianal disease
 - Family history of IBD, CRC
 - Labs
 - CBC, ESR, CRP
 - Electrolytes
 - Stool cultures



Table 6. Montreal classification of extent of ulcerative colitis (UC) (Satsangi 2006)

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is perianal extend of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Table 7. Montreal classification of severity of ulcerative colitis (UC) (Satsangi 2006)

Severity		Definition
S0	Clinical remission	Asymptomatic
S1	Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2	Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3	Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 37.5°C, haemoglobin of less than 10.5 g/100 ml and ESR of at least 30 mm/h

Abbreviation: ESR, erythrocyte sedimentation rate.

There are differences between the child versus the adult with CD (Table 1). The cardinal symptoms include crampy abdominal pain, diarrhea (watery, may be bloody or may show signs of malabsorption), weight loss, fatigue, extraintestinal symptoms. There are clinical differences between CD and UC (Table 8).

The Montreal Working Party has recommended that the term “indeterminate colitis” should be reserved only for those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either Crohn disease or ulcerative colitis after full examination (Silverberg 2005).



Table 8. Clinical features which are suggestive of CD rather than UC

-
- Involvement of the terminal ileum; however, “backwash ileitis” occurs in 10-20% of UC patients, particularly extensive disease (Haskell H 2005);
 - Skip lesions; note that “cecal patches” are seen in 20% of UC patients (D’Haens G 1997);
 - Rectal sparing; however, this may be the beneficial effect of rectal 5-ASA/steroid enemas and;
 - The histological presence of granulomas is suggestive of CD, but these are also seen in 5% of UC patients (Lee 1997)
-

The severity of CD is assessed by clinical indices, such as the “CDAI”, (Crohn disease Activity Index). The CDAI is heavily influenced by the subjective impact of symptoms such as abdominal pain, diarrhea, and poor sense of well-being (Best 1976). There is only a weak association between the patient’s symptoms and the appearance of the bowel mucosa as seen by endoscopy, but there is a strong correlation between clinical indices and CD-specific measures of health-related quality of life (HRQOL).

QOL measures add important information on the person’s emotional and social functioning (Bernklev 2004). These patient-reported outcomes (PRO) may be more valid and reliable than physician assessment outcome measures (FDA, 2006). The HRQOL is multi-dimensional, is reported directly by the patient, without “filtering” by the physician. HRQOL as well as other PRO instruments provide “...an integral picture of the interactions between a patient’s disease, their treatment, and quality of life-positive effects resulting from the efficacy of a treatment and negative effects caused by adverse events...” (Rutgeerts 2008).

There are several useful, valid, reliable and easy-to-use PRO instruments, such as the Inflammatory Bowel Disease Questionnaire (IBDQ) (Bernklev 2004), the SNORT-Form 36-Item Health Survey (SF-36) (Bernklev 2005; Juan 2003; Welch 1995), the EuroQOL-5 dimensions (EQ-5D) plus health status visual analogue scale (VAS) (Cohen 2002; Casellas 1999, König 2002), and the Work Productivity and Activity Impairment-Specific Health Problem (Reilly et al, 1993), which has been adapted for persons with CD (Reilly 2006). These measures may be used to determine a normal life assessment, which combines measures of disease activity, HRQOL, work productivity and daily activity (Feagan 2009).

An important property of a PRO score is the MCID, the “minimal clinically important difference” (FDA, 2006; Mathias 2006). The MID, minimal important difference, is the smallest difference in a PRO score that patients perceive as beneficial, and that would indicate the need to change treatment (Coteur et al, 2009). In clinical trials, and reflecting everyday clinical practice, the MCID or MID are more important outcomes than small, unimportant yet possibly statistically significant changes in an activity index such as CDAI (Coteur 2009).



Extraintestinal manifestations (EIMs) occur in about 25-40% of CD and UC patients, especially if the colon is involved (Table 8). Erythema nodosum has many associations (Table 9), but in the context of CD or UC, it usually occurs in the setting of disease activity.

Table 9. Extraintestinal manifestations (EIM) of IBD

<u>EIM</u>		<u>Association with active IBD</u>	
○ Erythema nodosum		90%	
○ Ocular inflammation		78%	
○ Large joint arthropathy (Type I)		80%	
○ AS, symmetrical small joint arthropathy (Type II)		independent	
		extensive, but quiescent disease	
<u>Frequency of EIM, %</u>		<u>UC</u>	<u>CD</u>
○ Type I arthropathy		31	24
○ Erythema nodosum		1	6
○ Ocular inflammation		5	3
○ Primary sclerosing cholangitis		2.4-7	0.7-12

Abbreviation: AS, ankylosing spondylitis

(Jess 2006, Jess 2004, Ekbom 1990, Fireman 1989)

Patients with one EIM are more likely to develop another except that the patient with UC-associated primary sclerosing cholangitis (PSC) does not usually develop other extraintestinal manifestations (EIMs) (Orchard 2002). The usefulness of the EIMs is to anticipate other symptoms which the patient may develop and to treat those early and to recognize that some EIMs become symptomatic before the worsening of the bowel symptoms.



Table 10. GI causes of erythema nodosum

-
- Inflammatory bowel disease (erythema nodosum usually occurs in the setting of gastrointestinal disease activity)
 - Behçet's disease (Ocular-oro-genital ulcers)
 - Infections: Strept throat, Salmonella, Campylobacter, Shigella (Diarrhea always present), Yersinia enterocolitica (Can mimic inflammatory bowel disease or occur without gastrointestinal complaints; probably rare outside of Northern Europe), HBV
 - Paniculitis (Skin lesions usually easily distinguished from typical erythema nodosum, and very rarely occur in advance of established diagnosis of pancreatitis)
-

Adapted from: Mirowski GW, and Mark L A. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006. page 450.

5. Diagnosis

The diagnosis of CD is made by the evaluation of compatible symptoms and signs, compatible hematological, serological, and biochemical blood tests, endoscopic, histopathological and diagnostic imaging findings, as well as exclusion of other pathologies (Panes 2007). These same features are used to differentiate between UC and CD (especially Crohn's colitis) (Baumgart & Sandborn 2007). Also, CD and UC must be differentiated from other causes of enteritis and colitis (Baumgart 2007).

➤ Blood Testing, including Serological Markers

The CRP (C-reactive protein) is neither sufficiently sensitive nor specific to be useful to make the diagnosis of IBD (Fagan et al. 1982), nor to necessarily follow the clinical course. In known CD patients, high baseline CRP values may help to identify those who will respond to infliximab (Louis 2002).

Blood tests are useful to suggest possible active inflammation, as suggested by anemia, leukocytosis and thrombocytosis. Dehydration and electrolyte disturbances associated with vomiting or diarrhea may be reflected by abnormal primary (Na^+ , K^+ , Cl^- , HCO_3^-) or secondary (Ca^{2+} , Mg^{2+}) electrolytes, or elevated serum urea or creatinine.

On immunofluorescent staining, the IBD-specific antineutrophil cytoplasmic antibody (ANCA) has perinuclear highlighting (pANCA), and is DNase sensitive (Duerr H 1991). IgA and IgG antibodies to *Saccharomyces cerevisiae* (ASCA) are seen in less than 5% of the non-IBD population, in ~10% of UC patients, and in ~60% of those with CD (Ruemmele 1998). A third of asymptomatic persons positive for ASCA will develop CD within a mean of 38 months (Vidrich 1995).

In about half of CD patients (but not in UC or healthy controls) there are serum antibodies to the *E. coli* outer membrane porin C (OmpC), the *Pseudomonas fluorescens* CD-related protein (I2), and the anti-flagellin (CBCR1) marker. A combination of these markers may help to support but not make a diagnosis of UC or CD, or to distinguish between the two (Dubinsky et al. 2002). Double-positive



combinations are also potentially predictive (Peeters et al. 2001, Quinton et al. 1998, Joossens et al. 2002); for pANCA⁺ / ASCA⁻, there is a PPV of 90% for UC, and predicts that 64% persons with IBDU (IBD unclassified) will later evolve into a picture which is compatible with UC. For the combination pANCA⁻ / ASCA⁺, there is a PPV of 90% for CD, this combination (pANCA⁻ / ASCA⁺) predicts that 80% of persons with IBDU will develop CD. There is also a predictive factor for triple-positive combinations: CD patients who are positive for ASCA, anti-OmpC, and anti-I2 are more likely to require small bowel surgery (OR, 8.6: p<0.001) (Mow 2004).

Children with CD who are immunoreactive against multiple microbial antigens are more likely to develop penetrating or structuring disease (Dubinsky 2006). These serological markers may also be useful to predict clinical course and therapeutic response. For example, a higher pANCA is predictive of chronic pouchitis post-IPAA (Fleshner et al. 2001). A higher ASCA – anti-OmpC, anti-I2, or anti-Cbir 1, are predictive of an earlier age of CD onset, structural and penetrating disease, or the need for future small bowel surgery (Vasiliauskas 2000, Mow 2004, Targan 2005). pANCA, ASCA, OMPC and Cbir 1 are not necessary for the diagnosis of IBD (Sandborn 2004), but may help to confirm the diagnosis made by other means (Kane 2008). ASCA, OMP-C, Cbir - 1 may be associated with complicated small bowel disease (Dotan 2006).

Table 11. Sensitivity, specificity, PPV and NPV of serological markers in persons with Crohn disease or UC

Marker	Diagnosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ASCA	CD	50-65	70-85	80	64
pANCA	UC	65-80	70-85	64	80

Adapted from: Targan SR. *AGA Institute PostGraduate Course book*. page 47.

Genetic testing with NOD2/CARD15 is not recommended as a diagnostic test (Vermeire 2004), “as the likelihood of a positive test in patient without the appropriate family history, or a negative test in a patient with appropriate signs and symptoms, is still relatively unknown and the results will be misleading (Kane 2008).

➤ **Fecal tests**

The presence of white blood cells (WBC) in the stool is supportive of an inflammatory process, but is neither sensitive nor specific for the diagnosis of IBD. Stool cultures need to be performed to exclude infectious causes of colitis or infectious causes of symptoms in persons with known CD or UC. Stool cultures should always include *C. difficile*, even in the person who has not recently been on antibiotics, and include cytomegalovirus (CMV) in the immunocompromised individual. Some persons with CD may need 72-hour stool collections to assess for possible fat or bile acid malabsorption.



➤ Urine tests

Urine calprotectin and lactoferrin are sensitive markers for inflammation in general, but are not specific for IBD. A stool calprotectin greater than 10mg/L predicts organic disease, with a sensitivity of 89% and a specificity of 79% (Palmon 2008). An elevated stool calprotectin or lactoferrin level > 7 mg/mL is 100% sensitive and 85% specific for pouchitis in the person who has had a colectomy and IPAA (ileal pouch anal anastomosis) (Parsi 2004, Johnson 2008).

The increased excretion into the urine of orally injected compounds (such as mannitol, lactulose, sucralose, PEG [polyethylene glycol], chromium or EDTA) may be used as markers of intestinal permeability. This increased intestinal permeability in active CD reflects increased intestinal inflammation (Parrilli 2006). When there is increased intestinal permeability in a person with CD who is clinically well, there is an increased risk of their suffering a clinical recurrence within one year (Vogelsang 2008), with a positive predictive value (PPV) of 44-75%, and a negative predictive value (NPV) of 46-49% (Vogelsang 2008).

Because intestinal permeability may be enhanced by much more than small intestinal CD (eg NSAIDs, alcohol, infections), these tests are too non-specific to be used for diagnostic purposes, but in a research setting may be useful to predict the presence of subtle disease activity.

➤ Diagnostic Imaging and Endoscopy

It is unclear what is the sensitivity and specificity for the diagnosis of CD using upper GI barium series, small bowel follow-through, air contrast barium enema, CT colonoscopy or enteroscopy, MRI or MRI enteroscopy, endoscopic ultrasound (EUS), optical colonoscopy, enteroscopy, esophagogastroduodenoscopy (EGD), colonoscopy with intubation of the terminal ileum, push or double-balloon enteroscopy, or video capsule endoscopy. Colonoscopy is an important procedure to be performed in persons with CD and UC (Table 12).

Table 12. Indications for colonoscopy in patients with IBD

-
- Differentiating IBD from other diseases, and differentiating Crohn's from ulcerative colitis
 - Establishing the extent of the disease, and any complications (fistula, strictures)
 - Evaluation of abnormalities on radiographs
 - Strictures
 - Masses
 - Evaluation of disease not responsive to standard therapy
 - Therapeutic applications
 - Bleeding control
 - Dilation of strictures
 - Obtaining biopsies
 - Screening for malignancy and malignant precursors
-



Useful Practice Points:

➤ If IBD is suspected: If you “Imagine,” then “Image”

- Ulcerative Colitis (UC) 100/10⁵
- Crohn’s Disease (CD) 200/10⁵
 - Ileum 40%
 - II + C 40%
 - Colon 20%
 - Imaging
 - ACBE ± sigmoidoscopy/colonoscopy
 - Small bowel (FT, enteroclysis, CT, MRI)

➤ Distinguishing IBD from IBS

- Demography

	<u>IBD</u>	<u>IBS</u>
– Young Female	3/103	3/101
– Alarms	++	-
– Labs	++	-

➤ Why distinguish between UC and CD

- Acute-targeted 5-ASA; CYA; surgery
- Maintenance-5-ASA for UC, AZA for CD
- Steroid resistant AZA for UC/CD TNF β
- Nutritional complications
- CRC surveillance (CD-C involvement)
- Type/timing of surgery

It is important to note that in 2.6-24% of persons given oral sodium phosphate solution for preparation of a colonoscopy, aphthous ulcer-like colonic ulcerations may be seen which may be confused with CD (Preiksaitis 1998).

The earliest intestinal radiological lesions in seen CD are tiny aphthous ulcers, and later large ulcers develop (Figure 1).



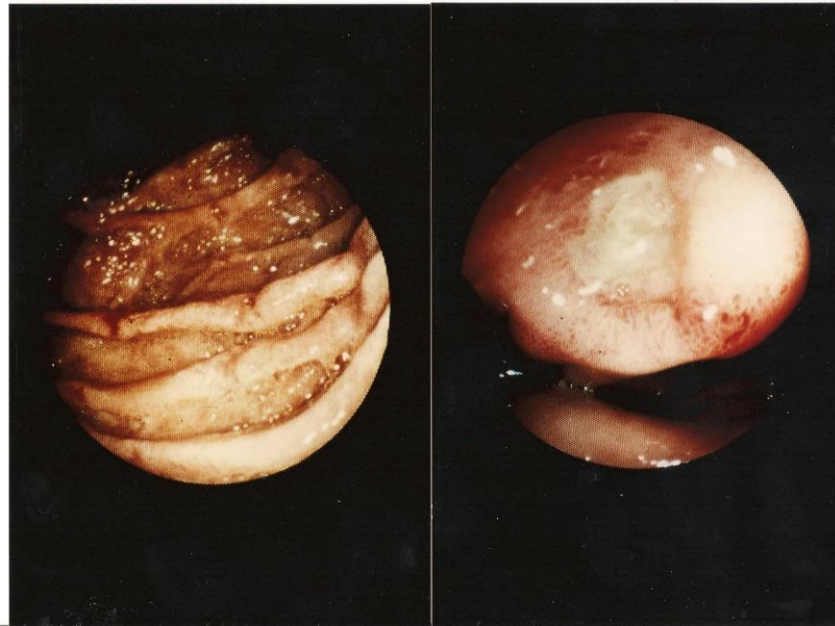


Figure 1. These are stellate-shaped, serpiginous or deep, and may give a cobblestone appearance on barium x-rays.



Figure 2. A small bowel CT finding in CD include abnormal thickening of the bowel wall, perienteric stranding, and intra-abdominal abscesses (Hellers 1999). EUS and MRI are particularly sensitive to detect perirectal and perianal fistulae, as well as abscesses. CT enterography/enteroclysis as well as MR enterography, with or without gadolinium, show promise for the diagnosis of CD and its complications (Masselli 2004).

➤ Histopathology

- The key diagnostic test to establish IBD from non-IBD conditions is the histopathology of mucosal biopsies obtained at endoscopy, or full thickness



biopsies obtained from surgical or autopsy specimens (Yusoff 2002). The cardinal histological features of IBD are 1) architectural distortion (including crypt distortion [non-parallel, variable diameter, cystic crypts]), crypt branching, shortening, decreased density, irregular mucosal surface; 2) inflammatory features – increased lymphocytes or plasma cells between the bases of the crypts and in or close to the muscularis mucosae (Kane 2008) (Figure 3).

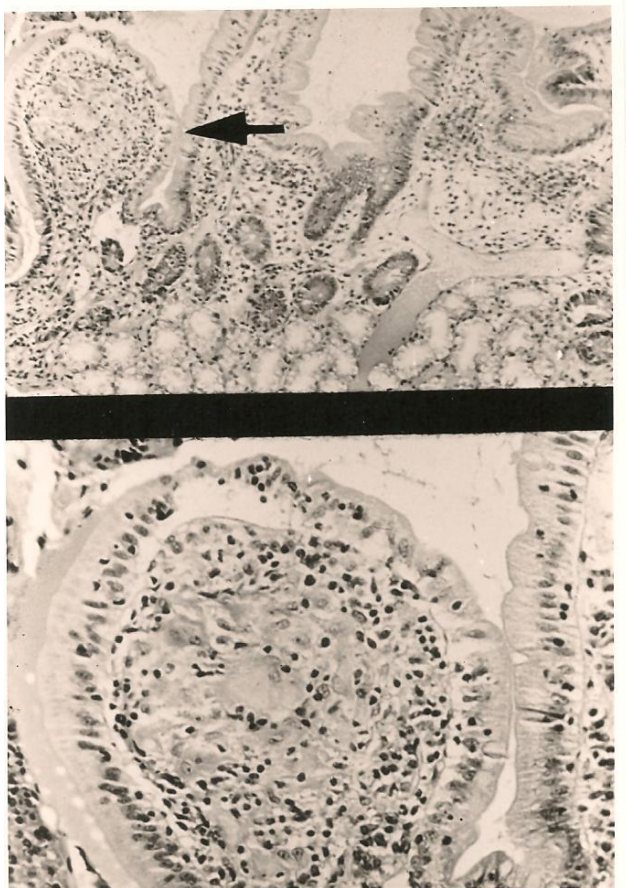


Figure 3. Microscopic mucosal granuloma in an endoscopic biopsy from the duodenum of a patient with Crohn disease.

There are usually more plasma cells on the right versus left side of the colon; and 3) metaplasia: pseudopyloric metaplasia in the ileum, as well as Paneth cell metaplasia (in especially on the left side of the colon). While granulomas may be detected in up to a third of persons with Crohn disease, their presence of granuloma is not necessary to make the diagnosis of CD. Detection of granulomas in biopsies or surgical specimens, however, may reflect an earlier stage in disease course or pathogenesis (Freeman, 2007). These histological features help the pathologist to distinguish between UC and CD of the colon (Geboes 2008) (Tables 12 and 13).



Table 13. Histological features which favour CD

-
- Patchy crypt architectural changes
 - Patchy inflammation
 - Mucin at sites of active inflammation
 - Irregular muscularis mucosae
 - Cryptitis
 - Epithelial Granulomas
 - Fissures
 - Transluminal lymphoid aggregates
 - Transmural disease
 - Submucosal nerve fiber hyperplasia with ganglionitis
-

Table 14. Histological features which favour UC

-
- Severe, widespread distortion
 - decreased crypt density, and irregular crypt surface
 - heavy, diffuse, mucosal lamina propria cell increase
 - Paneth cell metaplasia in biopsies taken distal to the hepatic flexure
 - Thickened but not irregular muscularis mucosae
-

There is diagnostic variability in the accuracy of pathologists in distinguishing UC vs. CD. In CD, the diagnostic accuracy of the pathologist is 60-74%, with difficulty experienced in making this distinction in early, treated or fulminant disease (Bentley 2002). Transmural lymphoid aggregates (specificity, 90%; PPV, 62%), granulomas in the subserosa unrelated to mucin or foreign bodies, fissures, transmural disease, submucosal nerve fiber hyperplasia with gaanglionitis all favour CD (Swan 1998). On the basis of histology, biopsies give the diagnosis of CD and UC in 64% and 74%, respectively, in UC, increasing to 96% with additional clinical information and supporting evidence (Bentley 2002).

UC and CD must be distinguished from acute self-limited (infectious-type) colitis (ASLC) (Table 14), in which the patient may have the same symptoms as IBD, including extraintestinal symptoms such as iritis, episcleritis, arthropathy, pyoderma, gangrenosum, and erythema nodosum (Surawicz 2008).



Table 15. Histological features on mucosal biopsy of acute self-limiting colitis (AC) which help to distinguish it from chronic idiopathic ulcerative colitis (UC)

Histopathological feature	ASLC	IBD
○ Crypt distortion	-	+
○ Inflammation	Acute	Acute/chronic
○ Increased plasma cells or lymphoid aggregates at crypt bases	-	+
○ Granulomas	Only with crypt abscesses*	+
○ Pyloric metaplasia in the terminal ileum	-	+
○ Paneth cells in the left side of the colon	-	+

*crypts are straight, parallel and close, possibly with bulging and a “necklace of cells” around any crypt abscess

There may be an elevated WBC count in ASLC, but stool cultures are positive in only about half of persons with suspected bacterial colitis. Clostridium difficile-associated disease (CDAD) may occur by itself, or in association with IBD, when it may be severe (especially in persons with colonic disease or who are on immunosuppressants), and the typical pseudomembranes may be absent on sigmoidoscopy or colonoscopy (Issa et al. 2007, Rodemann et al. 2007), so the possibility of CDAD always needs to be considered and excluded by stool culture. Infectious colitis may be patchy, enteritis may occur, and colonic ulcers may also occur (especially with tuberculosis and amebiasis), although the sarpyginous ulcers of CD are not usually seen). The colonic biopsy is the best test to distinguish between IBD and ASLC in the adult.

These typical histological features for the adult with IBD may be different for the child: crypt distortion is less common (only 34%) (Robert 2004), yet rectal sparing and patchy involvement is more common (26% and 21%, respectively) (Glickman 2008). Also, these histological features may be different for the adult or child who presents with fulminant colitis (UC or Crohn's colitis), where there may be fissures, transmural inflammation, and rectal sparing. Local enema/suppository therapy may result in rectal sparing. In acute colitis there may be patchy disease (59%) (Kleer 1998), as well as fewer histological features of chronicity such as basal lymphoid aggregates or basal plasmacytosis.



Useful Practice Points:

Is it important to distinguish between Crohn disease and Ulcerative Colitis?

- Crohn—Mouth to anus:
- Different complications in Crohn disease
 - Malabsorption
 - RLQ Mass
 - Perianal disease
 - Fistulae
 - Skip Lesions
 - Bleeding
 - Dilation
- Ulcerative Colitis:
- Different treatments
 - Acute
 - UC-CyA or CyA
 - CD-CyA not effective
 - Maintenance
 - UC-5-ASA (not effective in CD)
 - CD-AZA/MTX
 - Surgery

Abbreviation: AZA/ MTx, Azathioprine/ methotrexate; CD, Crohn disease; CyA, cyclosporin A; RLQ, right lower quadrant; UC, ulcerative colitis

➤ How often is a diagnosis of UC changed to CD, and vice versa?

About 10% of patients who are diagnosed with colonic IBD may initially not have sufficient diagnostic features to make a firm diagnosis of UC or CD (Meucci 2008). These persons are considered to have “indeterminant colitis” or IBD unclassified (IBDU) (Gebos 2008). When surgical specimens are used for diagnostic purposes and the diagnosis of the type of IBD is unclear, the term “colitis of uncertain type or etiology (CUTE)” is used. Over time, about one third of IBDU patients are re-classified as CD, 1/3 as UC, and the rest remain IBDU (Burakoff 2004). Over time, about 3% of persons with CD are reclassified as having UC, and 3% of UC patients are reclassified as having CD (Moum 1997).

Capsule endoscopy (CE) is proving to be useful to identify persons as having small bowel abnormalities. In the person who is thought to have UC and CE shows small bowel lesions, the diagnosis likely needs to be changed to CD (Mow 2004). In persons initially thought to have UC and who have an IPAA, about 4% are reclassified to CD (Yu 2000). Pouch failure occurs in as many as 30% of these CD patients who were misclassified as having UC (McLeod 2002).



Useful Practice Points:

- Is the diagnosis of IBD correct?
 - Suspect diagnosis from symptoms and signs (GI, non-GI)
 - Compatible x-ray or endoscopic changes
 - Compatible or diagnostic biopsy
 - Indeterminate, UC, Crohn's
 - For some, only time will tell

6. Clinical Course

At the time of diagnosis of CD, the terminal ileum is involved in ~47%, colon alone in ~28%, ileocolon in ~21%, and the upper GI tract (Jejunum, duodenum and stomach) in ~3% (Louis 2001). This distribution remains relatively stable over time. At the time of diagnosis of CD, ~70% have non-stricturing, non-penetrating (ie. inflammatory CD), ~17% structuring, and ~13 % have penetrating disease (fistulae or abscesses) (Louis 2001). Over a 10-year interval, of those persons who were initially diagnosed with the “inflammatory” form of CD, ~27% progress to stricturing and ~29% to penetrating disease (Podolsky 2002). A longer term study explored the natural history of Crohn disease over more than two decades and confirmed that the behaviour of Crohn disease progresses from a largely inflammatory process to a more complex disorder complicated by stricture formation and penetrating or fistulising disease complications (Freeman 2003). However, the clinical course may also have prolonged asymptomatic periods, often for more than a decade, before symptomatic recurrence is defined (Freeman, 2003). This may have implications for the clinical management of patients with Crohn disease where critical evaluation of treatments suggested for prevention, rather than control of symptoms is needed.

The rate of hospitalization for CD is about 20% per year (Berstein and Nabalamba 2006). About 53-57% of the cost of the disease is due to hospitalization, especially for surgery (Juan 2003). A quarter of CD patients are unable to work fully one year after onset of their CD, and 15% after 5-10 years (Carter et al.2004). Over the lifetime of the CD patient, 75% will require surgery (Carter 2004), and 25% require surgery within 10 years of diagnosis (Stange et al.2006). Mortality rates for persons with CD are either similar to that of a general population (Jess 2006), or are slightly increased, especially in younger persons, who tend to have more severe diseases (Wolters 2006).

One year after diagnosis, 10-30% have had an exacerbation of their symptoms, 15-25% have low disease activity, and 55-65% are in remission. Thereafter, between 13 to 20% of CD patients have chronic active disease, 67-73% have chronic intermittent CD, and 10-13% remain in remission for several years (Loftus 2002) (Table 15).

After surgical resection for failure of medical therapy, endoscopic recurrence is early and rapid (73% at 1 year, 85% at 3 years), with symptoms occurring later (1 year, 2%, 3 years, 34%) (Schwartz et al.2002). It is unknown why there is this disconnect between active inflammation and symptoms. While improvements of the patient's symptoms (as reflected in an activity index such as CDAI and quality of life) are



desirable outcomes, the longterm focus needs to be healing of the underlying inflammation (and of course, to discover the cause of CD).

Table 16. Comparison of the Clinical Course of CD and UC

	UC Course	CD Clinical Course 1 year after diagnosis	
○ Clinical remission at any point in time	50%	Relapse	10-30%
○ Overall Intermittent course	90%	Low Activity	15-20%
○ 3-7 years after diagnosis in remission	25%	Remission	55-65%
○ Yearly Relapse	18%	Chronic Active	13-20%
○ Intermittent Relapse	51%	Chronic Intermittent	67-73%
		Remission for 10 yrs	13%
○ 10 year Colectomy Rate	10%	Surgery by 20 yrs	>75%
○ Change in site of involvement over 25yrs		Change in behavior	
		NSNF → S	27 %
		NSNF → F	29 %

Abbreviations: F, fistulizing CD; NSNF, non-stricturing and non-fistulizing; S, stricturing (Baumgart 2007)

➤ Triggering Factors for relapse

Both CD and UC have chronic recurring clinical courses. A recurrence of symptoms (“flares”) does not necessarily indicate recurrent inflammation, and the severity of symptoms does not reflect the severity of underlying inflammation.

In the patient with known IBD who presents with a recurrence of symptoms, the symptoms may be related to an incidental infection such as giardiasis, CMV or *Cl. difficile*, small intestinal bacterial overgrowth, a drug reaction (eg NSAIDs, 5-ASAs or antibiotics), food intolerances such as milk, bile acid induced diarrhea due to partial interruption of the enterohepatic circulation, or associated IBS-like symptoms. A recurrence of symptoms due to a recurrence of the IBD may be related to stopping maintenance medications, changing smoking habits, pregnancy, and possibly stress.

Clostridium difficile-associated disease (CDAD) may occur in association with IBD. It may be severe (especially in persons with colonic disease or who are on immunosuppressants), and the typical pseudomembranes may be absent on sigmoidoscopy or colonoscopy (Issa et al. 2007, Rodemann 2007). Thus, the possibility of CDAD needs to be considered and excluded by stool culture.

In some persons, stress and distress do affect the ups and downs of IBD symptoms and/or inflammatory activity, as well as being a factor which may influence the patient’s disease experience (Levenstein 2008). The psychosocial aspects of the patient’s care are of great importance in the therapeutic relationship between the physician, the patient, and the person in the patient. “Quality of life is improved in those



receiving quality professional care and guidance, and by strong peer and family support, as provided by the patient's informed and understanding physician, health care personnel and family" (Moser 2008).

Useful Practice Point:

- Even patients with IBD have IBS-like symptoms
 - IBS-like symptoms shouldn't be treated as IBD
 - Anti-diarrheal agents
 - Anti-cholinergics
 - Anti-biotics
 - Bile acid sequestrants
 - Analgesics
 - Exercise caution when/if using analgesics

7. Management

➤ General Principles

In a research setting the efficacy of a treatment for CD is often reported as a change in the score of the Crohn disease activity index (CDAI) by a given number of points (eg. 70 points, a "response") and a reduction in the CDAI to or below a given value (eg. 250, "remission"). However, there are a number of often important goals to achieve with therapy in CD (Table 16). Understanding the rationale of the different management of persons with CD requires an appreciation of the natural history of the disease. Therapeutic efficacy is balanced against adverse effects and costs (both direct and indirect). Induction of remission in this context is based on symptom improvement, with only anti-TNF therapy being reliably associated with endoscopic healing (Rutgeerts 2006, Hommes 2006). This in turn may be associated with reduced time-to-time relapse (D'Haens 2002), as well as a decline in IBD-associated hospitalization and the need for surgery at one year (Rutgeerts 2006).

Table 17. Goals of Therapy in CD

-
- Cure the disease (not yet possible)
 - "normal life"-quality of life (QOL)
 - normal mental health
 - Induction and maintenance of clinical remission of intestinal and extraintestinal symptoms
 - Endoscopic and histopathological remission
 - Normal nutrition
 - Normal ability to go to school, to work, to raise a family, to enjoy leisure time and to be free of worry about the financial costs of their disease
-

Patients with IBD need accurate information about their condition, they must have a sense of control over themselves and their illness, and like all of us, they need strong social support (Moser 2000, Moser 1996, Sewitch 2001, Kennedy 2004). For example,



denial and social withdrawal, as a means of coping with depression have a major negative impact on the person's quality of life, and possibly also on the disease process itself (Janke 2005, Mussell 2004). Thus, it is important to incorporate psychological care into the management of persons with IBD.

Part of the therapeutic discussion in CD includes a review of the diagnosis, and the exclusion of precipitating factors; the informing of the patient that in a small proportion of persons, the initial diagnosis of CD may be changed to UC, or UC to CD; that every treatment may have adverse effects; that there are a number of therapeutic options; that surgery may be an option, and that there is a risk of colon cancer in persons with Crohn's colitis or UC, and of small bowel adenocarcinoma and lymphoma in CD.

As best as possible, therapeutic discussion must be evidence-based, yet modified carefully by the included needs of the patient. Physicians must recognize the potential bias in their therapeutic choices for patients, based on their interaction with the pharmaceutical industry (Wazana 2000).

In order to fully appreciate the therapeutic gains of various treatments in persons with Crohn disease (CD), it is useful to appreciate that about 25% of CD patients with an attack (flare) of acute CD disease will go into remission, without the use of active therapy (ie placebo response), and about 33-50% will remain in remission, even when not on maintenance therapy.

An attack or relapse of CD is considered to occur when the CD symptoms flare (as indicated, for example, by an increase in their CDAI as reflected by symptoms of pain, diarrhea, loss of sense of well-being, abdominal tenderness), in association with an elevation of markers of inflammation (decreased hemoglobin concentration; increased WBC, platelets, ESR, CRP); characteristic changes in endoscopy, and diagnostic imaging, histopathology and possibly increases in fecal lactoferrin or calprotectin or increased intestinal permeability assessed by lactulose/mannitol urinary excretion test. It must be stressed that therapeutic trials of drugs used in CD and UC have focused on the improvement of symptoms, or QOL. Several systems have been developed to score the endoscopic severity of C, but there is a poor correlation between the endoscopic and clinical scores of activity, or biological markers of activity such as CRP. The issue of the importance of mucosal healing remains unclear.

Useful Practice Points: First Line Therapy for IBD

➤ Diagnosis	➤ Complications
➤ Information	○ Nutrition
➤ 5-ASAs	○ Osteoporosis
	○ Psychological



Useful Practice Points:

- What to do when Symptoms Come Back: Is this IBD, or Something Else?
 - Infection
 - Pregnancy
 - Drugs
 - Other conditions (stress)
 - Non-adherence to maintenance Rx
 - Change in smoking habits
- Is this a Severe Recurrence of Symptoms?
 - > 6 BM/day
 - Blood
 - Pain, malaise
 - Fever
 - Extraintestinal symptomizing arthralgias, Aphthous Ulcers, rash
- Is this a recurrence of IBD?
 - 3-day D/C 5-ASA
 - Double dose 5-ASA
 - Start prednisone 40 mg (AEs) for 2 weeks, then taper
 - Call your “GI”, “GIM”, or “GS”
 - If no response, or quick return of symptoms with taper:
- What will the referral MD likely do?
 - Confirm the diagnosis
 - R/O
 - Infections (stool cultures)
 - Obstructions (abdominal film)
 - Abscess (ultrasound, MRI)
 - Full dose 5-ASA, start on prednisone
 - Judicious decision re: “scoping”
 - Consider immunosuppression
- Tips on staying on top® of IBD
 - Causes of chronic diarrhea
 - Distinguish between
 - IBS & IBD
 - UC & CD
 - First line therapy for UC, CD
 - 5-ASA
 - Maintenance 5-ASA
 - What causes recurrence of symptoms

Abbreviations: AE, adverse effects; D/C, discontinue; GI, gastroenterologist; GIM, general internal medicine specialist; GS, general surgeon

Nutritional assessment is of utmost importance in the care of the patient with IBD. A major later section is dedicated to this topic.



Table 18. Evidence Based Recommendations for therapy in IBD

Medication	Indication	CD	UC
➤ 5-ASA	○ Induction	No (2c)	Yes (1B)
	○ Maintenance	No (2c)	Yes (1A)
➤ Corticosteroids	○ Induction		
	– Standard	Yes (1c)	Yes (1c)
	– Budesonide	Yes (1c)	No
	○ Maintenance		
	– Standard	No	No
	– Budesonide	No (2c)	No
➤ Antibiotics	○ Induction		
	– Inflammatory	No (2d)	No (2d)
	– Fistulizing	Yes (2c)	
	○ Maintenance	No (2d)	N/A
➤ AZA/6-MP	○ Induction	No (2c)	No (2d)
	○ Maintenance	Yes (2c)	Yes (2c)
➤ MTX	○ Induction	Yes (2c)	No (2d)
	○ Maintenance	Yes (2c)	No (2c)
➤ CyA	○ Induction (IV)	No (2d)	Yes (2d)
	○ Maintenance	No (2c)	-
➤ TNFB	○ Induction		
	– Inflammatory	Yes (1b)	Yes Ambulatory (1b) Hospitalized (2d)
	– Fistulizing	Yes (1c)	
	○ Maintenance	Yes (1a)	Yes N/A
➤ Anti- α 4 integrin antibodies	○ Induction	Yes	-
	○ Maintenance	Yes	-

A, high quality evidence; 5-ASA, 5-aminosalicylic acid; B moderate-quality evidence; C, low-quality evidence; 95% CI, 95% confidence interval; D, very low-quality evidence; IV, intravenous; N/A, not applicable; NNH, number needed to harm; NNT, number needed to treat; UC, ulcerative colitis; 1, strong recommendation; 2, weak recommendation. [^aNNT] should NOT be compared between therapies, as trials evaluated different severities of disease and used different end points to define remission, ^bNNT for symptom improvement and not remission.

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- **Accelerating the induction of remission of inflammatory CD**

Much of the practice of the care of the patient with severe active CD is derived from data from severe UC. This management will be reviewed here, as well as in the chapter on UC. About a third of UC patients will require therapy with glucocorticosteroids (GCS, “steroids”) (Faubion 2001), and one in six UC patients will have a sufficiently severe flare that they will require hospitalization (Truelove 1955). This severe attack may occur when the diagnosis is first made, or at a time when the UC patient’s flare becomes progressively more severe and does not respond to oral GCS. Unlike UC, cyclosporine (CyA) is not effective in persons with severe and active disease.

The use of AZA/6-MP is not an option in the acute setting, because of the effect of immunosuppression takes in 8-12 weeks of therapy. If the patient who has more than one flare per year while being adherent to taking maintenance doses of 5-ASA, the use of AZA/6-MP needs to be considered. The probability of an IBD patient remaining in remission increases over time, so that the longer they are in remission, the more likely they are to stay in remission.

- Sulfasalazine (SASP) and Mesalamine (5-ASA)

SASP (Sulfasalazine) has a modest effect in active CD of the colon, especially if given to GCS-naïve patients, or when the SASP is given with GCS (Summers 1979, Van Hees et al. 1981). The evidence is weak for 5-ASA (mesalamine) being efficacious for acute CD, with NNT (number-needed-to-treat) being relatively high. (Meta-analyses of 5-ASA in active CD: has shown a statistically superior to placebo, but the 18 CDAI [Crohn disease activity index] unit difference is not statistically meaningful (Hanauer 2004).

The 5-ASAs have different release patterns from their formulations, with the purpose of targeting particular parts of the gastrointestinal tract (Table 17). They are often given 3 to 4 times a day, but MTX for example is effective when given once a day. This once a day dosing is good for the patient, may improve their compliance with the medication, and their quality of life. Even though SASP / 5-ASA have many potential mechanisms of action (reduction of the function of prostaglandins and leukotrienes, reduction in cytokine and free radical production, reduction of leucocyte function and adhesion) (Novak et al. 2008), their actual means of achieving efficacy in UC or CD is unknown.

Useful Practice Points:

Are you prescribing the right 5-ASA preparation?

- Mesalamine vs Salazopyrine-cost, AEs
- PO-dose, duration, target site
- Local-enemas, suppositories ± PO



Table 19. Anatomical location of the release in the GI tract of orally administered 5-ASA products

- Mesalsal®/Salofalk®: terminal ileum (pH > 6)
- Asacol®: terminal ileum; cecum (pH > 7)
- Pentasa®: release begins in jejunum
- Dipentum® and sulfasalazine: colon (diazo bond)
- Balsalazide® (available in the USA): colon
- Generic 5-ASA (modeled after Asacol): terminal ileum, but may be released at pH 5.5 (in proximal GI tract which is the problem with it)
- MMX (once a day) – colon

Useful Practice Points:

- 5-ASAs for IBD
 - Mesalamine
 - Plus sulfa
 - Plus coating
 - Release pattern
 - P .O. SB+C Pentasa
 - TI Salofalk
 - C Asacol (400 mg)
 - P .R. Enemas (4 g), suppositories (500 mg)
- Choosing a 5-ASA product
 - Adverse effect
 - SASP 30%
 - Mesalamine 1 to 5%
 - Dosing
 - QID-TID-BID-once a day!
 - Route
 - Cost
 - Theoretical Differences
- Use of Mesalamine in IBD
 - Acute 4 g P.O., P.R.
 - Caution: slow onset, long duration
 - Maintenance 2 g
 - UC |
 - CD ± (limited use)
 - For life

Individual studies may suggest that mesalamine may be useful maintenance therapy after surgery for the patient with CD. For example, Asacol®, the pH 7-dependent 5-ASA, reduces the risk of recurrence of CD after surgery (Steinhart 2007). Unlike the efficacy of mesalamine (5-ASA) in UC, 5-ASA has only a modest benefit (10%) of maintaining a medically-induced remission in CD (Cammà 1997) (Edwards). However, in meta-analyses, 5-ASA has a slightly better effect (NNT, 10) maintaining a surgically-induced remission of CD (NNT, 10) (Cottone 2000).



Sulfasalazine (SASP) use is associated with mostly minor adverse effects (AEs) in about one person in four. Reversible sperm abnormalities are common in men taking SASP. The AE profile of mesalamine is less than 5% (Loftus 2004), and only 10-20% of persons intolerant to SASP show the same AEs with 5-ASA (mesalamine) (Scribano 2008). There is no clear dose-response relationship between 5-ASA AEs, and therapeutic response, but there may be a dose threshold to achieve clinical efficacy (Mansfield 2002). Some clinicians find that taking 5-ASA/SASP medications with food, and gradually increasing their dose will help to establish better patient tolerance. Interstitial nephritis is rare with chronic (maintenance) use of 5-ASAs. Adding topical (enema) 5-ASA is useful for the person with left-sided colonic disease, and continuing the oral with the topical (enema) therapy provides added benefit (Marteau 2005). Persons with impaired renal or hepatic function may need to avoid 5-ASA compounds. The 5-ASA drugs increase the value of the patient's INR, as well as increases the blood concentrations of 6-TGN and methotrexate, and decreases digitalis levels; allopurinol increases 6-TGN; and ACE inhibitors increase the 6-MP-associated risk of anemia, and leucopenia.

Useful Practice Points:

- Ask yourself a few questions:
 - Is the diagnosis of IBD correct?
 - Are you prescribing the right 5-ASA preparation?
 - Are you using GCS appropriately?
 - Should an immunosuppressant be used?
 - Why are you not using an immunosuppressant?
 - Is there a good reason to use biological therapy?

○ Glucocorticoids (GCS)

About 43% of CD patients will require GCS (Faubion et al. 2001). Treatment with GCS indicates worsening of the disease severity, with 38% requiring surgery and 28% becoming steroid-dependent (Knutson 2003).

There is sound evidence to support the short-term use (no more than 4 months) of GCS in the patient with symptomatically active CD (Summers 1979, Malchow 1984, Modigliani 1990). The NNT for steroids in CD is only 2. Longterm steroid maintenance is without benefit, is complicated by adverse effects, and must be avoided. Because of the common and/or serious adverse effect profile of GCS, this point needs to be emphasized: do not use GCS for long term use in persons with CD.

In persons with a non-severe flare who do not respond to the full flare-dose of 5-ASA, GCS are introduced at a dose of prednisone 40 mg/day for mild and 60 mg/day for moderate disease activity. Be certain to warn the patient and record in the medical record the fact that you have discussed with the patient the many adverse effects of using GCS. Expect that about three persons in four will begin to respond to GCS within two weeks. When there is a convincing clinical response, begin to slowly taper the prednisone at the rate of one 5 mg tablet per week (e.g. 40 mg/day, then 35 mg per day for one week, then 30 mg/day for one week etc). Once the patient has tapered down to 15 mg/day, slow the rate of taper to even further one half a 5mg tablet (ie. 2.5mg) per week. This is the time to discuss with the patient



the pro's and con's of maintenance (continuous) therapy with some other agent (ie, do not use GCS long term).

In the outpatient setting, oral prednisone will achieve clinical remission in 60-70% of patients (Braegger 1992). When UC patients do not respond to oral therapy, steroids may be efficacious with IV therapy (Jamerot 1985). This is presumably also true in CD.

Steroid dependence (continued need to use GCS because of relapse with dose reduction, or a relapse within 3 months after tapering GCS) occurs in 28-36% of CD and 22% of UC patients (Faubion 2001, Munkholm 1994). Steroid resistance (failure to respond to GCS) is also common, and the mechanisms are complex (Table 18). Only about 29% of CD patients achieve mucosal healing with GCS (Modigliani 1990). The importance of mucosal healing as a therapeutic objective is only now becoming recognized.

Entocort® is coated budesonide target for ileocolonic release. For terminal ileal and/or right-sided colonic CD, Entocort® is similarly efficacious as prednisone, with a much lower risk of steroid-related adverse effects. Entocort® used in CD for up to 12 months increases the time to relapse, but should not be used for longer. Oral Entocort® has limited effect in UC because more disease is localized in the distal colon. Entocort® enemas may be used in left-sided UC or Crohn's colitis.

The therapeutic therapy of budesonide therapy is not improved with the addition of metronidazole and ciprofloxacin (Steinhart 2002), and the combination of cipro' plus metronidazole is not superior to methyl prednisolone (Prantera 1996).

Table 20. Molecular mechanisms of steroid resistance

-
- Abnormalities in absorption/metabolism (liver disease)
 - Altered number of GCS receptors or altered numbers of isoforms (α , β , δ)
 - Altered affinity of GCS for GCS receptors
 - Reduced affinity of the GCS receptor ligands to bind DNA
 - Altered expression of transcription factors (AP-1, NF-k B) and/or cytokines (IL-2, IL-4, p38 activated MAP kinase)
 - Genetic factors (primary steroid resistance, MDR-1 [P-glycoprotein 170], HLA class II allele DRB1*0103)
-

Adapted from: Farrell RJ, and Kelleher D. *J Endocrinol* 2003; 178(3): 339-46.



Table 21. Common and/or serious adverse effects of the use of glucocorticosteroids

Adverse effect	Frequency
➤ Alopecia	-
➤ Arterial hypertension	+++
➤ Bone marrow suppression	-
➤ Dermatitis	+
➤ Gastrointestinal Toxicity	+
➤ Hirsutism and/or gingival hyperplasia	-
➤ Hyperglycemia and diabetes mellitus	+++
➤ Hyperlipidemia	++
➤ Impaired wound healing	+
➤ Lymphoma or malignancy	-
➤ Myalgia and/or arthralgia	+
➤ Nephrotoxicity	-
➤ Neurotoxicity ^a	+ (psychiatric)
➤ Osteoporosis	+++
➤ Pneumonitis	-

^aNeurotoxicity includes mainly peripheral neuropathy, headaches, tremor, convulsions, akinetic mutism, and insomnia. ? , Incidence unknown; - not reported; + rarely reported; ++ commonly reported; +++ very frequently reported adverse effect limiting usage of the drug.

Abbreviation: MTOR, mammalian target of rapamycin

Adapted from: Benten D, et al. *Nature Clinical Practice Gastroenterology and Hepatology* 2009;6:1:23-36.

GCS may result in AEs in almost every body system (Table 19), and depending on the dose and duration of use, AEs may occur in half of users. Steroids cause osteoporosis by changing the optimal ratio of Rankl relative to OPG/OCIF. The damaging effect of steroids is greatest in the first 6 months of their use. The ways to reduce the risk of GCS is to use these agents only when absolutely necessary, use steroid-sparing cotherapy (AZA/6-MP, MTX, anti-TNF therapy), use steroids with low systemic bioavailability (Entecort®, budesonide, for acute care of ileocolonic CD). Residronate, a biophosphonate, is approved in the USA to help to reduce the development of steroid –associated osteoporosis (Compston 2003).



Useful Practice Points:

- Are you using GCS appropriately?
 - Moderately severe disease
 - Warn about side effects!
 - Caution about short term use only
 - Inform about escape from steroid-dependency and resistance
 - Use locally acting Entocort® for SB/C-CD
 - Dexa scan and bisphosphonates

○ Antibiotics

Metronidazole is superior to placebo to treat active CD, especially Crohn's colitis. The benefit is small in terms of reducing the CDAI, and not in terms of improving the remission rate (Sutherland et al. 1991). The combination of budesonide, cipro' plus metronidazole is no better than budesonide alone in persons with active CD at any site (Steinhart 2002). Short-term AEs of metronidazole occur in about half of users, and include a metallic taste in the mouth, gastrointestinal upset, and an antabuse-like reaction when taken with alcohol. The polyneuropathy associated with longterm use of metronidazole is not always reversible. Skin reactions and a mild elevation of hepatic transaminases may occur with ciprofloxacin. More distressing AEs which may occur with cipro', either used by itself or with steroids, includes tendonitis and rupture of the Achilles tendon (Scribano 2008). Metronidazole increases the effects of statins, sildenafil, calcium channel blockers and the patient's INR.

Probiotics do not have a benefit on the rate of post-operative clinical recurrence, and probably do not improve endoscopic recurrence rates (Prantera et al. 2002, Chermesh et al. 2007).

○ Immunosuppressants

- Azathioprine/6-MP

Compared to placebo, azathioprine (AZA) or its active metabolite 6-MP are effective in both inducing (OR, 3.09) or in maintaining (OR, 2.27) remission in CD (Pearson DC 1995). AZA inhibits thiopurine methyl transferase (TPMT) activity (Dewit 2002), thereby increasing the risk of neutropenia, especially in the 11% of the population who carry a heterozygous mutation in the TPMT gene, or the 0.3% who are homozygous (Lennard 1989). The purine analog antimetabolites AZA and its metabolite 6-MP are metabolized further to the active 6-thioguanine (6-TG). 6-TG is incorporated into nuclear RNA, thereby inhibiting the production of DNA in replicating lymphocytes. This in turn reduces lymphocyte proliferation. In addition to impeding lymphocyte proliferation, 6-TG inhibits the inflammatory effect of NK (natural killer) and cytotoxic T-cell function (Novak et al. 2008).

The NNT to achieve remission with AZA/6-MP has been shown by meta-analysis to be 5 (OR 2.36; CI, 1.57-3.53); for steroid sparing effect, the NNT is 3 (OR 3.86; CI, 2.14-6.96) (Sandborn W et al. 2004), and for maintaining remission, the NNT is 7



(Camma et al. 1997). There is no added benefit of combining AZA plus MTX (Soon SY et al. 2004). The relapse rate after stopping AZA is 37% at 1 year, 56% at 2, and 65% at 3 years (Solomon et al. 1993). If AZA maintenance is stopped, the patient will recover the benefit of AZA maintenance if the AZA is restarted.

Mucosal healing achieved with steroids or azathioprine (AZA) does not necessarily lead to lower relapse rates after discontinuation of therapy (Lemann 2002).

Immunosuppressors are being used increasingly and earlier in IBD patients. The AEs of azathioprine (AZA)/ 6-MP are either dose-related or allergic in nature (Table 19). About 5-10% of persons on AZA/6-MP may develop allergic non-dose dependent AEs soon after the medication has been started. These allergic reactions include nausea, abdominal pain, pancreatitis, fever, malaise, skin rash, and arthralgias. Dose-dependent AEs include leucopenia and hepatic toxicity. In persons with IBD who are treated with AZA/6-MP, there is a 4-fold increased relative risk of developing lymphoma (Kandiel 2005); altogether thankfully the absolute risk remains low. In persons with reduced TDMT activity, the enzyme responsible for the conversion of AZA to its active metabolite (6-TG), the risk of myelotoxicity when using the standard rather than a reduced dose of AZA/6-MP is increased 4-fold (Gisbert 2006). In support of measuring AZA metabolites (such as 6-TG), weight based dosing of AZA/6-MP still underestimates the dose 50% of the time (Morales 2007). Allopurinol increases 6-TGN; and ACE inhibitors increase the 6-MP-associated risk of anemia and leucopenia.

- Methotrexate

The therapeutic benefit of methotrexate (MTX) is about 20%, giving a NNT of 5 (Feagan 1995), with a modest efficacy for maintenance of remission (Feagan 2000). MTX must not be used if pregnancy is planned. Regular monitoring of CBC and liver transaminases is essential. The patient on longterm MTX has an increased risk of developing hepatic fibrosis.

When used longterm, methotrexate (MTX) may be associated with the development of hepatic fibrosis or hypersensitivity pneumonitis. MTX is contraindicated in pregnancy because of its teratogenicity. MTX is superior to placebo to induce and maintain remission in CD (Alfadhli 2005).



Table 22. Gastrointestinal complications of immunosuppression

➤ Infection ○ CMV ○ HSV ○ <i>Candida albicans</i>, <i>tropicalis</i> ○ <i>Yersinia enterocolitica</i> ○ <i>C. difficile</i> ○ Microsporidia ○ <i>Strongyloides stercoralis</i> ○ <i>H. pylori</i>	➤ Biliary tract ○ Thickened gallbladder wall ○ Sludge ○ Stones ○ Dilated ducts ○ Hydrops
➤ GI malignancy ○ Lymphomas, including Malt lymphoma ○ Skin cancer ○ Kaposi sarcoma ○ Colorectal cancer ○ Post-transplant lymphoproliferative disorder (PTLD) (EBV)	➤ Pancreatitis ○ Acute (CMV, hypercalcemia, alcohol, cholelithiasis, AZA, CyA)
➤ Cervical dysplasia Diverticular disease, diverticulitis	➤ Liver ○ Hepatitis ○ Methotrexate-associated fibrosis
➤ Perforations (upper or lower GI tract)	➤ Mucosal injury ○ Diarrhea ○ Ulceration (surgery, NSAIDs; steroids, AZA or MMF-induced slowing of intestinal cell turnover)

Abbreviations: AZA, azathioprine; CyA, cyclosporin A; EBV, Epstein Barr virus; PTLD, post-transplant lymphoproliferative disorder.

Adapted from: Helderman J, and Goral S. *J Am Soc Nephrol* 2002; 13: page 277-287.

Useful Practice Points:

- Immunosuppressants in Crohn's disease
 - Why are you not using an immunosuppressant?
 - Steroid-resistant/-dependent
 - Maintenance therapy

A number of other immunosuppressive agents have been used in patients with CD (Table 21). Methotrexate (MTX) levels are reduced by tetracycline, and increased by penicillin; 5-ASA and NSAIDs; folic acid deficiency worsens MX toxicity.



➤ Anti-TNF therapy

In the patient with active inflammatory CD who has failed an adequate course of standard therapy with GCS and immunosuppressants, anti-TNF therapy is an option. Relative contraindications (Table 20) must be carefully considered before initiating this therapy and adverse effects (Table 21). The major AEs of infections and lymphoma may be the result of the use of the combination of an anti-TNF, AZA/6-MP and GCS (Lichtenstein 2006). IFX is considered to be useful for hospitalized UC patients with severe or moderately severe UC (Jannerot 2005). There have been no reports of hepatosplenic T-cell lymphoma in IBD patients on monotherapy with anti-TNF therapy, or a combination of infliximab or adalimumab with methotrexate. If anti-TNF therapy is added to AZA or MTX because of failure to respond to these immunosuppressants, then it would appear to be reasonable to stop immunosuppressant once the anti-TNF therapy has been started, especially since withdrawal of aziothioprine and continuation of the infliximab (IFX) alone has no effect on the continued response to IFX, as compared to patients on both IFX and AZA (Van Assche 2008.). For patients with secondary loss of response to IFX, switching to ADA gives “recapture” remission rates of 21% at 4 weeks and 40% at one year; switching from IFX to certolizumab pegol at 6 weeks gives a “recapture” response of 60% and remission of 40% (Rutgeerts 2008).

The two large international placebo-controlled randomized clinical trials in CD (RCTs) support the results of earlier smaller studies of clinical response and maintenance of remission in CD when using the anti-TNF biological agent, infliximab (IFX) (Kohn 2008). There are many further studies of infliximab as well as adalimumab and certolizumab in CD. Note that from many studies using TNF blockers (TNFB) such as infliximab (IFX), adalimumab (ADA), or certolizumab (CER) exclude those CD patients who were non-responsive to induction therapy.

Useful Practice Point:

- Antibiotics in Crohn's Disease
 - Best evidence for MTZ, not Cipro' or Cipro + MTZ
 - Metallic taste
 - Peripheral neuropathy
 - Antabuse-like reaction
 - May be treating bacterial overgrowth
 - Warn about AAD or C.difficile development



Table 23. Immunosuppressive agents commonly used in gastroenterology or hepatology, and for each their mode of action, common toxic effects, and recommended monitoring

Agent	Mode of action	Monitoring	Toxic effects
➤ Cyclosporine (CyA), tacrolimus	Calcineurin inhibitor: suppresses IL-2-dependent T cell proliferation	Blood level of CyA, cholesterol, magnesium, Creatinine, BP, BS	Renal, neurologic, hyperlipidemic, hypertension, hirsutism
➤ Prednisone	Other gene transcription; cytokine inhibitor (IL-1, IL-2, IL-6, TNF, and IFN gamma)	BP, BS, annual eye exam, DEXA scan	(see previous question)
➤ Azathioprine (Imuran®)	Inhibition of T and B cell proliferation by interfering with purine synthesis (↓DNA/RNA)	White blood cell count, liver enzymes	Bone marrow suppression, hepatotoxicity
➤ Methotrexate	Folate antimetabolite (↓DNA)	Liver biopsy after 1,500 mg (only 2 years maintenance therapy)	Diarrhea, bone marrow suppression
➤ Mycophenolate mofetil (Cellsept®)	Inhibition of T and B cell proliferation by interfering with purine synthesis	White blood cell count	Neutropenia, thrombocytopenia, hyperlipidemia
➤ Sirolimus (Rapamycin)	Inhibition of TORC, which disrupts IL-2 induced intracellular signalling in lymphocyte	Blood level	Cytokine release syndrome, pulmonary edema, increased risk of infections
➤ OKT3	Blocking of T cell CD3 receptor, depletion of effector T cells and T regs, preventing stimulation by antigen	CD3 ⁺ count	Hypersensitivity reactions with basiliximab
➤ IL-2 receptor blocker	Competitive inhibition of IL-2 receptor on activated lymphocytes	None	

Abbreviations: BP, blood pressure; BS, blood sugar; DEXA, DEXA scan for bone mineral density; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Adapted from: Martin P, and Rosen HR. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/Diagnosis/Management* 2006: page 2049.

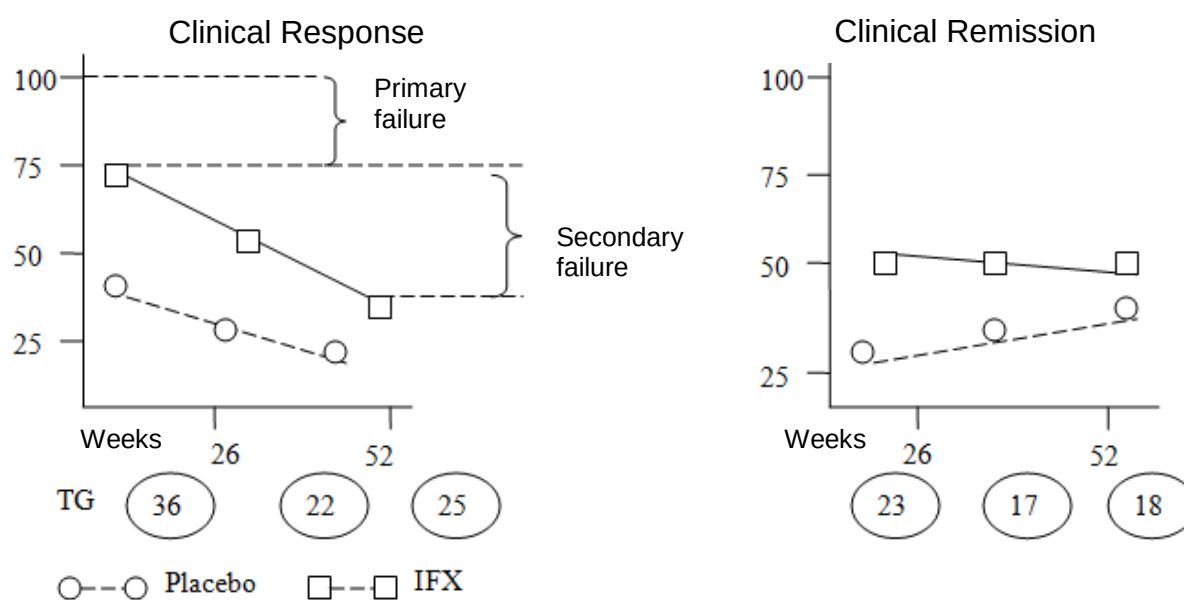


Table 24. Relative contraindications to anti-TNF therapy

- Allergy to anti-TNF
- Intestinal stenosis
- Fistulizing disease with abscess
- Fistulae to bladder
- Untreated active infection (TB, HBV, HCV)
- Multiple sclerosis, optic neuritis
- Congestive cardiac failure (grade III, IV)
- Lymphoma
- Pregnancy
- Acute liver failure

Abbreviations: HBV, hepatitis B viral infection; HCV, hepatitis C viral infection; MS, multiple sclerosis; TB, tuberculosis; CyA, cyclosporin; BP, blood pressure; BS, blood sugar; WBC, white blood cell count

When determining the NNT, the therapeutic gain must be recognized, eg IFX response minus placebo response. For example, in the Act 1 and 2 studies, the rate of clinical remission fell over time, the proportion of patients in remission was only about half, and the TG over time was only about 20% (Figure 4). Thus, while anti-TNF has changed the way in which some physicians change the way CD is treated, and while some patients do very well, in fact the therapeutic gains are small, these rates may become higher once the reason for the development of primary and secondary treatment failure has been overcome (Table 22).



Abbreviation: TG, therapeutic gain (clinical response/ remission with IFX minus placebo)



Figure 4. The Act 1 and 2 Randomized clinical trials of Infliximab for induction and maintenance of remission in patients with active Crohn disease.

Mucosal healing prolongs the time to relapse with IFX (D'Haens, et al. 2002). When relapse occurs, “it is striking that upon relapse, endoscopy shows an identical pattern of lesions and of locations of disease as observed prior to healing under biologic treatment” (Rutgeerts et al. 2008). Note that there may be drug-drug interactions with agents used in therapy of CD (Table 24).

Table 25. A definition for primary and secondary infliximab failures in patients with inflammatory bowel disease (IBD) and their proposed mechanisms

-
- Primary – lack of response due to high pre-treatment TNF- α levels, or TNF- α independent inflammatory pathways
 - Secondary – loss of initial symptomatic response to anti-TNF
 - Mechanisms
 - Antibody to TNF
 - Increased clearance of TNF
 - Non-TNF α dependent
 - Development of IBD-related complications e.g. stricture, abscess
 - Non-IBD related symptoms (e.g IBS)
 - Anti-I (infiximab) antibodies, (e.g., use of on demand infusions):
 - Rapid infliximab metabolism
 - Low trough infliximab levels
-

Abbreviations: IBD, inflammatory bowel disease; IBS, irritable bowel syndrome

Table 26. Useful background summary pointers of IBD drug interactions

-
- 5-ASA increases INR, 6-TGN and methotrexate, and decreases digitalis levels
 - Allopurinol increases 6-TGN
 - ACE inhibitors increase the 6-MP-associated risk of anemia, leucopenia
 - Methotrexate (MTX) levels are reduced by tetracycline, and increased by penicillin; 5-ASA and NSAIDs; folic acid deficiency worsens MX toxicity
 - Metronidazole increases the effect of statins, sildenafil, calcium channel blockers and $\uparrow$ INR
 - Steroids cause osteoporosis by changing the optimal ratio of Rankl relative to OPG/OCIF. The damaging effect of steroids is greatest in the first 6 months of their use
 - Anti-TNF therapy causes 6.4 fold increase in mortality rate in persons with pre-existing pulmonary disease (256-97)
-

Abbreviations: MTX, methotrexate; OCIF, osteoclasto genesis inhibitory factor; OPG, osteoprotegerin



Useful Practice Points:

- Is there a good reason to use experimental biological therapy?
 - Failed standard step-up medical therapy: 5-ASA→GCS→AZA/MTX
 - Willing, informed patient, with good cost coverage for Rx

- **Maintenance of remission**

Steroids provide no benefit to prevent relapse of CD (Sims and Steinhart 2001, Steinhart 2003). Budesonide prolongs the time to achieve a CD recurrence at 1 year (Hellers 1999), but should not be used for longer. Thus, steroids should be used for maintenance therapy in CD (or UC). The locally acting steroid Entocort® may be used in mild or moderately active ileal or ileocolonic CD, but must not be used in UC, because it is ineffective for flares, and is also ineffective for maintenance. If the patient is steroid-refractory (failure to enter remission despite high-dose and IV GCS) or steroid-dependent (remission obtained with GCS, but either a reflare as the GCS dose is tapered, or a reflare within 3 months stopping the GCS), the patient should be started on either immunosuppressive therapy (AZA/6-MP, MTX) or anti-TNF therapy; colectomy also remains a viable option.

There is superior IFX response in persons who have already been on, or who are concurrently on AZA (Hanauer 2002, Su 2005) or MTX (Alfadhli 2005). This benefit is in terms of greater initial clinical efficacy, less secondary loss of response, and less overall toxicity including less development of antibodies to infliximab (ATI). Longer duration of remission with IFX plus AZA has been shown in children with CD (Cottone 2000). Giving a bolus of steroid plus histamine is useful to prevent the redevelopment of infusion reactions to infliximab (secondary prophylaxis), but has no role as primary prophylaxis (given as a routine to prevent the first infusion reaction) (Forbes 2008).

- **Comparison of therapies in CD and UC**

There are differences as well as some similarities in the therapy for induction and maintenance of remission of CD and UC (Table 25). SASP and 5-ASAs are much better for treatment of mild/mild-moderate UC than CD, and are also much better for maintenance of remission in UC than CD. Entocort® has no role for induction of remission in UC, or for maintenance of remission in either CD or UC. There is only limited data supporting TNFβs as rescue induction therapy for steroid failures in severe UC, or as maintenance therapy.



Table 27. Comparison of Therapies of CD and UC

	CD		UC	
	Induction	Maintenance	Induction	Maintenance
➤ Sulfasalazine (SASP)			+	+
➤ Mesalamine(5-ASA)	+	+/-	+	+
➤ Metronidazole / Cipro	+ (colitis)	+ post-resection	-	-
➤ Glucocorticosteroids (GCS) prednisone	+	no	+	
➤ Budesonide	ileocolonic	Up to 12 months	-	-
➤ Azathioprine (AZA), 6-MP	+	+	+	+
➤ Methotrexate (MTX)	+	Post-resection	-	-
➤ Cyclosporin (CgA)	-	-	+	-
➤ TNFB				
➤ Infliximab (IFX)	+	+	+	+
➤ Adalimumab (ADA)	+	+		
➤ Certolizumab	+	+		

Abbreviations: TNFB, TNF blockers, anti-TNF drugs

(Adapted from Schreiber 2007, Pearson 1995, Alfadhli 2005, Hanauer 2002, Sutherland 2003, Shibolet 2005, McDonald 2005).

➤ **Pregnancy**

The effect of IBD on pregnancy and of pregnancy on IBD will not be considered here. When CD becomes active during pregnancy, the disease is treated as if the CD patient were not pregnant, except that the use of methotrexate or thalidomide is prohibited (Table 27). A summary of useful background, pointers about IBD and pregnancy is made in Table 28. It is important to be aware of the interactions between IBD-treating medications and other drugs, and the effect of non-IBD treating drugs on the efficacy of medications used to treat IBD (Table 24). Colectomy and ileoanal anastomosis increases infertility 3-fold (Waljee 2006) and the incidence of abnormal PAP smears is increased in women with IBD (Kane 2008).



Table 28. FDA category for pregnancy, and recommendations for breast feeding of medications used in patients with IBD

Drug	FDA category	Recommendations for breast feeding
➤ Balsalazide	B	Yes
➤ Mesalamine	B	Yes
➤ Sulfasalazine	B	Yes
➤ Olsalazine	C	LHD
➤ Rifaximin	C	LHD
➤ Amoxicillin/clavulinic acid	B	Probably compatible
➤ Metronidazole	B	No
➤ Ciprofloxacin	C	LHD
➤ Corticosteroids	C	Yes
➤ Cyclosporin	C	No
➤ Tacrolimus	C	LHD
➤ Thalidomide	X	No
➤ AZA/6-MP	D	LHD
➤ Methotrexate	X	No
➤ Adalimumab	B	LHD
➤ Infliximab	B	LHD
➤ Loperamide	B	Yes
➤ Diphenoxylate	C	No

Abbreviation: LHD, limited human data

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Table 29. Summary pointers of IBD and pregnancy

- Colectomy and ileoanal anastomosis increases infertility 3-fold (Waljee 2006.)
- The incidence of abnormal PAP smears is increased in women with IBD (Kane 2008).

While earlier studies have suggested poor outcome of pregnancy in IBD patients with active disease (Miller 1986), this has not been confirmed more recently (Mahadevan 2007). In a community based study from northern California, the activity of IBD at conception usually carries through the pregnancy as well as post-partum period (Young 2009). Although the only contraindications to vaginal delivery in Crohn disease is active perianal disease, the likelihood of having a Caesarean section is increased 1.5 times above that of non-IBD women (Cornish



2007). Having an extensive episiotomy at delivery may contribute to the 18% risk of a woman developing perianal diseases after childbirth (Ilnyckyj 1999). Breastfeeding may or may not be a risk factor for the development of Crohn disease in the infant (Klememt 2004; Jantchou P, 2005). Flexible sigmoidoscopy during pregnancy does not increase the risk of premature labour (Cappell 1996). Only 29-44% of IBD patients breastfeed their infant (compared to an American standard of 60%), and 43% of those mothers who breastfeed their babies flared, possibly because 74% of those who flared had stopped maintenance medications (Kane 2005).

○ Management of Perianal CD

There are several methods used to classify fistulae. Likewise, there are several diagnostic tests that may be useful to diagnose the presence of fistulae in CD, and the anatomical position (Table 28) (Schwartz 2001).

Table 30. Different schemes for the classification of any type of gastrointestinal fistulae, based on anatomy, output volume, and etiology

Scheme	Classification
➤ Anatomical	➤ Internal, external – Low, high ➤ Simple, complex
➤ Relationship to dentate line: high (above) or low (below)	
➤ Relationship to the anal sphincters	○ Inter-sphincteric ○ Trans-sphincteric ○ Supra-sphincteric ○ Extra-sphincteric
➤ Simple	○ low, single external opening, no pain or fluctuation, no rectovaginal fistula (RV) or anorectal stricture
➤ Complex	○ high, multiple external openings, pain or fluctuation, RV fistula or anorectal stricture, active rectal inflammation.
➤ Output volume	➤ Pancreatic – Low (<200 ml/day) – High (≥200 ml/day) ➤ Intestinal – Low (<500 ml/day) – High (≥500 ml/day)
➤ Etiological	➤ Underlying disease



Printed with permission: Messmann H, et al. *Best Practice & Research Clinical Gastroenterology* 2004, page 811.

There are open-label studies but no randomized, controlled trials (RCTs) of the use of ciprofloxacin (cipro'), metronidazole, or cipro' plus metronidazole in perianal disease (Siemanowski and Regueiro 2008), and no studies of maintenance therapy. Antibiotics may be a useful "bridge" to the use of immunomodulators (Dejaco 2003). Studies where the secondary endpoint was fistula healing show benefit of AZA/6-MP (Pearson et al. 1995). There is limited evidence for a possible benefit of low-dose tacrolimus (0.05 mg/kg over 12 hours) (Gonzalez-Lama 2005).

The treatment of perianal CD has been revolutionized with the introduction of anti-TNF therapy (Siemanowski B and Regueiro M 2008). Anti-TNF is effective in closing (Present 1999) and maintaining closure (Sands 2004) of perianal fistula when therapy (IFX, 5mg/kg) every 8 weeks.

Table 31. Treatments for perianal CD

➤ Medical	➤ Surgical
○ Drugs used to treat Crohn disease ○ CO₂ laser ablation ○ Hyperbaric O₂ ○ Injection of silver microspheres with antibiotic	○ Seton surgical placement ○ Glue ○ Fistulotomy ○ Endorectal advancement flap ○ Fecal diversion ○ Proctocolectomy ○ Fistulectomy

Abbreviations: CD, Crohn disease; DRE, digital rectal examination; EUA, examination under general anaesthesia; EUS, endoscopic ultrasound; PF, perianal fistulae

* Patients who have a single fistula and no rectal inflammation on endoscopic examination will often respond to a fistulectomy.

In the Accent II study, those CD patients with perianal fistulas who were initial responders to IFX ($\geq 50\%$ reduction in draining fistulas), by week 54 of treatment, 36% of those on IFX and only 19% of those on placebo had a complete cessation of drainage of all their fistulas, even though most of the patients did not achieve complete closure of their fistulas over the course of one year (Baert 2003). This reflects the fact that fistulas may remain active long after they stop draining (Schwartz 2005). Complete healing may be assessed by EUS or MRI. In the CHARM study (Colombel 2007), again as a secondary outcome measure, at 56 weeks 33% of these treated with adalimumab (ADA) versus 13% of these given placebo had closure of their fistula. Patients may enjoy a better fistula closure rate and a more durable response to IFX if they have an examination under anaesthesia and seton placement prior to medical therapy (Regueiro 2003).



8. Surgery

Up to 80% of CD patients will require IBD-related surgery during the lifetime of their illness. There are the usual indicators for surgery in CD such as obstruction and proliferation, as well as failure of medical therapy, perianal sepsis, drainage of abscesses, as well as perianal, enterocutaneous, enterovaginal or enterovascular fistulas. A side-to-side rather than an end-to-end anastomosis results in fewer complications but no difference in recurrence rates (Smillis 2007).

In the first year after surgery, symptoms will develop in 20-30%, and for every year thereafter 10% will develop symptoms. Curiously, there is a disconnect between post-operative symptoms and recurrent inflammation: 70% of post-surgery CD patients develop endoscopic lesions in the first year after surgery, usually in the preanastomatic ileum, in bowel that was both macroscopically and microscopically normal prior to surgery, and yet only about a third of these persons with post-operative recurrent CD will have symptoms (Rutgeerts 1990, Rutgeerts 1991) (Table 32).

Table 32. Two Year Recurrence Rates after Surgery for CD

	PL	5-ASA	6-MP
➤ Clinical recurrence rate	77%	58%	50%
➤ Endoscopic recurrence rate	64%	63%	43%

Abbreviations: PL; placebo (Hanauer 2004)

For CD structures less than 5 cm in length, endoscopic dilation may give immediate success rates of 71%-100% (Van Assche 2008), with 0%-11% having a complication of proliferation or bleeding. The symptomatic recurrence is 13-100% after an initially successful balloon dilation. Repeat dilation is appropriate, "...but the length of the symptom-free interval will be the main parameter used to decide between surgery and re-do endoscopic balloon dilation" (Van Assche et al. 2008). Endoscopic stenting may reduce the recurrence rates after endoscopic balloon dilation (Matsushashi 2000), but the injection of steroids into the affected area may actually accelerate relapse (East 2007).



Table 33. Sub-acute small bowel obstruction in CD

Causes	Diagnostic procedures*	Management
➤ Active inflammatory CD	○ Plain abdominal films	– Treatment of inflammatory CD (avoid anti-TNF)
➤ Adhesions, bands	○ Conventional CT	
➤ Stricture	○ CT enterography	– Through-the-scope balloon dilation
➤ Fruit pits	○ Small bowel (gastrograffin) x-ray	– Adjuvant steroid injection into narrowing
➤ Gallstone ileus	○ Abdominal ultrasound	
➤ Enterolith	○ Doppler ultrasound	
➤ Endometriosis	○ MR enterography	– Expandable metal stents
	○ FDG-PGT (18F-fluorodeoxyglucose positron emission tomography [PET])	– Stricturoplasty
		– Open or laparoscopic surgical resection

Fibrostomatic disease has a more indolent course, whereas persons with abscesses or fistulas as the indication for the initial surgery tend to have the same type of aggressive disease when it recurs post-operatively. Sub-acute small bowel obstruction is common in CD, and when this occurs in the setting of previous surgery for CD, the physician must distinguish between surgery-associated bonds and adhesions, versus the development of active inflammatory CD, versus a CD-related stricture (Table 31). The usual diagnostic procedures may be considered. In addition to the usual management of the patient, the obstruction and the CD, there are a number of CD-associated therapies which may be considered.

*the use of capsule endoscopy is contraindicated because of the possibility of a stricture, which would potentially lead to the need for surgery to remove the capsule.

Abbreviations: CD, Crohn disease; PET, positron emission tomography; SBO, small bowel obstruction

9. Nutrition and CD

○ Nutritional Deficiencies

There is a high prevalence of nutritional deficiencies in IBD, especially in CD (Table 32) (Lochs 2009). The origins of malnutrition in CD are multifactorial (Table 36) but dietary restrictions (due to intolerance of diet or therapeutic fasting) are the most important.



Table 34. Frequency of Nutritional deficiencies in IBD

Nutritional deficiencies	CD (%)	UC (%)	Nutritional deficiencies	CD (%)	UC (%)
➤ Weight loss	65–75	18–62	➤ Potassium	6–20	+
➤ Hypoalbuminaemia	25–80	25–50	➤ Vitamin A	11	Not reported
➤ Intestinal protein loss	75	+	➤ Vitamin B ₁	+	Not reported
➤ Negative nitrogen balance	69	+	➤ Vitamin C	+	Not reported
➤ Anaemia	60–80	66	➤ Vitamin D	75	+
➤ Iron deficiency	39	81	➤ Vitamin K	+	Not reported
➤ Vitamin B ₁₂ deficiency	48	5	➤ Zinc	+	+
➤ Folic acid deficiency	54	36	➤ Cu	+	+
➤ Calcium	13	+	➤ Metabolic bone disease	+	+
➤ Magnesium	14–33	+			

Table 35. Causes of malnutrition in IBD

- Decrease in oral intake
 - Restrictive diets
 - Therapeutic fasting
 - The disease itself: diarrhea, abdominal pain, nausea and vomiting, etc
 - Alteration in taste: due to drugs, vitamin and mineral deficiencies, pro-inflammatory mediators
 - Anorexigenous effect of pro-inflammatory cytokines
- Gastrointestinal losses
 - Diarrhea
 - Rectorrhagia/hematochezia
 - Loss of mucus and electrolytes
 - Protein-losing enteropathy
- Metabolic disorders
 - Increase in resting energy expenditure
 - Enhanced fat oxidation



- Increase in nutritional requirements
- Inflammatory states
- Increased basal oxidative metabolism
- Infectious complications
- Post-surgery
- Drug interaction
 - Glucocorticosteroids and calcium reabsorption
 - Corticoids and protein catabolism
 - Salazopyrine and folate malabsorption
 - Methotrexate and folate deficiency
 - Cholestyramine and liposoluble vitamin malabsorption
 - Antimicrobials and vitamin K
 - Anti-secretors (PPI₀, H₂-RAs) and iron malabsorption
- Poor absorption of nutrients
 - Reduction of the absorptive surface: intestinal resection, enteric fistulas
 - hypertrophy of the villi with increased immature enterocytes
 - Blind loops, bacterial overgrowth
 - Poor absorption of bile salts with ileal inflammation or resection

(Lucendo 2009)

Abbreviations: PPIs, proton pump inhibitors; H₂-RAs, H₂ receptor antagonists

Also included are: the increase in energy requirements, the malabsorption of nutrients in the case of extensive intestinal involvement, gastrointestinal losses and the interaction between nutrients and drugs (Lucendo 2009). Furthermore, the underlying inflammatory mediators of the physiopathology of IBD (Cabr  2001), such as tumor necrosis factor (TNF)- α , and interleukins-1 and -6 can increase catabolism and lead to anorexia.

In quiescent, IBD energy and substrate metabolism is normal, or shows the typical changes of a shortage of energy intake with a decrease in carbohydrate and an increase in fat oxidation. During the active phase, patients develop a mixed picture of an inflammatory reaction and malnutrition, with slight increases in energy expenditure and a relative increase in fat and decrease in carbohydrate oxidation. These changes are non-specific and are quickly reversible when patients are given nutritional support.

Enteral nutrition may be of benefit as primary therapy in children with CD, even to the point of being steroid-sparing and improving the child's growth and development. It is unknown what is mechanism of the benefit of enteral nutrition in CD beyond the nutritional benefit itself (Table 34). It is also now known why enteral nutrition fails as primary therapy in adults with CD. The value and benefits deriving from the use are of enteral nutrition directly dependent on the geographical location of the disease, its



extent and severity and Enteral feeding is therefore especially indicated for CD patients when the small intestine is affected, while there is no evidence which supports the use of enteral nutrition in the treatment of UC except for the correction of nutrient deficiencies (Lucendo 2009). Intestinal rest is not beneficial to control IBD (Greenberg et al. 1988).

Apart from the intake of calories, proteins and micronutrients, enteral nutrition using liquid formulas has therapeutic function, especially in children with CD (Heuschkel 2004) (Table 34). This therapeutic effect is independent from the nitrogen source used (Goh 2003). The fat composition of the enteral diet seems to be important in terms of its therapeutic effect (Gonzalez-Huix et al. 1993), as this fat composition could be the key factor of the diet's therapeutic action on the disease (Gassull 2002). The n-3 PUFAs (polyunsaturated fatty acids) may be prove effective for maintaining CD in remission, although more extensive studies are required in order to unequivocally establish the utility of these therapies (Lucendo 2009).

Table 36. The possible mechanisms of the beneficial effect of enteral nutrition in CD

-
- Improvement of nutritional status
 - Down regulation of pro-inflammatory cytokines
 - Anti-inflammatory effects
 - Promote epithelial healing
 - Decrease gut permeability
 - Decrease antigenic load to the gut, bowel rest
 - Modification of gut flora
-

(Hartman 2009)

Probiotics are “live micro-organisms which, when consumed in adequate quantities, confer a health benefit on the host” (Shanahan 2004). Prebiotics are “non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one, or a limited number of bacteria in the colon, thus improving host health” (Bengmark 2005, Lim 2005). The rationale behind prebiotic use is to increase the endogenous numbers of beneficial bacterial strains including lactobacillus and bifidobacterium. Another viable option is to use both prebiotic and probiotic administration in conjunction, referred to as synbiotics (Bengmark 2005, Bengmark 2005). The rationale behind synbiotic treatment is that the combined probiotic and prebiotic would exert a beneficial effect greater than would be observed when administered individually.

Probiotics may function via the modulation of cell proliferation and apoptosis (Ichikawa 1999). Probiotics have the potential to be beneficial in the treatment of IBD due to their capacity to prevent the colonisation of pathogenic bacteria, reduce inflammatory cytokine expression, enhance epithelial cell proliferation, inhibit apoptosis



and provide metabolic energy for enterocytes (Geier et al. 2007) It may also be the case that our genetic profile may predispose our responsiveness to probiotic treatment, as is the case with chemotherapy (Kaneta 2002; Kihara 2001). Identification of these “probiotic responsiveness genes” may lead to screening to determine i) whether a patient will be responsive to probiotic therapy, and ii) to which probiotics they would respond more efficiently (Geier 2007).

There is no reliable reproducible evidence to support the use of probiotics in the induction or maintenance of remission of CD. The mode of action of probiotics is not completely understood. There have been a large number of probiotic species identified, most of which have differing mechanisms of action. Further complexity stems from the finding that the mode of action of a given probiotic can differ based on the presence of other probiotics or enteric bacteria in the surrounding environment, and also the disease setting in which the probiotic is used (Shanahan 2004).

10. Colon Cancer Surveillance

From the data in UC, it is assumed that the same principles for surveillance for colorectal cancer (CRC) apply in the person with left-sided Crohn’s colitis (CC) or CC plus PSC. For further details on this topic in UC, please see the chapter on UC. There is an increased risk of CRC in UC (Chambers 2005, Eaden 2001) (Table 37, Figure 5).

Table 37. Risk of CRC in UC over time

Duration of UC, years	Pancolitis, %	All patient risk, %
10	5	2
20	20	8
25	40	-
30		18

*Includes localized left-sided disease as well as pancolitis

The standardized incidence ratio (SIR) for CRC to develop in UC is above 3, and for Crohn’s colitis (when over one third of the colon is affected), SIR for CRC is 2 (Lashner 2008). In UC patients, the first “screening” colonoscopy should be done after 8-10 years of pancolitis, or after 15 years of left-sided colitis (Chambers 2005) (Table 34). If there is only proctitis, then no special screening is necessary beyond the guidelines for the “average risk” individual. If primary sclerosing cholangitis (PSC) is diagnosed in the patient with UC, screening colonoscopy should be done immediately at the time of PSC diagnosis, and then with annual surveillance colonoscopies thereafter (Itzkowitz 2005).

There are numerous guidelines for colorectal cancer screening in the person with pan UC (Table 37), and these principles are often applied to CC.



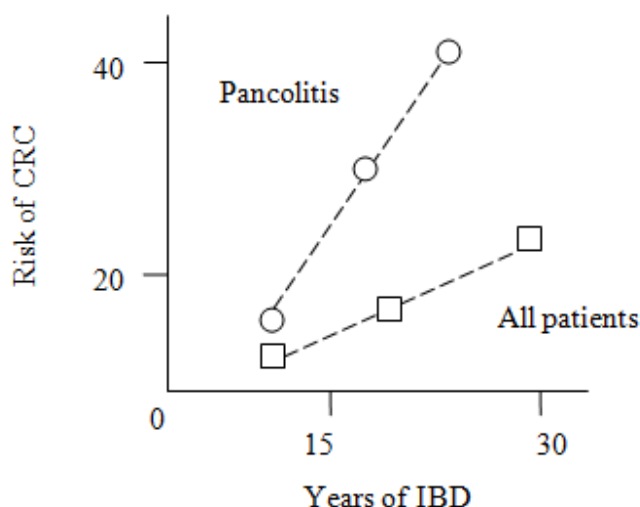


Figure 5. Risk of developing colorectal cancer (CRC) in persons with UC

Table 38. Guidelines for colonoscopic surveillance of UC patients for dysplasia/CRC

Years of UC	British Guidelines ¹	American Guidelines ²
10	q3yr	Colonoscopy every 1-2 years
19		
20	q2yr	Colonoscopy after every 1-3 years after 2 negative examinations, until the disease has been present for 20 years
29		
30		
40	q1yr	Colonoscopy every 1-2 years

(Cornell 2008); ¹ (Eaden 2002, Mpofu 2004); ²(Kornbluth 2004, Itzkowitz 2005)

A simplification of this approach would be to perform a colonoscopy every 1-2 years after the initial screening in all UC/CC patients. CRC surveillance in UC increases life expectancy by 1.2 years (Provenzale 1995), with cost-effectiveness similar to other accepted medical practices such as Pap smear testing (Provenzale 1998).

At the time of screening colonoscopy for CRC, the colonoscopist takes multiple untargeted random mucosal biopsies are taken from 4 quadrants every 10 cm of bowel, at intervals suggested by various guidelines. In the hands of expert pathologist, the risk of false-positive and false-negative diagnosis of dysplasia is 5% and 48%, respectively (Provenzale 2001).

A number of methods have been introduced to improve the diagnostic sensitivity and specificity of detecting dysplasia or colorectal cancer, including improved training of endoscopist and improved equipment, and as well as new laboratory procedures (Table 38). While such a surveillance program for UC and Crohn's colitis is the community standard of care in Canada, there is no evidence that it saves lives or is cost-effective. The likelihood of finding dysplastic lesions in UC and CC may be increased as compared with white light colonoscopy (WLC) by using targeted biopsies in conjunction with new endoscopic imaging



modalities (Kiesslich 2008). These include chromoendoscopy, narrow band imaging, optical coherence tomography, confocal laser endomicroscopy, and CT colography.

Table 39. Proposed methods to Improve Colonoscopic Surveillance for Dysplasia and Colorectal Cancer

➤ Improved Endoscopist	○ Heightened intensity and strictness of training, with certification of competence ○ Regular introduction and maintenance of quality control methods ○ Improved bowel preparation ○ Improved patient sedation identification of cecal landmarks ○ Slow withdrawal of scope
➤ Improved Equipment	○ Chromoendoscopy ○ Narrow band imaging (NBI) ○ Coherence tomography ○ Confocal laser endomicroscopy ○ CT colography
➤ Laboratory Testing	○ p53, β-catenin, p16

Chromoendoscopy (intravital staining, contrast endoscopy) permits assessment of the pit patterns (Jung 1999). Chromoendoscopy, as compared with conventional WLC and random biopsies, increases the diagnostic yield of intraepithelial neoplasia by 3- to 4.5-fold. Chromoendoscopy is included in USA guidelines for surveillance in patients with longstanding UC (Itzkowitz 2005).

Narrow band imaging (NBI) illuminates the tissue surface, and allows optimal visualization of the microvascular structure of the mucosal layer (Gono 2004). Both chromoendoscopy and NBI increase the sensitivity by 17% and the specificity by 31% of the differentiation of neoplastic from non-neoplastic lesions in UC.

Optical Coherence Tomography (OCT), based on optimal interferometry, provides real-time high-resolution images formed by detecting light that is reflected back from the mucosal subsurface tissue microstructure. The diagnostic sensitivity and specificity to detect transmural inflammation is 70% and 83%, respectively (Shen 2004). Clearly, WLC is inferior to chromoendoscopy, NBI and OCT for the detection of early neoplasia.

In confocal laser endomicroscopy, a confocal laser microscope is incorporated into the distal top of a conventional video endoscopy (WLC), allowing subsurface analysis of the intestinal mucosa and *in vivo* histology. A fluorescent contrast agent is applied. High contrast images are obtained from the confocal endomicroscope, as well as simultaneously obtaining standard endoscopic standard images. Surface and subsurface analysis is obtained, with an accuracy of 99% (sensitivity, 97%; specificity, 99%) to detect the presence of neoplastic changes (Kiesslich 2007).

CTC (CT colonoscopy) is now approved in the USA for use in CRC screening in non-IBD patients. Strictures, pseudopolyps and fistulae can be seen in IBD



(Carrascosa 2007, Andersen 2006). The use of CTC for CRC screening/surveillance in Crohn colitis or UC has not been validated.

The drawback to WLC is that the dysplastic lesions which may develop in UC may be flat and not detectable, or elevated yet small and thus not readily detectable. These Endoscopically detectable and elevated lesions have been called DALMs (dysplasia-associated lesion or mass) (Blackstone 1981). On the basis of the gross appearance of these lesions, DALMs are further classified as adenoma-like or non-adenoma-like (Odze 1999).

Similar to sporadic adenoma, the adenoma-like DALMs which occur in UC are “well-circumscribed, smooth or papillary, non-necrotic, sessile or pedunculated polyps, that are usually easily removed by routine endoscopic methods...” (Odze 2008). The non-adenoma-like lesions include “velvety patches, plaques, irregular bumps, and nodules, wart-like thickenings, structuring lesions, and broad-based masses...not typically amenable to be removed by colonoscopy”.

The adenoma-like DALMs have a low probability of associated malignancy (Rutter 2004), and so can be managed by endoscopic polypectomy plus continued colonoscopic surveillance. In marked contrast, the non-adenoma-like DALMs have a 36-85% risk of either synchronous or metachronous cancer (Odze 1999, Bernstein 1994).

If the adenoma-like DALMs occur proximal to the area of colitis (at least with the example of UC), they are managed as if they were unrelated to the UC, ie as if they were sporadic adenomas, with endoscopic removal followed by regular colonoscopic surveillance (Odze 2004). In marked contrast, the adenoma-like DALMs which occur in an area of colitis (eg, UC-associated dysplastic lesion rather than a sporadic adenoma) must be considered as having a high malignant potential, and total colectomy is required (Friedman 2003).

About half of these UC patients who have had a sporadic adenoma removed by colonoscopy will have a recurrence of an adenoma, again requiring polypectomy and further follow-up (Friedman 2003, Odze 2004). The approach of polypectomy and colonoscopic follow-up is the standard of care, as long as the adenoma has been completely removed, the margins are free of dysplasia, and there is no flat dysplasia anywhere in the colon either close to or away from the polyp.

Immunohistochemical changes (such as p53, B-catenin, APC, p16) have too low a sensitivity and specificity to be used to help distinguish between the sporadic and the colitis-associated adenomas which occur in the patient with UC (Odze 2000).



11. Practical Steps in IBD Care

Preventing Common Errors in the care of Patients with IBD: Ask yourself a few questions

- Is the diagnosis of IBD correct?
- Are you prescribing the right 5-ASA preparation?
- Are you using GCS appropriate?
- Should an immunosuppressant be used?
- Why are you not using an immunosuppressant?
- Is there a good reason to use biological therapy?

What does the Primary Care Physician (PCP) Need to/Want to know about IBD?

- Typical patient presentation & profile
- Major differential
- PCP-based investigations
- First line therapy for new IBD
- Identify and treat a recurrence
- When to refer

About IBD?

- Number of patients 300/105
- Number of PCPs 1/103
- Every PCP will have 2 to 3 IBD patients
- Number of PCP/GI in Canada 35,000 vs 500

How does the Patient Walk into Your Office?

- Diarrhea, pain, malaise, pallor
- Alarm symptoms: blood, nocturnal symptoms, fever, weight loss
- Extraintestinal symptoms: mouth, joints, skin, liver, kidney
- Perianal disease



Have you considered Organic Causes of Chronic Diarrhea?

- Stomach – ZES, Rx, resection
- Hepatobiliary – Jaundice, pruritus (cholestasis)
- Pancreatic – alcohol, trauma, cystic fibrosis
- SB-LV, “F’s” foul, flush, fat, food, flatus
- LB-SV, tenesmus, incontinence

Abbreviations: SB, small bowel; LB, large bowel; SV, small volume; LV, large volume

Do I need a Second Opinion for the IBD/IBS-D Patient?

- Celiac disease – antitransglutaminase
- Bacterial overgrowth – H₂ breath test with lactulose
- Bie salt wastage – 72 hour stool collection
- Microscopic colitis – rectal biopsy

Abbreviations: IBS-D, diarrhea-predominant irritable bowel syndrome

If IBD is suspected. If you “imagine”, Then “Image”

- Ulcerative Colitis (UC) 100/10⁵
- Crohn’s Disease 200/10⁵
 - Ileum 40%
 - II + C 40%
 - Colon 20%
- Image
 - ACBE ± sigmoidoscopy/colonoscopy
 - Small bowel (FT, enteroclysis, CT, MRI)

Why distinguish between UC and CD?

- Acute-targeted 5-ASA; CY5; surgery
- Maintenance 5-ASA for UC, AZA for CD
- Steroid resistance AZA for UC/CD TNFβ
- Nutritional complications
- CRC surveillance (CD-C involvement)
- Type/time of surgery



First Line therapy for IBD

- Diagnosis
- Information
- Complications
 - Nutrition
 - Osteoporosis
 - Psychological
 - 5-ASAs

5-ASAs for IBD

- Mesalamine
 - Plus sulfa
 - Plus coating
- Release pattern
 - PO
 - TI
 - C
 - PR
- SB + C Pentasa
 - Salofalk
 - Asacol (400 mg)
 - Enemas (4 g), suppositories (500 mg)

Are you prescribing the right 5-ASA preparation?

- Mesalamine vs Salazopyrine – cost, AEs
- PO – dose, target site
- Local – enemas, suppositories $\pm$ PO

Are you Choosing the correct 5-ASA product?

- Adverse effect
 - SASP 30%
 - Mesalamine 1 to 5%
- Dosing
 - QID – TID – TID once a day!
- Route
- Cost
- Theoretical Differences



Use of Mesalamine in IBD

- Acute 4 g P.O., P.R.
 - Caution: slow onset, long duration
- Maintenance 2 g
 - UC
 - CD $\pm$ (limited use)
 - For life

What to do when Symptoms Come Back: Is this IBD, or Something Else?

- Infection
- Pregnancy
- Drugs
- Other conditions (stress)
- Non-adherence to maintenance Rx
- Change in smoking habits

Is this a recurrence of IBD?

- 3-day D/C 5-ASA
- Double dose 5-ASA
- Possible use of antibiotics
- Start prednisolone 40 mg (AEs) for 2 weeks, then taper
- Call your “GI, “GIM” or “GS”
 - If no response, or quick return symptoms with taper

Abbreviations: AE, adverse effects; D/C, discontinue; GI, gastroenterologist; GIM, general internal medicine specialist; GS, general surgeon

Is this a Severe Recurrence of Symptoms?

- > 6 BM/day
- Blood
- Pain, malaise
- Fever
- Extraintestinal symptoms: e.g. Arthralgias, Aphthous Ulcers, rash



Are you using GCS appropriately?

- Moderate severe disease
- Warn about side effects!
- Caution about short term use only
- Inform about escape from steroid-dependency and resistance
- Use locally acting Entocort® for SB/C-CD
- Dexa scan and bisphosphonates

Should An Immunosuppressant be used?

- CyA-UC
- In acute UC (not CD), a bridge to maintenance therapy
- Requires AZA
- Is the colon worth saving?
- Deaths

Immunosuppressants in Crohn's disease

- Why are you not using immunosuppressant?
- Steroid-resistant/-dependent
- Maintenance therapy

Is there a good reason to use experimental biological therapy?

- Failed standard medical therapy: 5-ASA→GCS→AZA/MTX
- Willing, informed patient
- Adequate medical insurance to provide for long term use

What will the referral MD likely do?

- Confirm the diagnosis
- R/O
 - Infections (stool cultures)
 - Obstructions (abdominal firm)
 - Abscess (ultrasound, MRI)
- Full dose 5-ASA, start on prednisolone
- Judicious decision re: "scoping"
- Consider anti-TNF therapy for failed AZA, MTX

Abbreviations: AZA, azathioprine; MTX, methotrexate



IS the diagnosis of IBD correct?

- Suspect, diagnosis from symptoms and signs (GI, non-GI)
- Compatible x-ray or endoscopic changes
- Compatible or diagnostic biopsy
- Indeterminate, UC, Crohn's
- For some, only time will tell

“Tips on staying on top®” of IBD

- Causes of chronic diarrhea
- Distinguish between
 - IBS & IBD
 - UC & CD
- Standard first line therapy
- What causes recurrence of symptoms

Is it important to distinguish between Crohn's and Ulcerative Colitis?

- Acute
 - UC-CyA
 - CD-TNF β
- Maintenance
 - UC-5-ASA
 - CD-AZA/MTX
 - Surgery

Is it important to distinguish between Crohn's disease and Ulcerative Colitis?

- Crohn's – mouth to anus
 - Malabsorption
 - RLQ Mass
 - Perianal disease
 - Fistulae
 - Skin lesions
- Ulcerative Colitis
 - Bleeding
 - Dilation



Do patients with IBD ever have IBS-like symptoms?

- IBS-like symptoms shouldn't be treated as IBD
 - Anti-diarrheal agents
 - Anti-cholinergic agents
 - Anti-biotics
 - Bile acid sequestrants
 - Analgesics
 - Exercise caution when/if using analgesics

**Any Last Minute Questions about Therapy in Crohn's disease:
Suggestions?**

- Less use of 5-ASA, antibiotics
- More use of Imuran, methotrexate
- Appropriate cautious use of TNF β s



Chapter 10: Scientific Basis of Colonic Disorders

G.K. Turnbull, M. Burnstein, J.A. Rowe and S.J. Vanner

1. Introduction

This chapter presents an overview of colonic physiology and the diseases that affect the colon. It discusses lower gastrointestinal bleeding, infectious diseases affecting the colon and diseases specifically involving the anus.

2. Function

The colon contributes to three important functions in the body: (1) concentration of fecal effluent through water and electrolyte absorption, (2) storage and controlled evacuation of fecal material and (3) digestion and absorption of undigested food. Although the colon is not essential for survival, its functions contribute significantly to the overall well-being of humans. The colon can be functionally divided through the transverse colon into two parts, the right and left colon. The right colon (cecum and ascending colon) plays a major role in water and electrolyte absorption and fermentation of undigested sugars, and the left colon (descending colon, sigmoid colon and rectum) is predominantly involved in storage and evacuation of stool.

3. Functional Anatomy

The human colon is a muscular organ measuring approximately 125 cm in length *in vivo*.

Figures 2 and 3 show images of a normal colon at colonoscopy. Its wall consists of the four basic layers found in other GI hollow visceral organs – the mucosa, submucosa, circular muscle and longitudinal muscle – but several important differences exist. The mucosa lacks the villous projections found in the small intestine and presents a relatively smooth surface, but numerous crypts extend from its surface. Cell types lining the surface and the crypts resemble those in the small intestine but are composed of significantly greater numbers of goblet cells. These cells secrete mucus into the lumen, and mucus strands can often be identified in association with stool. This observation is misconstrued by some patients as a response to underlying colonic pathology. The haustral folds, which help define the colon on barium x-ray, are not a static anatomical feature of the colon but rather result from circular muscle contractions that remain constant for several hours at a time. The outer or longitudinal muscle is organized in three bands, called taeniae coli, which run from the cecum to the rectum where they fuse together to form a uniform outer muscular layer. These muscular bands and elongated serosal fat saccules, called appendices epiploicae, aid in the identification of the colon in the peritoneal cavity.

The colon is innervated by the complex interaction of intrinsic (enteric nervous system) and extrinsic (autonomic nervous system) nerves. The cell bodies of neurons in the enteric nervous system are organized into ganglia with interconnecting fiber tracts, which form the submucosal and myenteric plexi. These nerves are organized into local neural reflex circuits, which modulate motility (myenteric), secretion, blood flow and probably immune function (submucosal). Serotonin (5-HT), released from enterochromaffin cells into the surrounding lamina propria, is an important signaling pathway to these nerves in response to chemical and mechanical stimuli.

Release of excitatory neurotransmitters such as acetylcholine, substance P and serotonin (5-HT) serves to activate local circuits such as those innervating muscle contractions. Their receptor subtypes provide pharmacological targets for the



development of drugs designed to alter colonic functions such as motility. The major inhibitory neurotransmitter is nitric oxide. The importance of the enteric nervous system is exemplified by Hirschsprung's disease, where there is a congenital absence of nitric oxide – containing inhibitory neurons over variable lengths of the rectum and colon. This results in an inability of the colon to relax in the affected region. Infants typically present with bowel obstruction or severe constipation. Barium x-rays identify the affected region as a constricted segment because the excitatory effects of the neurotransmitter acetylcholine are unopposed as a result of the absence of inhibitory neurotransmitter.

The autonomic nervous system comprises sensory nerves, whose cell bodies are found in the dorsal root ganglia, and motor nerves, the sympathetic and parasympathetic nerves. Parasympathetic nerves innervating the right colon travel in the vagus nerve, and those innervating the left colon originate from the pelvic sacral nerves. Parasympathetic nerves are predominantly excitatory, and sympathetic nerves are inhibitory. Autonomic nerves modulate the enteric neural circuits within the colon and participate in neural reflexes at the level of the autonomic ganglia, spinal cord and brain. Brain–gut connections are important both for perception of visceral stimuli (sensory) and in modifying colonic function (motor) in response to central stimuli. An example of a central stimulus that can evoke significant changes in colonic activity through this connection is acute stress. This stimulus provokes release of central hormones, such as corticotropin releasing factor. These hormones activate parasympathetic pathways that stimulate motility patterns in the colon, and can result in diarrhea.

4. Absorption and Secretion

The colon is highly efficient at absorbing water. Under normal physiological conditions, approximately 1.5 L of fluid enters the colon each day, but only about 100–200 mL is excreted in the stool. The maximal absorptive capacity of the colon is up to about 4.5 L per day, so that diarrhea (increased water in stools) will not occur unless the ileocecal flow rate exceeds the absorptive capacity and/or the colonic mucosa itself is secreting fluid. The fundamental feature of colonic electrolyte transport that enables this efficient water absorption is the ability of the colonic mucosa to generate a large osmotic gradient between the lumen and the intercellular space.

This osmotic gradient is created by electrogenic sodium transport. This depends upon the energy-dependent Na^+/K^+ -ATPase pump on the basolateral membrane, which pumps sodium from inside the cell against a large concentration gradient into the intercellular space (see Figure 6 in Chapter 6, “The Small Intestine”). Luminal sodium in turn enters the apical membrane of the cell through sodium channels, flowing down the concentration gradient created by the Na^+/K^+ -ATPase pump. In contrast to the small intestine, where sodium in the intercellular space can diffuse back into the lumen and become iso-osmotic, hypertonic solutions are maintained in the intercellular space of the colon because the tight junctions are much less permeable to sodium diffusion. The net result is that the hypertonic fluid within the intercellular space draws water passively into the mucosa from the colonic lumen. In the colon there is also a highly efficient absorption of sodium (Na^+): of the 150 mEq of Na^+ that enters the colon each day, less than 5 mEq is lost in the stool. In contrast to Na^+ , the tight junctions of the colon are highly permeable to potassium (K^+), allowing K^+ to move from the plasma to the lumen.



K⁺ pumped into the colonocyte by the Na⁺/K⁺-ATPase pump can also be secreted into the lumen. K⁺ is normally secreted into the lumen unless intraluminal potassium rises above 15 mEq/L. This handling of potassium may account for hypokalemia seen with colonic diarrhea and may play a role in maintaining potassium balance in the late stages of renal failure.

Other transport mechanisms, similar to those found in the small intestine (see Chapter 6, Section 5), are also found on colonocytes, which maintain electrical neutrality, intracellular pH and the secretion of salt and water. Nutrient cotransporters, however, are not found in the colon.

The regulation of water and electrolyte transport in the colon also involves the complex interplay between humoral, paracrine and neural regulatory pathways (see Chapter 6). One important difference is the effect of the hormone aldosterone, which is absent in the small intestine. Aldosterone is secreted in response to total body Na⁺ depletion or K⁺ loading, and in the colon, aldosterone stimulates sodium absorption and potassium secretion.

5. Motility of the Colon

Much less is known about the motility of the colon as compared to other regions of the GI tract. The movement of fecal material from cecum to rectum is a slow process, occurring normally over 3-4 days. Functionally, the contraction patterns in the cecum and ascending colon cause mixing, which facilitates the absorption of water, whereas in the sigmoid colon and rectum the contraction slow the movement of formed stool, forming a reservoir until reflexes activate contractions to advance and evacuate stool.

Several contractile patterns exist within the circular and longitudinal muscle of the colon. Ring contractions are due to circular muscle contraction, and these are either tonic or rhythmic. Tonic contractions are sustained over hours, form the haustral markings evident on barium x-rays and play a role in mixing. Rhythmic ring contractions are either intermittent or regular. Regular contractions are nonocclusive, occur over a few seconds, and migrate cephalad (right colon) and caudad (left colon). Presumably, they too play a role in mixing. Intermittent ring contractions occur every few hours, occlude the lumen, and migrate caudad. They result in the mass movement of stool, particularly in the sigmoid colon and rectum.

Contractions of the longitudinal muscle produce bulging of the colonic wall between the taeniae coli, but the physiological importance of this action remains poorly understood. The origin of the contractions of the longitudinal muscle is not completely understood, but it depends upon the slow wave frequency of smooth muscle.

Action potentials occur on the peaks of these membrane oscillations and hence they control the frequency of contractions. These slow waves originate in the interstitial cells of Cajal (ICCs), which serve as the pacemakers. This network of ICCs is interposed between the enteric nerves and the smooth muscle cells. Contractions are also modulated by paracrine, humoral and other neural pathways. The nature of the contractile patterns within the colon depends upon the fed state. This is best exemplified during eating when the “gastrocolic reflex” is activated. Food in the duodenum, particularly fatty foods, evokes reflex intermittent rhythmic contractions within the colon, and corresponding mass movement of stool. This action, which is mediated by



neural and humoral mechanisms, accounts for the observation by many individuals that eating stimulates the urge to defecate.

6. Digestion and Absorption of Undigested Food Products

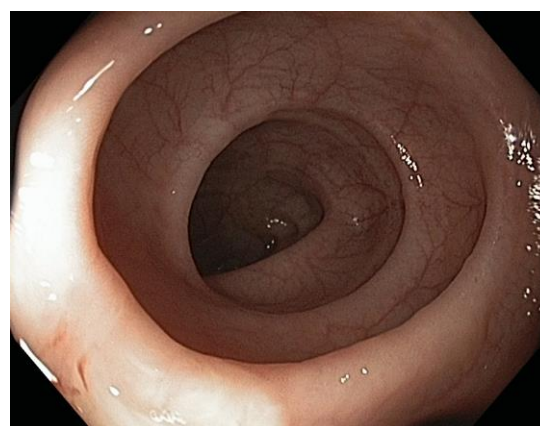
Greater numbers of bacteria (more anaerobes than aerobes) are found within the colonic lumen (10^{12-14}) than elsewhere in the GI tract. These bacteria digest a number of undigested food products normally found in the effluent delivered to the colon, such as the complex sugars contained in dietary fiber.

Complex sugars are fermented by the colonic bacteria, forming the short-chain fatty acids (SCFAs) butyrate, propionate and acetate. These SCFAs are essential nutrient sources for the colonic epithelium, and in addition SCFAs provide up to 500 cal/day of overall nutritional needs. They are passively and actively transported into the colonocytes where they become an important energy source for the cell through the β -oxidation pathway. The importance of this role of SCFAs is illustrated by the effects of a “dysfunctioning” colostomy, which diverts the fecal stream from the distal colon. Examination of this area devoid of luminal content typically reveals signs of inflammation, termed *diversion colitis*. This inflammation can be successfully treated with the installation of mixtures of SCFAs into the rectum, thereby providing the necessary energy source for the colonocytes.

Fermentation of sugars by colonic bacteria is also an important source of colonic gases such as hydrogen, methane and carbon dioxide. These gases, particularly methane, largely account for the tendency of some stools to float in the toilet. Nitrogen gas, which diffuses into the colon from the plasma, is the predominant gas. However, the ingestion of large quantities of undigested complex sugars such as found in beans or the maldigestion of simple sugars such as lactose can result in large increases in production of colonic gas. This can lead to patients' complaints of abdominal bloating and increase flatus.



1A



1B

Figure 1. Normal colon appearance at endoscopy.

Figure 1A. View of the normal submucosal vessels visible through the healthy transparent mucosa overlying the vessels.

Figure 1B. Normal transverse colon with a triangular appearance to the normal colon fold pattern



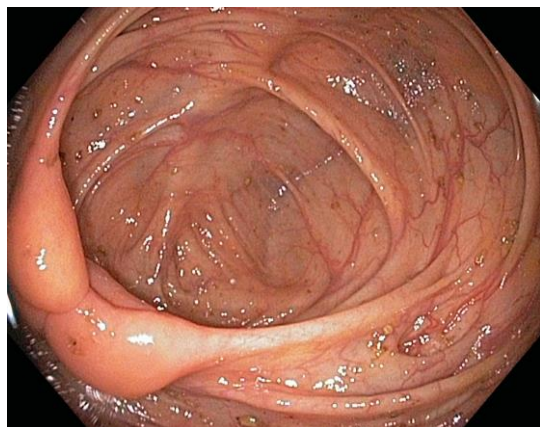


Figure 2. Normal ileocecal valve seen in the bottom left of the image, looking down at the cecal pole.

Bile salts are normally absorbed in the ileum, and long-chain fatty acids (LCFAs) in the upper small intestine. When bile salts or long-chain fatty acids are malabsorbed in sufficient quantities, their digestion by colonic bacteria generates potent secretagogues.

Bile salt malabsorption typically occurs following resection of less than 100cm of the terminal ileum, usually for management of Crohn disease. The excess bile salts pass into the colon where they stimulate cAMP and cause a secretory “choleraic” diarrhea. When the resection involves segments greater than 100 cm of ileum, the liver cannot sufficiently increase the synthesis of bile acids from cholesterol. A deficiency of bile acids enters the duodenum and if the concentration of bile acids is below the critical micellar concentration, bile salt micelles do not form, lipids are malabsorbed, and “fatty” Diarrhea (known as steatorrhea) develops.

The mechanisms by which multiple metabolites of bile salts and hydroxylated metabolites of long-chain fatty acids act as secretagogues provide an example of how multiple regulatory systems can interact to control colonic function. These mechanisms include disruption of mucosal permeability, stimulation of chloride and water secretion by activating enteric secretomotor neurons, enhancement of the paracrine actions of prostaglandins by increasing production, and direct effects on the enterocyte that increase intracellular calcium.

Non-pathogenic bacteria also signal to mucosal cells and can evoke cytokine signaling from colonocytes to effector cells (e.g. immune cells, nerves) within the colonic wall. Some species of bacteria stimulate pro-inflammatory responses whereas others are anti-inflammatory. These signaling pathways are enhanced when the tight junctions between epithelial cells are altered. These tight junctions are formed by proteins (e.g., occludens) and can be disrupted by a growing list of processes, e.g., inflammation such as Crohn disease and also noninflammatory states such as acute stress. This increased leakiness or permeability of the colon allows bacteria greater access to the epithelium and immune cells in the lamina propria. This bacterial-epithelial signaling underlies the rationale for the use of probiotics where “healthy” or anti-inflammatory bacteria are ingested (e.g., lactobacillus, bifobacteria) and alter the dynamic between the competing species of bacteria.



7. Imaging of the Colon / J.A.Rowe

A variety of modalities can be used to image the colon, depending on the person's clinical presentation. Traditionally, patients presenting acutely with abdominal pain would have conventional radiographs (views of the abdomen) before any further cross sectional imaging was performed. It is now quite common for patients to undergo either abdominal CT or ultrasound as their initial investigation. For patients requiring outpatient imaging for evaluation of abdominal pain, rectal bleeding, anemia or change in bowel habits, investigations may include barium imaging, ultrasound, endoscopic ultrasound (EUS), abdominal CT, or MRI. Specialized applications of ultrasound and MRI are used in preoperative staging of rectal cancer and in the imaging evaluation of fecal incontinence.

7.1. Conventional Radiography/Plain Films

Conventional radiography, or the abdominal series, includes a supine, erect or decubitus view and an image that includes the lung bases. This allows evaluation of the intestinal gas pattern and the presence of free air. A single supine view of the abdomen or 'flat plate' is used to evaluate for the presence of excessive amounts of stool. Patients with abdominal pain will often require imaging beyond the plain film. While a radiograph can be useful in the evaluation of the potential presence and level of obstruction, adynamic ileus, or pneumatosis intestinalis. Widespread use of CT and ultrasound has significantly decreased the demand for conventional radiography, particularly in the acute setting.

Figure 3. Plain x-rays of the abdomen showing normal supine and erect views of the abdomen.

Figures 3A. and 3B. are supine films and



3A



3B





Figure 3. Plain x-rays of the abdomen showing normal supine and erect views of the abdomen.

Figures 3A. and 3B. are supine films and

Figure 3C. Erect film of the abdomen.

7.2. Barium Imaging

Imaging of the colon has been traditionally achieved by performing a barium enema. Early in the 20th century, the single contrast technique was developed. An adequately cleansed colon is an important part of the examination. A bowel preparation will include a low residue diet for 1-2 days prior to the examination and a cathartic preparation. A tube is placed in the rectum and the colon is distended with a large volume of low density barium. Multiple spot images are obtained of the various colonic segments to visualize the entire colon free from overlapping loops. Later in the 20th century, the double contrast barium enema technique was developed. It involves the introduction of a small volume of high density barium through a small rectal tube, followed by insufflation of a large volume of room air, allowing good colonic distention and mucosal coating of the barium.

Some institutions routinely use pharmacologic agents such as glucagons, or the anticholinergic buscopan, to induce colonic hypotonia. However, a technically adequate study can usually be obtained without these agents. The goal of the double contrast barium enema is to evaluate each portion of the colon in air contrast and with the barium pool. Compression can be used to manage overlapping bowel loops. A series of spot images during fluoroscopic evaluation and subsequent standard series of abdominal radiographs performed by the technologist comprise a complete examination.

A single contrast enema may be adequate for the detection of larger colonic lesions, obstructing lesions, as well as the depiction of diverticular disease. A double contrast study is preferred for the assessment of mucosal abnormalities as well as the detection of small polypoid lesions. In particular, the findings of inflammatory bowel disease involving the colon are well depicted on a double contrast study. Figure 4 is a single contrast enema demonstrating multiple colonic diverticula (white arrow). Figure 5 is a single contrast study demonstrating a large cecal mass which proved to be an adenocarcinoma. Figure 6 is a double contrast barium enema showing multiple diverticula as well as a subcentimeter polyp (white arrow) which proved to be a tubular



adenoma. Figure 7 is a double contrast barium enema in a patient with ulcerative colitis depicting granular mucosa with some ulceration.

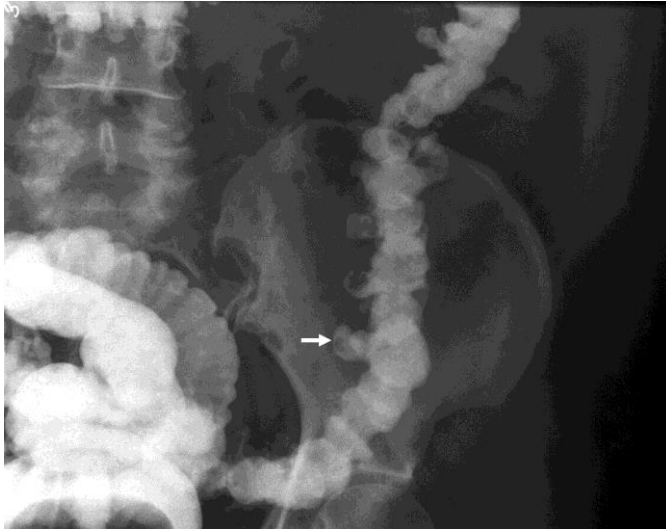


Figure 4. Single contrast enema demonstrating multiple colonic diverticula (white arrow).

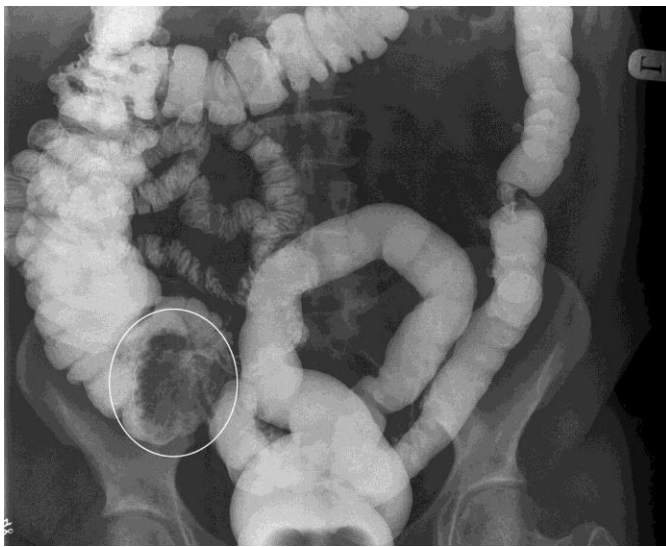


Figure 5. Single contrast study demonstrating a large cecal mass which proved to be an adenocarcinoma.





Figure 6. Double contrast barium enema showing multiple diverticula as well as a subcentimeter polyp (white arrow) which proved to be a tubular adenoma.



Figure 7. contrast barium enema in a patient with ulcerative colitis depicting granular mucosa with some ulceration from the distal transverse colon, beyond the splenic flexure and down the descending colon. The proximal transverse colon looks normal.

7.3. CT

Computerized tomography (CT) has become the primary imaging technique in patients who present with abdominal pain. This offers excellent evaluation of intramural and extracolonic pathology. The patient is given an overnight bowel preparation with positive oral contrast, to provide optimal evaluation of the colon, and is also given iodinated intravenous contrast at the time of CT scanning. In an urgent or emergent setting, the oral bowel preparation may be shortened or eliminated, positive contrast may be administered via the rectum. Unless there is a contraindication, intravenous contrast is recommended to evaluate the solid abdominal viscera, as well as to enhance the visualization of blood vessels and the bowel wall.

Common entities which are well characterized by CT include bowel obstruction, ischemia, ileus, malignancy, abscess, and diverticulitis. Figure 8 demonstrates sigmoid diverticulitis with a thick walled loop of sigmoid colon (white arrows) and extensive



pericolonic stranding. A moderate amount of free intraperitoneal fluid is also present. Figure 9 demonstrates diffuse concentric wall thickening of the splenic flexure in a patient with ischemic colitis. Figure 10 shows markedly irregular bowel wall thickening identified by the black arrows involving the cecum, ileocecal valve, as well as the terminal ileum, in keeping with a primary adenocarcinoma.

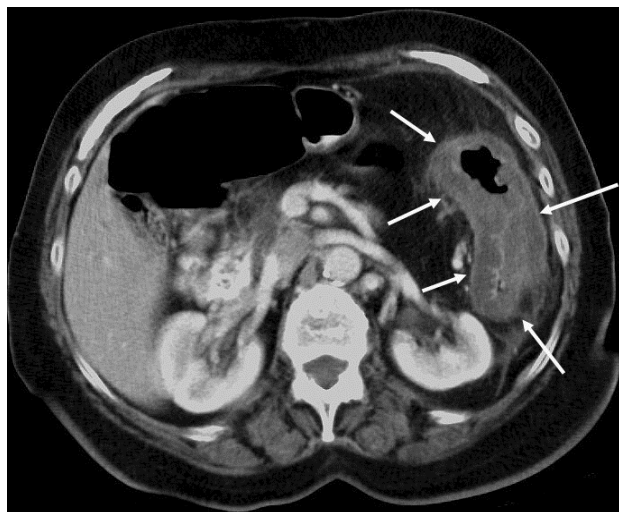


Figure 8. CT scan that demonstrates diffuse concentric wall thickening of the splenic flexure (white arrows) in this patient with ischemic colitis.



Figure 9. CT scan demonstrating diffuse concentric wall thickening of the splenic flexure (white arrows) in a patient with ischemic colitis.

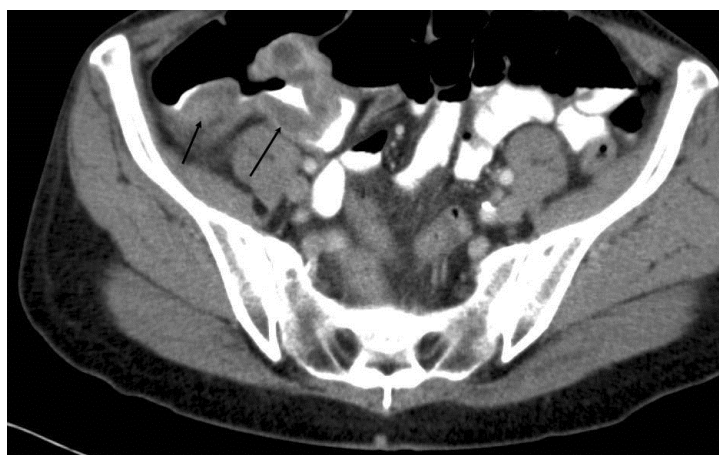


Figure 10. Shows markedly irregular bowel wall thickening identified by the black arrows involving the cecum, ileocecal valve, as well as the terminal ileum, in keeping with a primary adenocarcinoma.



7.4. CT Colonography

The barium enema has been a mainstay of colonic evaluation and can allow a diagnosis of neoplastic and inflammatory disease. The development of new technologies has highlighted the limitations of barium studies. While a barium study can evaluate the mucosa, it is unable to evaluate the lumen, bowel wall, and the extracolonic structures.

CT colonography (CTC), or “virtual colonoscopy,” is a minimally invasive method of imaging the colon. CTC uses a thin section CT of the insufflated colon. The patient undergoes a standard bowel preparation. A catheter is placed in the rectum. Room air or carbon dioxide is insufflated to achieve optimal colonic distention. In the absence of contraindications, intravenous buscopan is injected to achieve optimal colonic distention. Imaging is performed in both the supine and prone positions. Post processing software allows evaluation of the axial 2D images and 3D reconstructions, or endoluminal flythrough.

While conventional “optical” colonoscopy with biopsy is the gold standard for the detection of colorectal masses, the CTC is less invasive, requires no sedation and has minimal recovery time. CTC offers the added benefit of evaluation of potentially significant extracolonic abnormalities. Advantages over barium enema include an increase in sensitivity and specificity for detection of significant polyps as well as cancer. The radiation dose is however higher than a standard barium enema. For patients who have undergone failed optical colonoscopy, a CTC can be performed on the same day to eliminate the need for a repeat bowel preparation. CTC can also evaluate the proximal colon in patients with a known obstructing cancer. Evaluation of lymph nodes, local invasion and evaluation for distant metastatic disease can also be performed with this exam. CTC can be safely used in the evaluation of elderly patients or other groups of persons who may be at increased risk for conventional colonoscopy. Anticoagulated patients, those with a past history of incomplete colonoscopy, or those who cannot undergo conscious sedation can be evaluated with CTC.

With the current body of research, it is widely accepted that CTC has been clinically validated and ready for use as an investigation and screening technique in patients of average and increased risk of CRC. Continuing developments in 3D visualization software and computer assisted detection algorithms improve the utility of this technique. CTC has been proven to have greater than 90% sensitivity for the detection of polyps > 10 mm, and close to 100% sensitivity for detecting CRC. CTC is quite well tolerated in comparison to barium enema or colonoscopy.

Developing techniques for screening for colonic polyps/CRC include fecal tagging, which may eliminate the need for a cathartic preparation (often the most difficult part of any technique which evaluates the colon). With fecal tagging, the patient ingests small amounts of barium or iodine with the bowel preparation. Any residual stool or fluid will be of higher density which will allow them to be distinguished from polyps or other soft tissue density filling defects. Figure 11A (axial source image) and figure 11B (endoluminal reconstruction) in a patient with incomplete colonoscopy demonstrates a large polypoid mass (black arrows) subsequently proven to be adenocarcinoma. The white arrows denote the ileocecal valve.



In many institutions, CTC has replaced barium enema as the first line modality in the investigation of lower GI tract symptoms. CTC has proven to be an accurate and reliable diagnostic and screening tool. Its use is limited only by its availability.



Figure 11 A. Axial source image

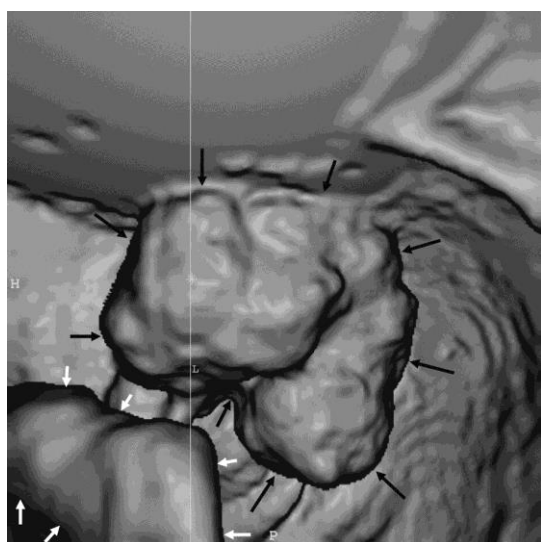


Figure 11 B. Endoluminal reconstruction These figures are from a patient with an incomplete colonoscopy demonstrated a large polypoid mass (black arrows) subsequently proven to be an adenocarcinoma. The white arrows denote the ileocecal valve.



7.5. MR Colonography

Still a developing technique, MR colonography (MRC) offers the potential for noninvasive evaluation of the colon, with the advantage of no ionizing radiation. As with CTC, the patient undergoes a standard bowel preparation. The patient is imaged in the prone position following colonic distension with 2500 ml of warm tap water introduced per rectum. Buscopan may be used to optimize colonic distention. Imaging is obtained pre- and post- gadolinium contrast enhancement, usually in the coronal plane. Imaging can be performed in a single breath hold. The data is evaluated on a workstation with both the source images and virtual endoscopic rendering of the lumen, allowing endoluminal flythrough. A combination of T1 and T2 weighted imaging provide bright and dark lumen colonography possible with one protocol. In addition to the evaluation of polyps and masses, MRC shows promise for the assessment of colonic involvement in inflammatory bowel disease. Further work needs to be done to fully validate this technique however the results are promising.

7.6. Imaging of Fecal Incontinence

Fecal incontinence affects up to 10% of the adult female population, largely due to prior obstetrical trauma. Surgical options exist in the correction of this important problem, and preoperative imaging is often required to characterize the abnormality. Endoanal ultrasound using a high frequency (10 MHz) endorectal probe is used to evaluate the anal sphincter complex. Ultrasound can identify the subepithelial tissue, the internal sphincter, the intersphincteric space, the longitudinal muscle as well as the external sphincter. This technique can confirm the presence or absence of sphincter defects. Ultrasound is also quite useful in the follow-up of the post surgical correction of fecal incontinence.

MRI is comparable to endoanal ultrasound in delineating sphincter anatomy, as well as any defects, which may contribute to fecal incontinence. Multiplanar T2 weighted images provide relevant anatomic information. Optimally, an endoluminal coil is ideal for demonstrating subtle changes in the sphincters, and provides the required spatial resolution. MRI is reasonably well tolerated, but takes longer than ultrasound to perform.

8. Fecal Incontinence

Understanding fecal incontinence requires knowledge of the normal function of the anorectum. Anatomically, the anorectum consists of the internal anal sphincter (IAS), the external anal sphincter (EAS), and the puborectalis muscles (PR). The IAS consists of smooth muscle and is a continuation of the circular smooth muscle of the rectum. The EAS is made up of skeletal muscle and surrounds the IAS, whereas the PR is a large U-shaped skeletal muscle that wraps around the upper anal canal at the anorectal junction above the EAS, and loops anteriorly to attach to the pubic bone. This creates an anatomical sling of muscle that pulls the anorectal junction forward when it tightens, thus closing the upper anal canal and creating the anorectal angle that is vital to the maintenance of fecal continence.

When stool (or gas or liquid) enters the rectum or sigmoid colon, the bowel dilates, and a normal rectoanal inhibitory reflex (RAIR) or rectosphincteric reflex is



initiated – that is, the IAS relaxes and, if the voluntary anal sphincter muscles also relax, the rectum empties through the anal canal (Figure 9). Fecal continence is maintained by anal contraction under voluntary control of the striated-muscle sphincters, the EAS and PR until the rectal pressure rise decreases and the resting tone of the IAS is restored. Thus, the “voluntary” sphincters (i.e., the EAS and PR) have the ability to be maximally contracted for approximately one minute, beyond which fecal continence is lost as a result of fatigue in the muscle if the tone of the IAS has not recovered.

Some patients with fecal incontinence will describe their problem as “diarrhea,” rather than loss of control of bowel function. All patients with a complaint of diarrhea should be asked if they have lost control of stool (ie. If they have fecal incontinence, or “accidents”), as this may indicate where the problem actually lies. Once fecal incontinence has been noted, it is then necessary to identify the frequency of the incontinence, whether both liquid and solid stool have been leaked, and whether the individual has an urge to defecate before the leakage occurs. A history of previous anorectal trauma (surgical, obstetrical, or otherwise) is important to note, as is the strength of voluntary anal canal tone on digital rectal exam (DRE).

Table 5. Drug therapy in irritable bowel syndrome

Symptom Drug Dosage

- Abdominal pain
 - Anticholinergics
 - Hyoscyamine 0.125 mg sl p4h prn (only available in US)
 - Dicyclomine 10–20 mg po tid – qid before meals
 - Calcium antagonists
 - Pinaverium bromide 50–100 mg po tid before meals
 - Antidepressants
 - Nortriptyline 10–25 mg po hs (increase by 10–25 mg increments every 5 to 7 days as tolerated)
 - Enteric opioids
 - Trimebutine 100–200 mg po tid before meals
 - Fedotozine NOT available in Canada
- Constipation
 - High fiber diet $\geq$ 30 g daily plus 2 L liquid daily
 - Osmotic laxatives
 - Milk of magnesia 15–30 mL po bid – tid
 - PEG 3350 powder 17 grams in 250 ml of liquid daily
 - Prokinetic agent
 - Tegaserod 6 mg po bid (NOT available in Canada)
 - Other agents
 - Misoprostol 200 µg po bid – qid before meals to stimulate diarrhea
- Diarrhea
 - Binding agent (resin)
 - Cholestyramine 4 g po once to four times daily



-
- Antimotility agents
 - Loperamide 2–4 mg po prn (maximum dose 16 mg/day)
 - Diphenoxylate 2.5 mg po qid prn
 - Alosetron 1 mg po bid (only available in US by special access)
 - Abdominal bloating, “gas” Simethicone up to qid prn
 - Motility agents
 - Domperidone 10–20 mg po qid
 - Tegaserod 6 mg po bid (NOT available in Canada)
 - Probiotics
 - VSL#3 1 cap po bid
 - Bio-K⁺ 1 cap po bid
-

Most patients presenting with fecal incontinence have “idiopathic” fecal Incontinence. Fecal incontinence may occur as the result of childbirth, surgical trauma, or other causes. With childbirth, many women suffer occult sphincter injury to the anal sphincters, both the internal anal sphincter and the external anal sphincters, and child birth may also cause damage to the pudendal nerves. The injury is often not recognized at the time of childbirth, so the sphincter weakness and fecal incontinence only becomes symptomatic years later, presumably with atrophy of the muscles with aging. Similar injury occurs with the urinary sphincters, and many women with “idiopathic incontinence” resulting from childbirth injuries present years later with both urinary and fecal incontinence. Sphincter injury at childbirth is more likely to occur with the first baby, if the baby is more than 4,600 g (10 lbs), if the second stage of labour is prolonged, if there are forceps or vacuum extraction used to assist the delivery. If an episiotomy is done to prevent tearing into the sphincters, or if there was a posterior occiput presentation of the baby’s head at delivery, there is an increased risk of anal sphincter injury.

Surgical trauma is the next most common cause of fecal incontinence. Surgery (ie. a vaginal hysterectomy) can put excess stretch on the pelvic floor nerves and muscles, causing injury that may lead to weakness of the anal sphincters. Another common source of fecal incontinence is disruption of the internal anal sphincter, either during a lateral internal sphincterotomy to treat an anal fissure or, more commonly, with the older “Lord’s” procedure of forceful three- or four-finger dilation of the anal sphincter under anesthetic, where the extent of damage to the sphincters is not predictable. The finding of perineal descent can be noted on examination of the perineum when the patient is asked to strain. This perineal dissent is associated with weakness of the pelvic floor muscles, as well as disruption of the normal anatomy. This gives rise to a mechanical disadvantage affecting the sphincter mechanism. Perineal descent may be associated with a rectocele or, in female patients, with a uterine prolapse. Rectal prolapse can also accompany weakness of the pelvic floor muscles and give rise to fecal incontinence.



LEARNING POINTS:

- Unless a careful history is taken, fecal incontinence (FI) may be confused with diarrhea
- DRE (digital rectal examination) gives important information on possible causes of FI
- Therapy is directed by diagnosis: if the use of bulking and anti-diarrheal agents is unsuccessful, or if there are not correctable anatomical abnormalities, then sufferers of FI may benefit from referral for further investigation and management with, for example, biofeedback training.

Therapy of fecal incontinence has improved over the past decade, primarily because of the introduction of biofeedback training. This technique allows the patient to practice tightening of the striated-muscle portion of the anal sphincter, usually with a surface electromyography (EMG) plug electrode held in the anal canal with audio and visual feedback that the patient can see and hear to encourage maximal contraction of these muscles. Increasing dietary fiber to help reduce the amount of liquid stool may help some patients, but if this increases stool frequency, the patient be better on a low fiber diet to help constipate the stool and reduce the chance of stool incontinence. Loperamide has been shown to increase the resting tone of the anal sphincters (especially the resting tone of the internal anal sphincter) and is a useful adjunct, especially if the stool frequency is increased. Cholestyramine may be useful when the patient has diarrhea or loose stool(s) since cholestyramine can make stool more solid (constipating effect).

Surgery is of greatest benefit in those patients who appear to have a mechanical problem, such as rectal prolapse or disruption of the anal sphincter. Surgery to correct perineal descent is often less helpful, since the muscle weakness that gives rise to the descent is not satisfactorily reversed by any of the surgical procedures currently used, and attempts to “suspend” the pelvic floor muscles cannot strengthen these muscles. Patients should refrain from excess straining if they have significant perineal descent, because this will serve only to worsen the pelvic floor muscle weakness.

9. Constipation

In the approach to a patient with constipation, it is first necessary to define what the patient means by the term. Many definitions exist, but the best clinical definition is that over 95% of the North American population has a stool frequency from three times a day to three times a week: therefore, patients who have a bowel frequency less than three times a week would be defined as being constipated. Many patients will describe their stool as “constipated,” meaning that the stool is hard or in pellets (scybalous), while other patients may have a stool frequency that falls within the “normal” range yet feel that their bowels have not completely emptied. This latter symptom is a frequent complaint of persons with IBS, and many patients with IBS will describe a constipated bowel habit (constipation - predominant IBS).

In Western culture the most frequent cause of constipation is an inadequate intake of dietary fiber. The concept of “fiber” has become quite confusing to many persons, with the increased emphasis on “oat fiber” for elevated cholesterol treatment. Many foods that people consider to be high in fiber (e.g., salads, lettuce, tomatoes and



celery) are in fact mainly water, and some vegetables may actually aggravate their symptoms. Fiber consists of complex carbohydrates that are incompletely digested by the small bowel, and are then “digested” by colonic bacteria, liberating short-chain fatty acids (SCFAs) and gases (flatus) from fermentation. The SCFAs and flatus may provoke and aggravate many of the associated abdominal symptoms (e.g., abdominal pain, “gas” and bloating). Cereal grain fibers that have more insoluble fiber (as opposed to soluble oat bran fiber) are best to increase stool frequency. The insoluble fiber should be added gradually over 8 to 12 weeks up to a maximum daily dose of about 30 g. Other fibers, in the form of “bulk laxative” preparations containing psyllium (isphagula), methylcellulose, or sterculia may be added to wheat bran fiber in order to accomplish this level of 30g fiber per day, without completely altering a patient’s diet.

Many patients who are constipated continue to pass dry, hard stool, despite an increase in dietary fiber, because they do not increase the water content of their diet. Fiber works in the gut by holding onto water and keeping the stool soft. In order to achieve this effect, the intake of liquids must be increased. For a 30 g/day fiber diet, it is recommended that patients drink eight 8 oz. glasses (i.e., 2 L) of non-caffeine-containing beverages per day. Secondary causes of constipation must be excluded. The patient with bowel obstruction can present with constipation. This possibility of organic disease should always be considered in a patient with the new onset of constipation after the age of 40 years (when the incidence of colon cancer rises).

A rarer cause of constipation is hypothyroidism. Not infrequently, patients with an underactive thyroid will present with the primary symptom of constipation. Hypercalcemia rarely reaches levels that produce constipation, but should always be considered, since this electrolyte disturbance can be a life-threatening disorder. Constipation in this setting is always resistant to therapy until the hypercalcemia is treated. Proctitis can present with a complaint of infrequent stool passage. This is due to the functional obstruction from spasm caused by the inflammation of the rectum. The colon more proximally continues to produce formed stool, which cannot pass easily through the inflamed rectum. Proctitis will usually be associated with excess mucus production, with or without blood in the stool, and proctosigmoidoscopy will diagnose this entity.

Another cause of constipation is diabetes mellitus, which results in impaired colonic motility due to dietary factors, as well as autonomic neuropathy of the enteric nervous system, seen with long-standing diabetes mellitus. Patients with diabetes may also develop diarrhea, which again has been linked to the autonomic neuropathy. Inactivity from whatever cause increases the likelihood of constipation. This is presumed to be secondary to reduced colonic activity due to a low fiber intake. Severe cardiopulmonary diseases of whatever cause that limit activity can also result in constipation.

Neurologic disorders that cause the patient to have a reduced ability to ambulate can have constipation as a feature. Some patients with diseases of the nervous system may have impaired awareness of rectal distention to signal a need to defecate, and nerve dysfunction (both peripheral and central) may impair normal colonic propulsion. Finally, the elderly may develop problems with defecation. Although constipation with fecal impaction occurs they may complain of “diarrhea” or “soiling” due to overflow incontinence of stool from the fecal impaction of the rectum inhibiting the normal resting



tone of the anal sphincter. Not surprisingly, many of these patients may respond to laxative therapy after the fecal impaction is removed, since this prevents the recurrence of the fecal impaction with overflow incontinence.

Some patients can aggravate longstanding constipation with regular laxative abuse, and some theoretical concerns remain that this practice may indeed damage the normal innervation of the colon, rendering it atonic and nonfunctional.

The physical findings are often minimal in the majority of patients with constipation, but specific secondary causes must be looked for. Signs of hypothyroidism may be present; signs of dehydration should be sought, as this may be an early indicator of hypercalcemia. Thorough cardiopulmonary and neurologic examinations are necessary to pick out associated diseases that may be treated, thereby improving the patient's overall health, and thus improving bowel function and the quality of their lives. On abdominal examination, inspection for evidence of distention, hyperperistalsis or masses may point to the source of the impaired stool passage. Localized tenderness of the abdomen must be noted, along with any evidence of liver, spleen or renal enlargement. A complete digital rectal examination and proctosigmoidoscopy is required in any patient with constipation so that the presence or absence of a fecal impaction, dilation or enlargement of the rectum or the presence of proctitis can be determined.

Pelvic Floor Dyssynergia

The majority of patients with constipation have a form of irritable bowel Syndrome. But, there is a small subgroup of patients who may have a specific disorder in colonic and/or anorectal function that produces constipation. These patients are almost always female, have delayed colonic transit, have anorectal dysfunction with impaired awareness to rectal distention, but no megarectum, or may have rectal outlet obstruction due to inappropriate contraction of the voluntary anal sphincters during defecation. This has been termed pelvic floor dyssynergia or anismus. These patients can present major therapeutic dilemmas, and warrant further investigation in specialized coloproctology units.

10. The Anal Canal / M. Burnstein

10.1. Functional Anatomy of the Anal Canal and Anorectal Spaces

10.1.1. The Anal Canal

The anal canal begins where the terminal portion of the large bowel passes through the pelvic floor muscles, and it ends at the anal verge. It measures roughly 4 cm in length, usually longer in men than women. The wall of the anal canal is formed by a continuation of the circular muscle of the rectal wall; the smooth muscle is thickened in this area to form the internal anal sphincters (IAS). This smooth-muscle sphincter is wrapped by skeletal muscle, the external anal sphincter (EAS). The top of EAS is formed by the U-shaped puborectalis muscle, which loops around the anus, arising and inserting on the pubis. This is felt posteriorly and laterally as the anorectal ring on digital examination. The longitudinal muscle coat of the rectum descends in the plane between the sphincters as the conjoined longitudinal muscle, and it sends fibers across the lower part of the EAS to insert on the skin (corrugator cutis ani, responsible for the anocutaneous reflex or "anal wink"). These fibers also traverse the IAS to insert on the submucosa ("mucosal suspensory ligament" or Treitz's muscle).



In approximately the mid-anus there is a rolling line of demarcation called the dentate line. Above the line is columnar epithelium; below it is squamous epithelium without appendages (the anoderm). The demarcation does not really occur at a line, but at a transitional zone of 0.5–1 cm in length.

As the rectum narrows into the anal canal, the mucosa develops 6 to 14 longitudinal folds, Morgagni's columns. Between the distal ends of the columns are small crypts. Anal glands open into the crypts. There are 4 to 10 glands, and they are lined by stratified columnar epithelium. About half of these tubular glands end in the intersphincteric plane. Blood is supplied to the anus via the inferior rectal artery, a branch of the internal pudendal artery. The inferior rectal artery crosses the ischiorectal fossa. The superior rectal vein drains the upper part of the anal canal via the inferior mesenteric vein to the portal vein. The middle and inferior rectal veins drain the upper and lower anal canal into the systemic circulation via the internal iliac and internal pudendal veins, respectively. Lymphatic drainage above the dentate line is via the superior rectal lymphatics (accompanying the superior rectal vessels) to the inferior mesenteric

nodes, and laterally along the middle and inferior rectal vessels to the internal iliac nodes. Lymphatic drainage from the anal canal below the dentate line may be in a cephalad or lateral direction, but is primarily to the inguinal nodes. Motor innervation of the EAS is via the inferior rectal branch of the pudendal nerve as well as the perineal branch of the fourth sacral nerve.

The IAS has sympathetic (motor) and parasympathetic (inhibitory) innervation. Parasympathetic supply is from the nervi erigentes (S2, S3, S4). Sympathetic innervation is from the first three lumbar segments via the preaortic plexus. Fibers from the preaortic plexus ultimately join the nervi erigentes to form the pelvic plexuses. Sensation below the dentate line (and for up to 1.5 cm above the dentate line) is carried by the inferior rectal nerve. Above the level of the inferior rectal nerve sensory distribution, there are only dull perceptions, mediated by parasympathetic fibers.

10.1.2. Anorectal Spaces

Around the anorectum there are a number of potential spaces filled with fat or connective tissue. These may become the sites of abscess formation. The perianal space is at the anal verge, and is continuous with the intersphincteric space. The pyramid-shaped ischiorectal (ischioanal) fossa is medially bounded by the EAS and the levator ani muscles. The lateral wall is the obturator internus muscle and fascia. The inferior boundary is the skin of the perineum, and the apex is the origin of the levator ani from the obturator fascia. Posteriorly is the gluteus maximus muscle, and anteriorly the transverse perinei muscles. On the obturator fascia is Alcock's canal, containing the internal pudendal vessels and pudendal nerve. The fossa is filled with fat, and contains the inferior rectal nerve and vessels, as well as the fourth sacral nerve. The two ischiorectal spaces communicate with one another behind the anal canal via the deep post-anal space.



Chapter 11: Diverticulosis, Ischemia, Infection
and Bleeding

G.K. Turnbull, M. Burnstein, J.A. Rowe and S.J. Vanner

1. Diverticulosis

In Western societies diverticulosis occurs in at least one person in two over the age of 50 years. The frequency increases with age. Diverticulosis or diverticular disease of the colon is due to pseudodiverticula in that the wall of the diverticulum is not full-thickness colonic wall, but rather outpouchings of colonic mucosa through points of weakness in the colonic wall where the blood vessels penetrate the muscularis propria.

These diverticula are prone to infection or “diverticulitis” presumably because they trap feces with bacteria. If the infection spreads beyond the confines of the diverticulum, an abscess is formed. Patients present with increasing left lower quadrant pain and fever, often with constipation and lower abdominal obstructive symptoms such as bloating and distention. Some patients with severe obstructive symptoms may describe nausea or vomiting. This can occur with or without abscess formation. Other causes of these symptoms include Crohn’s colitis with stricture formation, colonic cancer, and ischemic colitis.

On physical examination the patient often has localized tenderness in the left lower quadrant (the most prevalent site of diverticulae). With severe infection and an abscess, examination may show rebound tenderness. A palpable mass is often identifiable in the sigmoid colon.

Treatment consists of intravenous fluids, bowel rest by placing the patient on no oral intake or just a clear liquid diet, and broad-spectrum intravenous antibiotics. Antibiotics selection should be to cover both gram-negative enteric bacteria and anaerobic bacteria that are normally found in the colon. CT scan may be helpful in outlining the colon and identifying an abscess, and is preferable to barium enema for diagnosis in patients with an acute illness.

Many complications can occur in diverticulitis. These are listed in Table 1. Colonic stricture after resolution of diverticulitis is described further in Section 3.3. Bleeding occurs in less than 5% of diverticulosis patients; it is abrupt in onset, painless, and often massive. A bleeding diverticulum can be from either the left or right colon. Even though bleeding is more likely to occur in right colonic diverticulosis, the bleeding frequency is approximately equal because of the much higher frequency of left colonic diverticulosis. It is rare for patients with diverticulosis to have significant bleeding.

Table 1. Complications of diverticulitis

-
- Abdominal abscess/Liver abscess
 - Colonic obstruction
 - Fistulas
 - Colovesical
 - Colovaginal
 - Colocutaneous
-

Over 80% of diverticulosis patients will stop bleeding spontaneously. The rest will continue and require investigation and treatment (see Section 5). Segmental colonic



resection is reserved for that small group of patients who continue bleeding or have recurrent bleeding. Patients under the age of 40 with symptomatic diverticulitis should have surgical resection because this small subgroup is at greater risk of complications.



Figure 1A. The rounded openings of a several diverticulæ are shown, with the colonic lumen at the top of the image.

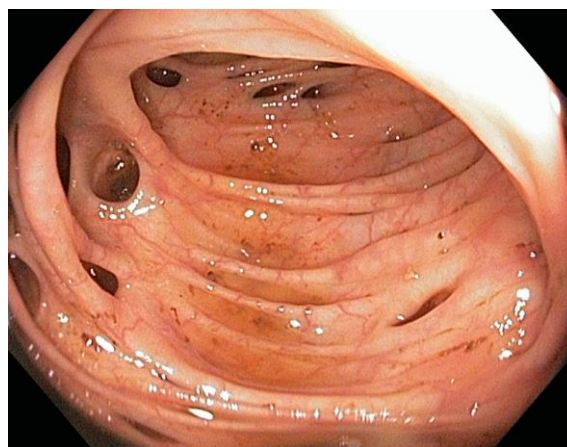


Figure 1B. Multiple diverticulum openings are shown, with the lumen at the upper half of the image. There is a larger opening to the left that can be confused with the lumen of the colon. With insertion of the colonoscope into a diverticulum, perforation is the result.

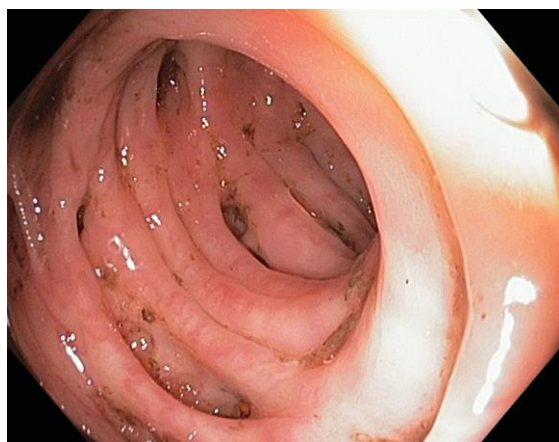


Figure 1C. The muscle in the sigmoid colon is hypertrophied with multiple diverticulum openings and the lumen towards the right of the image.

Figure 1. Examples of diverticulosis of the sigmoid colon at colonoscopy.

2. Colonic Ischemia

Colonic ischemia is the most common form of intestinal ischemia. It tends to occur in older patients, but can occur at any age. Patients usually present with sudden onset of abdominal pain and rectal bleeding (see lower GI bleeding). The pain from colonic ischemia is often not as severe as in other cases of acute intestinal ischemia. The majority of cases of colonic ischemia are self-limited, associated with ischemia of the left colon and/or transverse colon where the “watershed” area of the colonic vasculature supply to the colon is. Most cases have mucosal ischemia with the muscular wall of the colon relatively less prone to ischemia. This prevents transmural ischemia in most cases.



Colonic ischemia may be associated with previous aortic surgery, usually because the inferior mesenteric artery that supplies much of the left colon arterial supply is sacrificed during these operations. Colonic ischemia is also associated with underlying diseases that may decrease colonic mesenteric blood supply due to low-flow states, as in hypotension related to surgery or other conditions that can lower blood pressure, or medications including drugs such as cocaine that induce vasospasm. Certain diseases are more commonly associated with colonic ischemia; diabetes, vasculitis, rheumatoid arthritis and amyloidosis. In younger individuals, colonic ischemia is often associated with extreme exertion as a long distance running (marathon running or triathlon competitions). Young women may be more prone to colonic ischemia, possibly because of their taking the “pill” (oral contraceptive agent), or from associated IBS (irritable bowel syndrome), which is more common in young women and which is associated with an unexplained increased risk of colonic ischemia. Colonic obstruction can also be associated with an increased risk of colonic ischemia, be from a malignant obstruction or diverticular disease. The mechanism is presumed to be from reduced blood flow to the colon as the result of torsion or stangulation of the bowel, or very high pressures in the colonic lumen. Infections have also been linked to ischemia, especially colonic infection with cytomegalovirus or *E. coli* O157; H7. Both of these release toxins that cause local vasospasm and thereby result in ischemia. Constipation, the use of opiates with their side effect of constipation and laxative use have all been associated with colonic ischemia.

Transmural ischemia and infarction of the colon occur in about 20% of cases. The factors predictive for a more serious form of colonic ischemia are: right-sided colonic ischemia or colonic ischemia affecting both the right and left portions of the colon, hypotension, tachycardia, use of anticoagulants, and male sex (even though the incidence is much higher in women). Rectal bleeding is a predictor of less serious colonic ischemia and the use of NSAIDs seemed to lower the risk of severe ischemia. Hypotension and tachycardia would both predict more extensive ischemia, depending on the duration of the shock. Warfarin use may identify patients with underlying cardiac or coagulation disorders who would be at greater risk for ischemia. Rarely, patients with severe ischemic colitis will pass a bowel cast which is the necrotic lining of the bowel. This finding only occurs in the sickest patients, usually when there is extensive necrosis and gangrene of the colon.



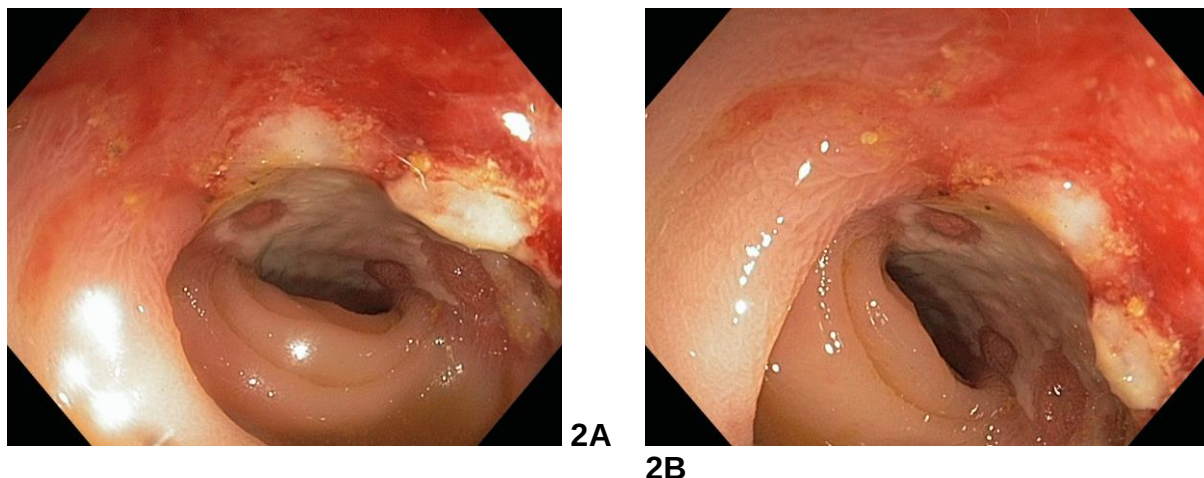


Figure 2. show ischemia of the colon at the splenic flexure where the mucosa in the near portion of the photos is just edematous but they there is ulcerated mucosa. On biopsy, the histology shows little inflammation and features indicating mucosa ischemia to distinguish this from ulceration at the splenic flexure from other diseases like Crohn's where the biopsies would show inflammation.

LEARNING POINTS:

- Have a high suspicion for ischemia in the person who has severe abdominal pain, which is out of keeping with the absence of abnormal physical signs
- Ischemia is more common in older persons, diabetics, those with coronary artery disease, irritable bowel syndrome, or persons on medications/drugs such as cocaine, OCA, or digitalis
- If the ischemic bowel progresses to gangrene or perforation, emergency surgery is necessary

Treatment is mostly supportive but early recognition of extensive or severe ischemia is important in selecting out those few patients who are likely to have a severe outcome. If there is rectal bleeding, colonoscopy should be considered if the patient shows signs of peritoneal irritation, abdominal imaging should be done first to ensure that the patient has not already had a colonic perforation. Biopsies of the affected colon are often not helpful, in that the pathology can be non-specific, but biopsies may help to distinguish from other conditions that appear like colonic ischemia (ie. Crohn's colitis which can also cause a patchy ulcerating lesion of the colon, with the rectal sparing typically seen with ischemic colitis). If cytomegalovirus infection is suspected, colonic biopsy for viral culture is the most accurate way to identify this infection. Antibiotics may help as they have been shown to lessen the ischemic injury when used in animal models of colonic ischemia, but no clinical trials exist to support this practice. Steroids should be used with caution, because they may increase the colonic ischemia and increase the risk of perforation. Other anti-inflammatory therapies have not been



evaluated, such as 5-ASA (mesalamine) therapies. These agents may have a role in patients who develop a chronic state of colonic ischemia, but this is also speculative.

Urgent surgery is when there is massive bleeding from colonic ischemia, if there is development of peritoneal signs, or evidence of toxic megacolon.

In patients with chronic colonic ischemia who do not improve over 2-3 weeks, especially if they develop a protein-losing enteropathy, surgery may be required. Surgery for strictures that develop after a severe case of colonic ischemia is best reserved for those patients who have definite symptoms of obstruction.

3. Infections of the Colon

3.1. *Shigella*

This infectious diarrhea is the classic cause of “bacillary dysentery.” The typical presentation of a shigella infection is fever, abdominal cramping, and watery diarrhea that usually becomes bloody within 24 to 48 hours of onset. The incubation period of shigellosis is from 36 to 48 hours. As the disease progresses, the symptoms become typical of colonic dysentery, with small, frequent stools and cramping and tenesmus that may lead to rectal prolapse in some individuals with prolonged straining.

Shigella is a gram-negative bacterium with only humans as its host. The organism is well adapted to causing disease in humans. As few as 200 organisms are needed to cause infection, as compared with other enteric infections requiring 10^6 organisms or more. *Shigella* can persist in food for weeks and on contaminated body surfaces for several hours. Pathogenesis is through production of a cytotoxin called Shiga toxin or similar toxins that are both cytotoxic and neurotoxic, very similar to the toxin produced by *E. coli* 0157:H7 species.

Shigella is a microinvasive bacterium that enters the host via the M cells in the intestine and then spreads laterally through the colonic mucosa to involve the basolateral membrane of the surrounding cells. It is seen mostly in travelers returning from endemic areas (tropical and subtropical). There is also a higher incidence of shigellosis in men who have sex with men (oral-anal sex). Treatment depends on the antibiotic resistance of the infecting strain of bacteria. *Shigella* species quickly develop antibiotic resistance. Patients should be encouraged to complete their course of antibiotics to prevent this.

Antibiotics shorten the duration of both symptoms and carriage of the organism. Untreated, shigella organisms can be excreted in stool for up to 6 weeks while the individual is asymptomatic. Fluoroquinolones are the antibiotics of choice because of the low incidence of resistance at present, but this may change. Ampicillin and trimethoprim-sulfamethoxazole are also effective against sensitive strains. If infection has been acquired overseas, a confirmed *Shigella* infection is best treated with a fluoroquinolone twice daily for 5 days. There are reports of a single large dose eradicating infection (unless the organism is *S. dysenteriae* 1).



Antimotility agents such as loperamide, diphenoxylate or narcotic analgesics are contraindicated with this infection because of the risk of developing a toxic colon. In general, antimotility agents should never be used in acute infectious diarrhea when bloody stool is present.

3.2. *Salmonella*

Infection with nontyphoidal strains of *Salmonella* results from ingesting foods contaminated with these organisms. These bacteria are endemic to poultry and cattle populations. Large epidemics have resulted from undercooked eggs, and these bacteria are also frequently found in pet reptiles and amphibians. *Salmonella* contamination of marijuana can be an important infection source in young adults. Recent outbreaks have been from contaminated raw vegetables, especially salads and tomatoes. The usual incubation period is from 8 to 48 hours after ingestion.

S. typhi, which causes typhoid fever, is found only in humans. It will not be discussed further other than to emphasize that all *Salmonella* species are related, and therefore can cause systemic illness of similar severity, especially in persons who are immunocompromised and those at the extremes of age (i.e., those under 2 years and the elderly).

Salmonella is an invasive bacterium that can cause septicemia after first multiplying in the mesenteric lymph nodes. Our usual resistance to being infected with salmonella is a result of the presence of gastric acid, the integrity of the intestinal flora, and intestinal motility to clear the bacterium. Increased risk of salmonellosis is associated with the use of purgatives, antimotility agents, broad-spectrum antibiotics and acid-suppression therapy, previous bowel surgery will, and diseases that predispose to infection as a result of impaired host defenses include sickle cell disease, systemic lupus erythematosus (SLE) and HIV/AIDS.

Treatment is usually symptomatic. Antibiotics should be used only if the patient is showing signs of bacteremia. Antibiotics often increase the development of a chronic carrier state. The antibiotics of choice are ampicillin, trimethoprim-sulfamethoxazole, the fluoroquinolones and the third generation cephalosporins (especially ceftriaxone, with its high biliary excretion) have been shown to be very effective in patients who need antibiotic therapy.

Treatment with antibiotics should normally be considered only for children under the age of 2 years or elderly persons with vascular disease.

Patients with metal implants in bones, lymphoproliferative disease, sickle cell disease, or HIV/AIDS. The site of chronic infection is usually the biliary tract. Disease of the biliary tree, especially cholelithiasis, requires surgery to correct the disease followed by a two-week course of therapy, which often leads to resolution of the chronic carrier state.



3.3. *Clostridium Difficile*

Many persons treated with antibiotics develop diarrhea (antibiotic-associated diarrhea), which stops when the antibiotic is discontinued. In a small portion of persons with AAD, there may be an infection with *C. difficile*. This spore-forming anaerobic gram-positive bacterium is the commonest cause of infectious diarrhea in hospitalized patients (nosocomial infection). *C. difficile* is not invasive, but with reduction of the normal colonic bacterial flora it multiplies, and produces two toxins, known as toxins A and B. Toxin A causes colitis. Toxin B is a cytotoxin that is often used as a diagnostic test for this infection.

Most commonly, infection is preceded by antibiotic therapy. Outbreaks in hospital frequently occur among the sickest patients, some of whom have not received antibiotics beforehand. Penicillins, cephalosporins and clindamycin are more likely to be associated with *C. difficile* infection, but all antibiotics, including metronidazole and vancomycin, have been associated with it. Antibiotics which have a lower risk of causing this infection are aminoglycosides, tetracycline, macrolides, sulfonamides and of course vancomycin. Other risk factors include agents that affect gut motility such as enemas, anti-diarrheal medications, and intensive chemotherapy. Acute flare-ups of colitis (ulcerative colitis or Crohn's colitis) can also be caused by *C. difficile* infection in persons who have not had prior antibiotic exposure. Patients with severe illnesses and advanced age are also more prone to manifest disease symptoms.

Diarrhea is the most common symptom of presentation, and is usually nonbloody. With prolonged diarrhea, some bleeding can result from local anorectal irritation. The typical appearance of a *C. difficile* infection at endoscopy is of "pseudomembranes" or whitish plaques on the surface of the colonic mucosa, with intervening areas of mucosa that appear almost normal. For this reason, a *C. difficile* infection is often called "pseudomembranous colitis" (PMC), but PMC may occur in the absence of a *C. difficile* infection. Unfortunately, these characteristic changes may not always be present in the rectum or left side of the colon, so colonoscopy is needed to detect right colonic pseudomembranes.

The diagnosis of *C. difficile* is usually confirmed by the presence of cytotoxin in the stool placed on tissue culture. The clinician must be alert to the possibility of this infection in susceptible patients, since in some patients neither the culture of *C. difficile* nor the presence of the cytotoxin in the stool is positive. A careful inventory of any antibiotic therapy in the last three months is crucial in considering this cause for diarrhea, as many patients will have taken the offending antibiotic several days to weeks before symptoms begin.

Metronidazole treatment is preferred to vancomycin (unless the more virulent strain NAP1 is suspected – see below) because both antibiotics show similar efficacy in treating this infection and metronidazole is about one-tenth the cost of vancomycin. Treatment with metronidazole is for 10 to 14 days, usually in a dose of 500 mg p.o. t.i.d.



The vancomycin dosage is 125 mg p.o. q.i.d. also for 10 to 14 days. It is effective only via the oral route, whereas metronidazole is also effective when given intravenously, as may be necessary in the occasional patient with postoperative ileus. With both regimens, there is a high relapse rate (up to 20%) of symptomatic infection.

The best method to prevent relapse is unknown, but relapsing symptoms may respond to retreatment of the infection with either metronidazole or vancomycin. There may be a role for the use of probiotics to prevent or to treat *C. difficile*. There has been emergence of a more virulent strain of *C. difficile*, called NAP1, which has a high mortality rate. NAP1 is often acquired in hospital rather than in the community, and is usually resistant to metronidazole. Therefore, patients who are very ill at presentation, with elevated white blood cell counts (>20,000), with fever and an elevated serum creatinine concentration should be started on vancomycin immediately rather than on metronidazole. The patients can have a decrease in diarrhea even though they are developing toxic megacolon. For this reason, NAP1 patients should always be monitored closely for the development of megacolon.

Another cause of AAD is right-sided hemorrhagic colitis from infection with *Klebsiella oxytoca*. *Klebsiella oxytoca* usually occurs after treatment with penicillin antibiotics (especially amoxicillin-clavulanate). This infection should be considered in individuals who appear to have *C. difficile* infection, but their stool cultures are negative for the organism or its toxin. *K. oxytoca* is identified by stool culture, but it has to be specifically cultured for or it will be missed on routine stool culture.

3.4. *Entamoeba Histolytica* (Amebiasis)

Entamoeba histolytica, the parasite that causes amebiasis infection is the only ameba that causes disease in humans. Other amebas are often found in the colon as normal commensals. *E. histolytica* is a cyst-forming parasite, but the cysts do not cause disease. The cysts are ingested and are resistant to destruction by gastric acid, and so pass to the colon. From the cysts in the colon, trophozoites develop from the ingested cyst. The trophozoites invade the colonic mucosa and cause disease, but trophozoites passed in the stool of symptomatic individuals cannot survive outside the body and rarely transmit infection. The cysts spread disease to others, and frequently unaffected carriers spread disease by excreting cysts. The disease is most prevalent in areas of the tropics where sanitation is poor. The amebae infect the colon and rarely the ileum, but the cecum is usually involved. The colonocytes are the initial site of disease. Invasion of the mucosa by trophozoites is due to the production of an “amebapore” molecule that causes the colonocytes to lyse. The lysed colonocytes are then ingested by the amebas, leading to ulceration of the colon. *E. histolytica* is an invasive pathogen and can spread hematogenously to other organs, especially the liver, and can lead to dissemination of the infection throughout the body.



The diagnosis of amebiasis is usually made by identification of *E. histolytica* on microscopic analysis of stool, but can also be made on identification of the ameba on histological examination of colonic biopsies. There is a decreased yield on stool analysis after barium studies or if antibiotics or mineral oil has been used prior to the collection of stool samples for culture. Diagnosis can also be made by indirect hemagglutination and ELISA tests on serum to detect infection, but if the patient is a carrier with only cyst excretion these tests are often negative. At colonoscopy the ulcers of the rectum and colon may have characteristic undermined edges. Sometimes the intervening mucosa looks normal in contrast to acute bacillary dysentery (see Section 3.7.1) and ulcerative colitis.

Chronic infection of the cecum with *E. histolytica* leads to a “coned” appearance on x-ray. Other colonic complications include perforation, ameboma (a granulomatous tissue reaction in the colon; the ameba mass can lead to obstruction or be mistaken for colonic malignancy), pericolic abscess and fistulas.

The liver is the commonest extra-intestinal organ infected, but *E. histolytica* can also spread to the brain, lungs, pericardium and eyes. There is an increased risk of disseminated disease and abscess formation if the patient is on steroids, is pregnant or is immunocompromised.

Treatment for acute amebic colitis is with metronidazole 500 (400–750) mg t.i.d. for 5–10 days. If the patient has chronic colonic disease with chronic shedding of cysts, diloxanide 500 mg t.i.d. for 10 days is the drug of choice. If diloxanide cannot be obtained, then paramomycin 25 – 30 mg/kg/day divided into three equal doses per day for 7 days, or iodoquinol 650 mg t.i.d. for 20 days can be used. Exceeding this maximal dose may cause optic neuritis.

Patients with amebic liver abscess should first be treated with metronidazole for 10 days, and then be given 10 days of diloxanide. All patients should be reassessed two to three months after treatment, to ensure that the parasite has been cleared and that there is no chronic carrier state with continued cyst excretion.

3.5. *Balantidium Coli*

B. coli is a large, ciliated protozoan that uncommonly causes an illness similar to amebic dysentery. *B. coli* is usually easy to identify in stool samples, owing to its large size. It is acquired in tropical or subtropical countries from exposure to pigs, which frequently carry this organism without signs of illness. Treatment is with tetracycline 500 mg q.i.d. for 10 days. *B. coli* is also sensitive to ampicillin and metronidazole.

3.6. *Blastocystis Hominis*

B. hominis is an anaerobic protozoan which is frequently found in asymptomatic individuals, *B. hominis* may be a cause of diarrhea in some patients found to have large numbers of this protozoan in the stool. Treatment is with either metronidazole 750 mg t.i.d. for 10 days or high dose trimethoprim/sulfamethoxazole.



3.7. *Dientamoeba Fragilis*

Dientamoeba Fragilis is also a protozoan related to Trichomonads, it is a human pathogen. *D. fragilis* commonly causes abdominal pain, diarrhea, bloating and other vague abdominal symptoms. This parasite should be ruled out in individuals who are suspected of having diarrhea predominant IBS, or of microscopic colitis (see below). Co-infection with *B. hominis* appears to be a common finding in some labs where parasite stool studies are still done by microscopy. If *D. fragilis* is identified, treatment has been associated with rapid clearing of symptoms. Treatment is with iodoquinol 650 mg TID for 20 days, doxycycline 100 mg BID for 10 days, or metronidazole 500 mg TID for 10 days.

4. Intestinal Nematode Infections

4.1. Roundworm (*Ascaris Lumbricoides*)

Roundworm or ascaris, one of the more common nematodes found in humans, is most often found in the tropics. Usually eggs are ingested from contaminated foods or dirty hands. The eggs hatch in the intestine and spread by the blood to the liver and then to the lungs. An eosinophilic pneumonitis develops the larvae migrate through the alveoli, up the trachea, through the larynx, where they are swallowed. Roundworms develop into adult worms in the small intestine. The adult worms can cause intestinal obstruction symptoms if large numbers are present, and can cause biliary symptoms if they migrate into the common bile duct.

4.2. Hookworm (*Ancylostoma Duodenale*; *Necator Americanus*)

Hookworm is a nematode which can infiltrate the skin from contaminated earth, found in areas with fecal contamination of the soil. A pruritic rash develops at the site of the hookworm entry into the body. The filarial larvae then travel to the lungs, migrate through the alveoli, up the trachea, through the larynx, where they are swallowed. After being swallowed, they cause nausea, diarrhea, vomiting, abdominal pain and flatulence. Many patients present with iron deficiency from a daily blood loss of 0.1–0.4 mL with each worm.

4.3. Whipworm (*Trichuris Trichiura*)

Whipworm can also cause iron deficiency if large numbers infect the GI tract. It primarily invades the colon. Bloody diarrhea develops with larger infestations. It is easily diagnosed by stool analysis looking for the typical eggs, but is increasingly diagnosed at colonoscopy during investigation of the bloody diarrhea, where the worms are easily seen if present.

4.4. Pinworm (*Enterobius Vermicularis*)

Pinworm is probably the commonest nematode worldwide. It usually causes pruritus ani, often worse at night when the worms migrate onto the perianal skin and lay their eggs. Pinworm is probably the most common nematode encountered in Canada, especially in children. Diagnosis is by identification of the eggs from the perianal skin, usually collected in the early morning before defecation.



4.5. *Strongyloides Stercoralis* (Strongyloidiasis)

Strongyloides stercoralis is widely found in the tropics. It is the only nematode that can multiply and reproduce its entire life cycle within the human host. This causes persistent reinfection over many years after the original infection. Larvae can penetrate intact skin or the eggs can be ingested. Filariform larvae that penetrate the skin travel hematogenously to the lungs and then, as with the other worms, travel into the airways, into the larynx, and are swallowed. In the intestine the larvae become adult worms. When the eggs are ingested, they become filariform larvae in the intestine; then the larvae invade the blood vessels, thus reinfecting the host.

Symptoms of strongyloidiasis vary and may include abdominal pain, diarrhea, nausea and vomiting. With mostly intestinal involvement of strongyloids diarrhea develops. In children, a syndrome similar to celiac disease with protein-losing enteropathy can develop. The majority of adult infections are asymptomatic, or are only intermittently symptomatic. Recurrent urticaria can develop where the worms infiltrate the skin, particularly the perianal skin and gluteal areas.

Diagnosis can be confirmed by stool analysis but can be falsely negative in up to 25% of cases, even after repeated stool analysis. The larvae look similar to hookworm. An ELISA test is useful for diagnosis, but there may be overlap with the presence of *Filaria* species. Eosinophilia is often present, even in asymptomatic individuals.

Thiabendazole is usually used to treat strongyloids, 25 mg/kg twice daily to a maximum of 3 g daily for two days, or for five days for disseminated disease. Albendazole or ivermectin may be used if the patient is unable to tolerate thiabendazole, but these drugs appear to be less effective than is thiabendazole against *S. stercoralis*.

With the hyperinfection syndrome, when large numbers of the worms are present (often in association with immune suppression, as with steroid therapy), antibiotics are often needed to treat the septicemia that results if the intestinal damage allows secondary bacterial invasion.

5. Sexually Transmitted Diseases of the Anorectum

There is an increasing incidence of venereal infections of the anorectal region, mainly accounted for by sexual practices among gay men. Many of these diseases may mimic nonvenereal conditions of the anorectum, and multiple venereal infections may coexist. While immunocompetent gay men are subject to infection with the usual venereal pathogens, HIV/AIDS patients may additionally suffer from opportunistic infections of the gut.

The common anorectal venereal infections seen in North America are discussed here.

Condylomata acuminata, or venereal warts, are seen in the perianal region and anal canal, as well as the vulva, vagina and penis. They are most often seen in men who have sex with men (MSM). The causative agent is believed to be a papilloma virus, which has an incubation period of one to six months. Symptoms are generally minor – itching, and occasionally bleeding. Perianal warts are frequently accompanied by warts within the anal canal, and these must be looked for at anoscopy. Many treatments exist. None has a better than 70% chance of eradicating the disease by a single application. For perianal and anal canal warts, electrocoagulation or laser destruction is preferred.



For extensive and persistent disease, immunotherapy with an autologous vaccine may be successful. Squamous cancer has been seen to arise in condylomata acuminata.

Neisseria gonorrhoeae may produce proctitis. The incubation period of gonococcal proctitis is 5 to 7 days. Gonococcal proctitis is most often asymptomatic. Symptoms may include mucopurulent discharge and tenesmus. Proctoscopy reveals a thick, purulent discharge on a background of mild, nonulcerative inflammation of the distal rectum. Gram's stain is unreliable, but culture of the pus confirms the diagnosis.

Serologic testing for syphilis should be carried out. Treatment for MSM is ceftriaxone, 250 mg IM once. *Syphilis* can affect the anal region. The incubation period ranges from 9 to 90 days. The primary lesion is a painful chancre, which may be mistaken for a fissure. However, chancres are off the midline, are often multiple, and have an atypical appearance. Bilateral inguinal lymphadenopathy may be present. The chancre regresses over 6 weeks. *Treponema pallidum* is demonstrated from the primary lesion by darkfield microscopy. Serologic testing will be positive within a few weeks of the appearance of the chancre. If untreated, the secondary stage of syphilis may involve the anal area 6 to 8 weeks after healing of the chancre. This takes the form of a rash or of condylomata lata – flat, wart-like lesions teeming with *Treponema pallidum*. Treatment of primary and secondary syphilis is with benzathine penicillin G, 2.4 million units IM given once. Sexual contacts should be treated prophylactically.

Herpes simplex 2 may infect the anorectum. The incubation period is 4 to 21 days. Constitutional symptoms are followed by severe anorectal pain. Small vesicles and aphthous ulcers are seen perianally, as well as in the anal canal and lower rectum. There may be tender inguinal lymphadenopathy. Viral cultures of the vesicular fluid will be positive for herpes simplex 2 and rectal biopsy has a characteristic appearance. Spontaneous resolution occurs over several weeks. Recurrences are frequent but less severe.

Immunosuppressed patients may develop a severe, destructive process. Treatment is with tub baths and analgesics. Topical acyclovir q8h for 5 days shortens the symptomatic period and the duration of viral shedding. However, oral antiviral therapy is the preferred method of treatment, as it decreases the severity of symptoms and will also decrease the disease duration. Acyclovir is given as 400 mg TID or 200 mg five times a day. Famciclovir 250 mg TID or valacyclovir 1,000 mg BID are equivalent in efficacy, but are more expensive than acyclovir. Intravenous acyclovir is used when there is proctitis in addition to anal and perianal disease. In the HIV/AIDS patient, acyclovir is used intravenously in the acute phase, followed by oral acyclovir for 6 months.

Chlamydia proctitis with non-LGV (lymphogranuloma venereum) serotypes is almost identical to gonococcal proctitis. However, the LGV serotypes are invasive and produce a severe proctocolitis with pain, tenesmus, discharge and diarrhea. Chlamydia is isolated from the rectum. Treatment is with doxycycline 100 mg po BID for 7 days, or azithromycin 1 g po as a single dose.

6. Lower Gastrointestinal Bleeding / S.J. Vanner

Lower GI bleeding often presents as a medical emergency. Like other medical emergencies, optimum patient care requires careful assessment and resuscitation. The



history and physical findings provide important clues to the etiology of lower GI bleeding, and are critical for determining the severity and location of the bleeding site.

Lower GI bleeding can be classified arbitrarily as major or minor. Patients presenting with the passage of significant amounts of bright red blood per rectum (BRBPR), together with hemodynamic compromise have major GI blood loss and are at risk of life-threatening hypovolemia. Be wary of the patient who may have stabilized temporarily or received intravenous fluids prior to a full clinical assessment. Historical clues to a major bleed include the occurrence of syncope or presyncope prior to the person seeking medical care. The vital signs, with particular attention paid to postural changes, are crucial to assessing severity. The passage of bright red blood per rectum usually originates from the colon. However, it is important to remember that brisk bleeding from a site in the upper GI tract may masquerade as a major lower GI bleed.

In contrast to the patient with major lower GI bleeding is the person who describes the passage of bright red blood per rectum as blood on the tissue paper or on the outside of formed stool in the absence of other symptoms. Such patients, whose general physical examination is normal, usually have a minor lower GI bleed. Most often this is due to local perianal pathology, but distal colon pathology should always be ruled out.

7. Determining the Site of Bleeding (Upper or Lower GI Tract)

In the clinical setting of a major lower GI bleed with the passage of bright red blood per rectum and hemodynamic compromise, there are a number of important clues that may raise the suspicion of an upper GI source. These include a past history or symptoms of peptic ulcer disease, NSAID/ASA use, prior abdominal aneurysm repair, alcohol abuse and coexisting liver disease. Unfortunately, the lack of upper GI symptoms does not exclude peptic ulcer disease, as a number of peptic ulcers present as major GI bleeds without a previous typical ulcer history. These painless bleeding gastric or duodenal ulcers are particularly common in persons whose peptic ulcer is associated with the use of aspirin (ASA) or nonsteroidal anti-inflammatory drugs (NSAIDs).

On physical examination, the finding of hypovolemic shock, particularly in a young person, should trigger immediate consideration of a proximal source of bleeding. Features of chronic liver disease and portal hypertension suggest esophageal or gastric varices as a possible cause. Most major upper GI bleeding, even in a young person, is accompanied by a transient rise in the BUN (blood urea nitrogen), whereas this is not typical in a lower GI bleed unless there is renal comorbidity.

When an upper GI source is considered, a nasogastric (NG) tube is placed. A nasogastric tube returning bloody gastric aspirate positively identifies a proximal source of bleeding. A negative aspirate will exclude significant bleeding from the esophagus or stomach but may fail to identify bleeding from the duodenum. Even aspirates with bile staining and no blood may fail to identify 5–10% of bleeding duodenal ulcers. When an upper GI source cannot be excluded with confidence, urgent upper endoscopy is required.

Another potentially confusing scenario involves the patient presenting with melena. Melena results from the digestion of blood as it travels through the GI tract, and



usually originates from the upper GI tract. However, occasionally the transit of blood from a bleeding right colon source is sufficiently slow that stool can appear as melena or melena mixed with dark red blood.

Positive fecal occult blood tests (FOBT) are another clue to gastrointestinal bleeding. Testing should be done with patients on a controlled diet (no red meat, vitamin C or aspirin) to minimize a falsely positive FOBT.

8. Major Lower GI Bleeding

Angiodysplasia and diverticular bleeding are the two most common causes of major lower GI bleeding, accounting for up to 70% of cases. Angiodysplastic lesions result from dilation and tortuosity of submucosal veins associated with small arteriovenous communication with submucosal arterioles. These lesions are typically multiple, less than 5 mm in diameter, and are most commonly found in the right colon and cecum. The pathogenesis of these lesions is unknown. They occur most commonly in elderly patients, and differ from congenital vascular lesions. Diverticula are located predominantly in the left colon, but diverticulae in the right colon bleed more frequently. The pathophysiology underlying diverticular bleeding is uncertain, but may result from rupture of arteries that penetrate the dome of the diverticulum.

A number of other possible but less common causes exist for lower GI bleeding (Table 2). Many of these more typically present with minor lower GI bleeding and a clinical picture dominated by other features such as diarrhea and anemia. Angiodysplasia, unlike diverticular bleeding, can also present with minor chronic GI bleeding, and may even present as chronic iron-deficiency anemia secondary to microscopic blood loss. In contrast to angiodysplasia and diverticular bleeding, which are relatively painless, bleeding secondary to colonic ischemia is typically preceded by minutes to hours of severe abdominal pain. Abdominal x-rays may demonstrate dilation of the bowel, thickening of the bowel wall, and “thumb-printing” (edema of the bowel wall). Thumb-printing is neither specific nor sensitive.

Table 2. Causes of Major Lower GI Bleed

-
- Very common
 - Diverticular disease
 - Angiodysplasia
 - Less common
 - Ischemia
 - Neoplasia
 - Inflammatory bowel disease
 - Hemobilia
 - Perianal disease
 - Aortoenteric fistula
 - Solitary rectal ulcer
-



Most major lower GI bleeding will stop without intervention and can be investigated electively, but up to 25% will continue to bleed and require immediate investigation and treatment. After resuscitation, the next priority is to identify the site of bleeding. Radionuclide scanning using technetium-labeled red blood cells is least invasive and readily available in most centers, but interpretation is fraught with false negative and positive results. Although angiography is less available and more invasive, it is more accurate and has the advantage of therapeutic intervention with embolization of the arteriole feeding the bleeding lesion. Colonoscopy can also be attempted to identify the bleeding lesion, and if angiodysplasia is evident it can be treated with electrocautery. However, unless the rate of bleeding is relatively slow, ongoing bleeding usually obscures the lumen, making it difficult to identify the responsible lesion and technically difficult to advance the colonoscope to the site of bleeding. In some cases, continuing bleeding (requiring transfusions of 6–10 units of blood) requires either urgent angiography with embolization or surgical resection with a subtotal colectomy.

9. Minor Lower GI Bleeding

Minor bleeding from the lower GI tract is a common complaint and requires a careful approach to differentiate minor pathology such as hemorrhoids and fissures from serious problems such as colonic tumors. Patients may notice blood only on the outside of formed stool or on the tissue paper. This suggests that the blood originates from the anal canal or the rectosigmoid region. Alternatively, some patients notice that the blood is mixed in the stool, suggesting that bleeding is more proximal within the colon.

Hemorrhoids are the commonest cause of minor bleeding (Table 3). Even when the history is very suggestive for hemorrhoids, endoscope assessment should be carried out to ensure that a rectal lesion such as proctitis or a tumor is not mimicking this presentation. Patients with ulcerative proctitis often have frequent bowel movements, but may pass only bright red blood and mucus. Radiation proctitis can present shortly after radiotherapy treatment, but is often delayed by many months or years. This condition results from chronic inflammation within the blood vessels, called endarteritis obliterans, and this indolent process underlies the delayed presentation.



Table 3. Causes of Minor Lower GI Bleed

- Very common
 - Hemorrhoids
 - Fissures
 - Other perianal disease
 - Proctitis
 - Less common
 - Neoplasia
 - Inflammatory bowel disease
 - Infectious colitis
 - Radiation colitis
 - Angiodysplasia
 - Ischemia
 - Rectal ulcer
-

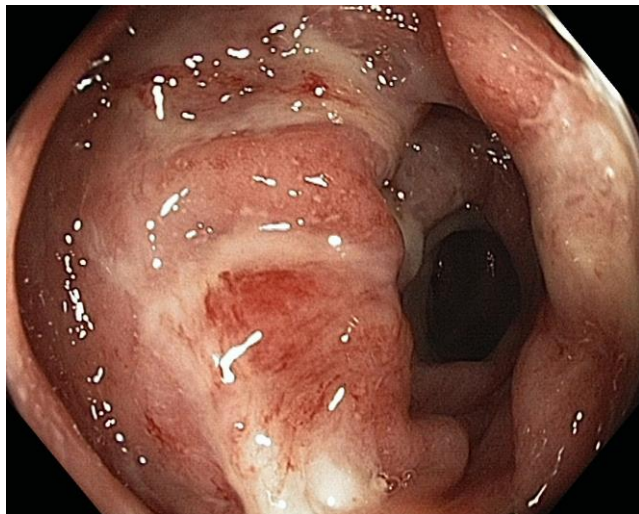


Figure 4. Endoscopic appearance of colitis. Note the diffuse reddening of the mucosa, which will bleed if touched. This patient had moderately active ulcerative colitis, but infection and other causes of colitis (eg. Ischemia) can look identical. Contrast this image with the image of ischemic colitis at the splenic flexure in Figure 2.



Chapter 12: Ulcerative Colitis and Other Conditions that cause Colitis-like Symptoms

G.K. Turnbull



1. Introduction

Ulcerative colitis (UC) along with Crohn disease are the two major inflammatory bowel diseases that affect the colon. The cause of UC is unknown, but it appears to have a genetic association with it being much more common if an individual has a relative with the disease. About 15% of UC cases have a genetic history of another relative with UC. The disease most commonly affects young adults before the age of 30, but can start in young children or in older adults. The incidence of UC has been fairly stable over the past 50 years, as compared with Crohn disease, which has had a significant increase in both incidence and prevalence.

Most patients with UC present with sudden onset of diarrhea with blood. The severity of symptoms can be quite variable. Sometimes the initial symptoms can be mild and the patient has some bleeding that then gradually clears, only to come back usually with more symptoms at a later date. Abdominal pain may also be present, but is usually mild in UC, and is mostly described as cramping pain associated with the bloody diarrhea. The disease can present with a severe exacerbation but this only occurs for the first presentation of UC in about 5% of cases. Sometimes, the patient has had mild episodes of rectal bleeding that clear, and then has a severe attack before UC is diagnosed. The disease can affect variable lengths of the colon, from just the rectum to the entire colon (pancolitis). The extent of the colon affected will often dictate how the patient presents. With more colon involved, there is more cramping with bloody diarrhea. The more severe attacks of UC are usually in persons with pancolitis. Patients who have just the rectum involved may even present with constipation, due to the inflamed rectum making it difficult for the formed stool from the proximal colon to be expelled.

The diagnosis of UC is confirmed by doing endoscopy and biopsy of the colon. Infectious causes need to be ruled out, as bacterial infections may mimic UC. After the diagnosis of UC has been made, the disease is prone to repeated flare-ups. To reduce the frequency and severity of the recurrent attacks of UC, life-long medication is usually required to control the disease ("maintenance therapy"). When the disease flares, it is important to repeat the stool cultures, especially for *C. difficile*, because this may cause flare-ups of UC without the patient previously having taken antibiotics.

1.1 Therapy

Treatment consists of oral and/or rectal 5-ASA based therapy (mesalamine or sulfasalazine) as first line therapy, for mild to moderate attacks ("flare-ups") of UC, then increasing therapy ("stepping up") depending on the response to 5-ASA therapy. The patient is usually started on 5-ASA because there are fewer side-effects with these medications and they have the additional benefit of helping to keep the disease in remission once a flare has occurred.

Sulfasalazine is usually dosed between 4 to 6 grams per day in split doses. It has frequent side-effects and for this reason, mesalamine was developed (it is the active ingredient in sulfasalazine) to try to minimize these side-effects. The dose of mesalamine is 4 to 4.8 grams per day, again in divided doses. Different coatings have been developed to deliver the 5-ASA to the colon. One coating, called MMX, allows the patient to take all their pills once a day in order to facilitate their compliance with the medication. Compliance is especially important for maintenance therapy to prevent UC flare-ups. When the sufferer



has distal disease in the rectum or rectosigmoid, 5-ASA or steroid containing enemas may be useful, either on their own or together with an oral preparation.

LEARNING POINTS:

- Ulcerative colitis and Crohn disease are common in Canada (3 per 1000 persons)
- The diagnosis is suspected from symptoms such as pain and bloody diarrhea, and is confirmed by characteristic changes on diagnostic imaging, and endoscopy with mucosal biopsies
- Most patients respond to 5-ASA compounds, which must be used long-term to reduce the frequency and severity of recurrent attacks
- Because an infection with *C. difficile* may cause an attack of UC, always culture the stools of a UC patient with recurrent symptoms
- The risk of CRC is increased in persons with UC for more than 10 years, and frequent colonoscopic surveillance is necessary

Prednisone is usually only used to control severe flare-ups of the UC and is used in oral doses of 40 to 60 mg/day, usually dosed once or twice a day (ie. 20mg PO bid). Although prednisone and other steroids are very effective in settling flares of UC, the goal of therapy should be to minimize the patient's exposure to steroid therapy, so that 5-ASA maintenance therapy controls UC activity. Prednisone should be tapered once the symptoms of the severe attack are abating, but unlike other illnesses where prednisone is used, the taper has to be gradual, usually only 5 mg per week (sometimes even more slowly) until the prednisone can be stopped. Steroids must never be used for maintenance therapy. Immunosuppressive therapy (see below) should be considered in a patient if there has been more than one UC flare in a year, which has been sufficiently severe to require steroid therapy.

The long-term complications of steroids mandate that patients with UC be on steroids as infrequently as possible and tapered off this drug once their disease flare has settled. During severe exacerbations of the disease, the patient is admitted to hospital, and IV steroids are usually used to maximize therapy and control the inflammation (bioavailability of steroid is much higher with IV than PO/PRN dosing). With severe attacks of colitis, the IV steroid is usually used for 48 to 72 hours at high dose (ie. Solumedrol 40mg bid) and the inflammation should be showing signs of improving. If the patient does not quickly improve, then alternate therapies should be considered, such as IV cyclosporine, IV/SC anti-TNF therapy, or colectomy. When the patient has a severe UC attack, they need daily examination of the abdomen, as well as abdominal views to ensure they are not developing megacolon, which is an indication for urgent colectomy.

During severe attacks, medications that can decrease intestinal contractility need to be stopped (ie) loperamide, anti-cholinergic medications, anti-spasm medications and the opiate doses used for pain control need to be minimized. Anti-motility drugs all tend to worsen the colonic inflammation, and toxic megacolon may result, an indication for urgent colectomy.

When patients have repeated attacks of colitis and the 5-ASA therapy is not controlling their colitis and preventing flares, then therapy with an immunosuppressive drug



should be considered. Imuran (azathioprine) or 6-mercaptopurine are the usual agents used to try to settle the disease flares. There is only minimal data on the use of methotrexate in UC. Immunosuppression may work best if started with steroid therapy and then the steroid tapered gradually once the Imuran has been started. These immunosuppressive agents have a slow onset of action (2-3 months). Imuran and 6-mercaptopurine are essentially the same drug, so reactions to one drug may occur with the other. Imuran is dosed at 2.5 mg/kg/day and 6-mercaptopurine is dosed at 1.5 mg/kg/day. They can cause bone marrow suppression and liver inflammation (hepatitis), so regular blood testing (CBC, alkaline, phosphatase, ALT) is needed if these drugs are to be used in order to identify if these complications are developing. If the WBC falls below 4, or if the liver enzymes become abnormal, the immune suppression will usually need to be stopped, or the dose reduced. Some patients may develop a drug fever with the drug, or can have drug-induced pancreatitis. If pancreatitis develops, the patient should not be given Imuran or 6-mercaptopurine again, because this is a type of allergic response to the drug and subsequent therapy with Imuran will lead to more severe and potentially fatal attacks of pancreatitis. Patients with UC needing immunosuppressive therapy should be followed by a specialist physician familiar with the complications of these drugs.

In the acute setting of a severe flare-up of UC, the patient may not respond to high dose steroid therapy and surgery is sometimes necessary to prevent perforation of the colon. Perforations have a high risk of mortality. After 48 to 72 hours of high dose steroids, the need for possible surgery should be considered. This drug infliximab can settle the UC flare under these circumstances and although it may not, many patients will opt for this therapy rather than undergo a colectomy. The dosage of infliximab is usually 5 mg/kg/dose given at 0, 2, and 6 weeks then given every 8 weeks after this. Again, specialist therapy is required in making this decision if infliximab therapy is needed for a patient not responding to steroid therapy. Patients should be transferred to a hospital with experienced surgeons who are familiar with colon surgery if a patient develops severe colitis and requires hospitalization and should be done early in the flare-up to facilitate a favourable outcome. If the patient does not respond to high dose IV steroids, or is unresponsive to infliximab, then surgery should be done if there is no response to avoid the patient having a colonic perforation due to severe colonic inflammation.

Surgery for UC requires the colon and rectum to be removed, so that no colonic mucosa remains to be inflamed. This is now done in a two stage operation where the colon is resected, usually leaving the rectum intact and an ileostomy created. Once the inflammation has been allowed to settle for a number of months and the patient recover from the severe inflammation, the next stage of the surgery is done.

Many patients now opt for a pelvic pouch created from the end of the ileum and anastomosed to the anus after the rectum is resected, preserving the anal sphincters. After the ileoanal pouch anastomosis had a chance to heal then the ileostomy is closed. This operation affords the patient the ability to still pass stool per anus without requiring a permanent ileostomy after total colectomy. This is a very challenging operation to do well and should only be done in centers where the surgeons specialize in colorectal surgery, to afford the patient the best chance of a good result. The main problem of this surgery is in young women who have not yet had children as there is a high rate of



infertility after this operation, presumably due to the extensive pelvic manipulation required for this operation.

2. Irritable Bowel Syndrome

Persons exhibiting symptoms from the lower GI tract are often suffering from the irritable bowel syndrome (IBS). The cause of IBS is largely unknown, but does sometimes occur after an episode of infectious diarrhea. IBS patients have no identifiable organic disease of the gastrointestinal tract, yet they experience frequent symptoms from the bowel. Large epidemiologic studies suggest that IBS occurs in at least 15% of the population. The commonest symptom that brings a patient to a doctor is abdominal pain. A positive diagnosis can be made, particularly in women, if the abdominal pain is present for at least three months in the last year, and if the pain is relieved by defecation. The abdominal pain is also associated with a change in stool consistency and stool frequency. These criteria are termed the Rome III criteria that have been shown to be reliable in making a positive diagnosis of IBS.

The following criteria are also used to help confirm a positive diagnosis. The more of these symptoms that are present, the more likely the diagnosis is irritable bowel. These symptoms are: abdominal bloating or distension, mucus in the stool, and difficult defecation. Patients who have difficulty with defecation may complain of “urgency,” with the sudden urge to pass stool and a fear of incontinence if defecation is not performed immediately. Many patients with this symptom will relate that they always identify where the toilet is when they are away from home.

The fear of incontinence can often greatly limit a patient’s ability to function normally in society. Other patients with difficult defecation may have to strain – defined as having to hold their breath and push when attempting defecation. Straining is defined as “constipation” when a patient must strain 25% or more of the time when trying to defecate. Finally, some patients describe a feeling of incomplete emptying after passing stool. This symptom has to be asked for specifically, as most patients will not spontaneously report it. Nevertheless, the symptom is commonly reported by patients with an irritable bowel.

The presence of mucus in the stool can be alarming to some patients, since they may interpret this to mean they have “colitis.” In the past, some doctors used to refer to irritable bowel as “mucus colitis,” which is a misnomer since there is no “colitis” or inflammation of the colon in irritable bowel. Mucus is a normal product of the colon, and only if mucus and blood are seen together should other diagnoses such as “colitis” be considered. The typical stool pattern described by patients with IBS is the change in stool character and frequency with the onset of abdominal pain.

Typically, patients will pass a normally formed stool (sometimes even a constipated stool) first thing in the morning. Then, with the attacks of abdominal pain, the stools become more frequent and looser, sometimes becoming liquid. Once bowel movements cease the pain is relieved, but the pain may recur again later in the day, often precipitated by eating high-fat foods or other gut stimulants (e.g., coffee). The vast majority of people with IBS have their symptoms begin in young adult life. One should consider other colonic diseases in patients over the age of 40 who develop these symptoms for the first time. Sometimes later in life patients can develop irritable bowel



after severe infectious diarrhea, but in this population as well, further investigations are warranted to ensure no other cause for the change in bowel function.

Those constipated patients who have infrequent stool alternating with occasional diarrheal stool have the most common presentation of irritable bowel syndrome. Yet there are a great many patients, almost all female, who have infrequent stool passage, and this group must be considered as separate from the usual irritable bowel syndrome patient for they may be among those rare patients with a secondary cause of constipation. IBS is a disorder affecting the entire gut, and these patients frequently have symptoms from other parts of the GI tract besides the colon, as well as from other organs. Upper GI symptoms are common in IBS; these include heartburn and dyspepsia. Dyspepsia symptoms in general occur more commonly than lower bowel symptoms, but may be due to many other causes, including reflux esophagitis, gastritis, peptic ulcer disease and, less commonly, biliary tract and pancreatic disease. When upper GI symptoms are associated with IBS, other underlying diseases must be considered.

Other associated symptoms include frequent headaches and urinary symptoms that are similar to bowel symptoms, in that patients can have urgency and frequency of urination. These symptoms are often worse at times when the bowel symptoms are troublesome. In women, irritable bowel symptoms can often be exacerbated or worsened around the time of menstruation. Indeed, bowel symptoms associated with menstruation occur in at least 50% of the normal female population.

When assessing a patient complaining of irritable bowel symptoms, remember that only a small proportion of patients with an irritable bowel present to doctors with these symptoms. Patients who consult a physician about their IBS symptoms often have psychological problems, with increased levels of distress and depression. It is important to inquire about these problems, as successful treatment often consists of dealing with the distress and/or depression that exacerbates the irritable bowel symptoms. These mental health symptoms may often be the reason that the patient has sought medical attention in the first place.

LEARNING POINTS:

- In young persons with recurrent abdominal pain associated with an altered bowel habit, and no alarm symptoms such as bleeding or weight loss, suspect IBS
- While a positive diagnosis of IBS may be made, most physicians are more comfortable performing blood and stool tests to exclude possible intestinal infection or inflammation
- The treatment of IBS is the care of the patient, as well as symptomatic management of symptoms

2.1. Differential Diagnosis

The altered bowel habits in persons with IBS include diarrhea (D), constipation, and diarrhea alternating with constipation (D/C). In the person suspected of having D-IBS, or D/C-IBS, consider other possibilities such as lactose intolerance, celiac disease, bile salt wastage, small intestinal bacterial overgrowth, or giardiasis (See Chapter 6: The small intestine).

All patients should have a thorough physical examination, looking for evidence of disease in other organ systems such as the thyroid, which can present with a change in



bowel habit. Patients with an irritable bowel will often have tenderness over the colon, particularly the sigmoid colon, on palpation. The identification of an enlarged liver or spleen or other abdominal masses necessitates further investigations for alternate diagnosis. A barium enema is rarely required in a young healthy adult with new onset of IBS symptoms. However, a patient over the age of 40 presenting with new onset IBS symptoms warrants at least a barium enema and a sigmoidoscopic examination. The barium enema should also evaluate the terminal ileum if there is pain on palpation in the right lower quadrant. A complete blood count with platelet count should be done, as an elevated platelet count is often a sensitive finding for underlying inflammation and in the presence of bowel symptoms could mean the presence of early inflammatory bowel disease. Crohn disease is more likely to present this way than irritable bowel.

The persistence of the abdominal pain, even though lessened after bowel movements, would suggest possible underlying inflammation of the gut rather than an irritable bowel. Ulcerative colitis usually presents with rectal bleeding. Rectal bleeding is not a symptom of irritable bowel and its cause must always be investigated. Fever, weight loss and symptoms that wake a patient from sleep, as opposed to early waking in the morning, are all symptoms that should be further investigated.

The presence of nocturnal symptoms, particularly with diarrhea waking the patient at night, is rarely due to an IBS. Occasionally patients with depression who have early morning waking report nighttime diarrhea, but in general further investigations are indicated.

2.2. Therapy

The therapeutic approach in IBS is as much reassurance as any specific therapies, as most patients do not have any “disease.” It is most important to do a thorough history and physical examination to ensure that the complaints are not due to any underlying disease. Once this has been confirmed, explain to the patient how the bowel can produce these symptoms and that there is no cause for concern. Since patients presenting with IBS symptoms frequently have more distress and tend to be more prone to seek medical attention for other minor medical conditions than other patients (so-called “illness behavior”), these patients may require considerable reassurance to convince them that they do not have serious disease. Part of this reassurance will be provided by screening blood tests such as a complete blood count with platelet count.

Sigmoidoscopic/colonoscopic examination will rule out most underlying early inflammatory bowel disease and any rectal pathology, particularly in patients complaining of defecation difficulties or a sensation of being unable to empty the rectum adequately. If diarrhea is present, the stool should be analyzed for pathogens.

Following these initial screening tests emphasis should be placed on the stresses present in the patient's life, which may trigger their bowel complaints. Evaluating the level of stress and taking steps to correct it will often be helpful. Many patients, particularly those who have symptoms of constipation, may be helped with a high-fiber diet (see Section 9, Chapter 10).

Drug therapy for irritable bowel is usually empiric, directed at the most troublesome symptom (ie. Pain, bloating, diarrhea, constipation). There is no single



drug that treats all the varied symptoms in irritable bowel. Occasional patients will continue to have intractable symptomatology. In this situation selected medications for specific symptoms may be helpful. Table 5 outlines some drugs that may be useful for specific symptoms. Drug therapy for IBS should always be restricted to short periods during exacerbation of symptoms, and patients should be taken off medications when they are well. As irritable bowel is a chronic condition and is probably “normal” for these patients, the chronic use of medications often reinforces the notion that they have a “disease.” Reassuring the patient that there is no association between irritable bowel symptoms and the development of more serious bowel disease such as colon cancer or inflammatory bowel disease can often alleviate some of the unreasonable yet very real concerns of many patients who present to doctors with these symptoms.

3. Microscopic Colitis

This condition has been recognized increasingly in which the patient with microscopic colitis presents with painless diarrhea. The colon appears normal on both radiologic and colonoscopic examination. The diagnosis is made from biopsies of the normal appearing colon. There are two types of microscopic colitis, “lymphocytic colitis” and “collagenous colitis.” On histological examination there is an increase in the inflammatory infiltrate of the lamina propria. In collagenous colitis, the basement membrane of the colonic mucosa is thickened by a band of collagen, and in lymphocytic colitis there is an increase in lymphocytes. The natural history of these diseases is unclear and no infective agent has been found. In most patients the disease appears to follow a benign course, but about half of patients continue to have significant diarrhea for more than two years.

The symptoms of microscopic colitis are usually controlled by antimotility agents such as loperamide, by use of 5-aminosalicylic acid–based therapies directed at the colon or oral budesonide enteric coated tablets. The most recent studies of therapy have found budesonide (Entocort) to be the most effective therapy. Cholestyramine 4 grams four times a day has also had reports of success in this condition. Glucocorticoids also control the diarrhea, but in view of the usually benign course of this illness in most patients, steroid therapy should be used only in severely symptomatic patients who cannot be controlled by other therapy.

4. Eosinophilic Colitis

Eosinophilic gastroenteritis is an uncommon inflammatory condition that affects primarily the upper GI tract and small intestine (see Chapters 4, 5 and 6). A separate condition, called “eosinophilic colitis” in which patients with connective tissue disease present with diarrhea of uncertain cause, with negative stool investigations. Like microscopic colitis, the mucosa looks normal on colonoscopy, and the diagnosis is made on mucosal biopsy. The mucosal biopsy shows increased eosinophils in the lamina propria. All patients initially respond to steroids, but not all patients resolve over time, and some may need prolonged steroid therapy. Because of its lower systemic toxicity, the use of budesonide (as with microscopic colitis) may be the best first line therapy for this rare condition.



Chapter 13: Colonic Neoplasia

G.K. Turnbull, M. Burnstein, J.A. Rowe and S.J. Vanner

1. Introduction

Colorectal cancer (CRC) is the second most common cancer (after lung cancer) in men and women combined in Canada . Unlike lung cancer, CRC has a high survival rate in patients diagnosed before it has spread beyond the confines of the bowel wall. Since CRC is a very common cancer, has a high survival rate with early curative surgery and is poorly responsive to other forms of cancer therapy, a high index of suspicion must be maintained in approaching patients with symptoms of colonic dysfunction (Table 1), especially if they are over the age of 40, when the incidence of CRC begins to rise. Increased CRC risk is also seen in patients with ulcerative colitis or Crohn's colitis, a history of uterine or ovarian cancer, or a family history of CRC or colonic adenomas (including familial polyposis syndromes).

The tumor, node, and metastasis (TNM) staging system has largely replaced the older Dukes' classification for staging CRC after surgical resection. Table 2 details the TNM staging system for CRC and compares it to the older Dukes' A to D classification. Other factors that increase the mortality from CRC besides the stage of the tumor, are poorly differentiated histology and vascular histological invasion by the tumor at the time of resection. Other poor prognostic indicators for CRC are cancers that have perforated, are adherent to adjacent organs and colon cancer presenting with complete bowel obstruction. Early recognition is of the utmost importance to try to identify CRC at an early, curative stage. Therefore, patients with intermittent symptoms are as important to investigate as patients with persistent symptoms, and the story of occasional blood in the stool in a patient over 40 years of age should not be attributed to local anorectal disease without first excluding a more proximal lesion.

Table 1. Presenting features of colon cancer

-
- Abdominal pain, including symptoms of bowel obstruction
 - Change in bowel habit
 - Abdominal complaints of recent onset
 - Rectal bleeding or melena stool
 - Abdominal mass
 - Iron deficiency anemia
 - Hypokalemia
-



Table 2. Colorectal adenocarcinoma staging*TNM stage Dukes' stage Tumor invasion 5 year survival*

T0N0M0 N/A Mucosa only 100%

T1N0M0 A Submucosa 90–95%

No lymph nodes or distant metastases

T2N0M0 B1 Muscularis involved 85%

No lymph nodes or distant metastases

T3-4N0M0 B2 Tumor to serosa (T3) or through 70–75%

serosa (T4)

No lymph nodes or distant metastases

T2N1M0 C1 Muscularis involved but not to serosa 35–65%

Lymph nodes involved

T3-4N1M0 C2 Tumor to serosa (see T3/4 above) 35–65%

Lymph nodes involved

TxNxM1 Distant metastases (liver) regardless <5%

Many patients with CRC may present with no gastrointestinal symptoms, but rather with an iron deficiency anemia due to chronic bleeding from the tumor. Patients may not see blood in the stool or note a melena stool, particularly when there is a right-sided colonic lesion. A change in bowel habit, often with constipation alternating with diarrhea, may be the first sign of obstructive symptoms from a CRC, and should never be ignored in a patient over 40 years of age with a recent onset of these symptoms. Some patients may present with primarily diarrhea if they have a high output of mucus and fluid from the tumor; in this instance the tumor is often sessile in appearance (see below) and large, with the histology of a villous adenoma. Some patients may have hypokalemia due to the large amounts of mucus secretion from the tumor.

Carcinoembryonic antigen (CEA) is a tumor marker that has limited use in diagnosing CRC but is often useful in following patients with CRC. A high CEA level before surgery often suggests a poor prognosis with probable metastases. A CEA level that does not fall to normal levels one month after surgery suggests that all the cancer has not been resected. After surgery, if the CEA falls, then regular monitoring of CEA levels may be useful to identify patients with early cancer recurrence. Sometimes a search for metastases will reveal a solitary lesion in the liver that may be surgically resectable, or with the early use of chemotherapy, may lead to a cure of the cancer.

2. Polyp–Carcinoma Sequence

Colorectal cancer can be prevented: there are a variety of histological types of colonic polyps, such as juvenile, inflammatory, hyperplastic, and adenomatous. For the majority of colorectal cancer (CRC) patients, the adenocarcinoma arises from an



adenomatous polyp. Polyps of 2 cm or larger have about 50% incidence of cancer, compared to a 1% risk in adenomas less than 1 cm in size.

Adenomatous polyps are a premalignant condition, and their identification and removal before becoming malignant prevents the development of CRC. These polyps can arise anywhere in the colon, but (as is the case for CRC) they are more frequently seen in the left colon. The majority of polyps are completely asymptomatic, but the occurrence of occult bleeding does increase as they grow. Unfortunately, polyps can still be missed, even with occult blood testing of the stool, since the blood loss may be intermittent. Examples of different polyps are seen in Figure 4. Three histologic types of adenomatous polyps occur: tubular, tubulovillous and villous. The malignant potential is greatest in villous polyps (40%) and lowest in tubular polyps (5%), with an intermediate risk in tubulovillous polyps (22%). The malignant potential may also be described pathologically .

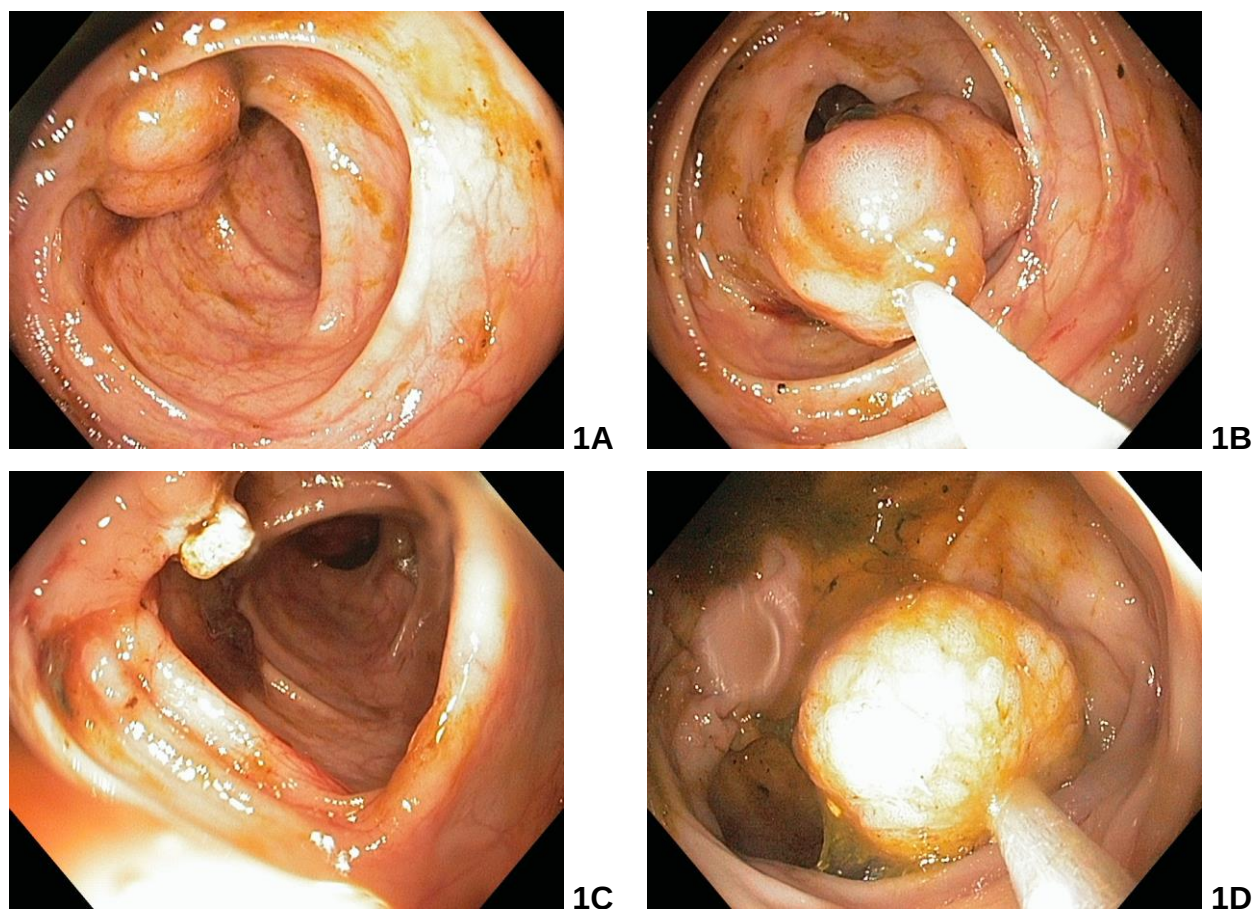


Figure 1. Demonstration of adenomatous polyp removal at colonoscopy.

Figure 1A. Sigmoid colon polyp.

Figure 1B. Polyp snared and ready to transect the stalk of the polyp using electrical current passing through the metal snare wire to completely remove the polyp. The normal tissue of the stalk is seen to the right of the snare in the middle of the image.



Figure 1C. The base of the resected polyp with the cautery burn evident on the remainder of the stalk.

Figure 1D. The polyp has been grasped in a Roth net, passed down the operating channel of the colonoscope after the snare is removed and polyp is now removed from the colon to be sent for pathology diagnosis. because the degree of “dysplasia”: can indicate a greater the risk of malignancy with higher grade dysplasia (ie. High grade versus low grade dysplasia). These polyps can often be completely removed by snare polypectomy at colonoscopy if they are pedunculated on a stalk, but sessile polyps that carpet a wide area of colonic mucosa (often villous polyps) can usually be completely removed only by colonic resection surgery.

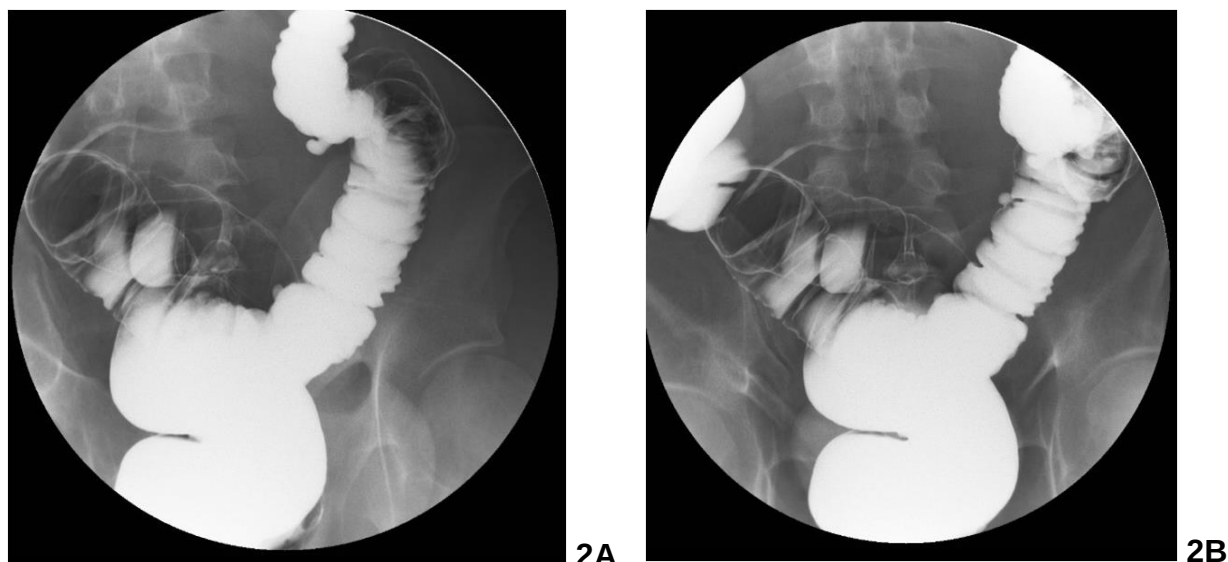


Figure 2A. & 2B. Filling defect in the mid sigmoid on barium enema, consistent with a 16 mm pedunculated polyp. The white arrow identifies the polyp.” Again, I have included the original image as well as the image on a Powerpoint slide to indicate where the arrow should go.

Since polyps precede cancer and removal of polyps “cures” the CRC, screening colonoscopy reduces the incidence of cancer. Other polyps as well may be present at the initial or index screening colonoscopy, and polyps and cancer tend to recur. This sets the stage for the rationale for performing follow-up surveillance colonoscopies (colon cancer surveillance program). The best time interval for this surveillance when polyps have been found in the past is probably every five years; longer intervals between surveillance colonoscopies may be safe but have yet to be tested. The cost-effectiveness of screening all persons over the age of 50 has not been proven but screening has been shown to reduce the incidence of CRC, especially in high risk groups for developing colon cancer.



LEARNING POINTS

- Because of the colonic polyp CRC sequence, CRC may be prevented by the early detection of adenomatous polyps, followed by a surveillance program
- Colonoscopy is the “gold standard” for screening for colonic polyps
- All persons over the age of 50 should have a colonoscopy
- Persons with a family history of colonic adenomas or CRC should have a colonoscopy, often before the age of 50

Screening for CRC has become very controversial as to the correct intervals, who to screen and the best tools to use for screening. The Canadian Association of Gastroenterology has published guidelines for CRC screening; there are guidelines published by the American Gastroenterological Association and the British Society of Gastroenterology.

3. Colon Cancer Screening

Particular conditions have been associated with an increased risk of CRC. All patients with the following conditions require some form of regular colon surveillance to detect polyps/cancer at its earliest stage to improve survival. The autosomal dominant “polyposis” syndromes of Familial Adenomatous Polyposis (FAP), Gardner’s syndrome and Turcot’s syndrome are now recognized to all be various expressions of disease caused by mutations of the APC gene (autosomal dominant inheritance). These conditions are manifested by early onset (usually before age 30) of innumerable colonic adenomatous polyps that eventually and invariably lead to CRC usually before age 40. Since the colon has too many polyps to remove by endoscopy-guided polypectomy these patients are referred at an early age for total proctocolectomy to remove the risk of CRC.

Most patients opt for an ileal pouch with anastomosis to the anal sphincters (ileal pouch, anal anastomosis IPAP), rather than an ileostomy (Brooke’s procedure), with the effluent. After colectomy these patients still need regular upper GI endoscopic surveillance, to detect, biopsy, and remove adenomatous polyps from the stomach and duodenum. They also need the ileal pouch endoscopically examined to ensure there are no changes from the transitional mucosa left behind at the anastomosis of the ileal pouch to the anus.

Genetic screening should be undertaken on persons with FAP, and their family members, looking for mutations in the FAP gene, which is the cause of this autosomal dominant disease.

There are other families (site-specific colorectal cancer, family cancer syndrome) that have a high risk of colon cancer (autosomal dominant inheritance), with more than two first-degree relatives in at least two generations, having had colon cancer or adenomatous polyps and at least one of the relatives has to be under age 50. This disease is called hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. All patients should be entered into a colon cancer surveillance program of colonoscopy and/or air contrast barium enema starting at age 21. Patients with HNPCC are to have the colon screened every two years until age 40, when they should have yearly screening. Ideally, screening is done with colonoscopy if possible as



polyps are frequently encountered and need to be removed when found. Female patients with HNPCC also have an increased risk of endometrial and ovarian cancer and need yearly pelvic ultrasound and/or vaginal ultrasound after age 40 to identify suspicious lesions as early as possible.

The other group of patients at increased risk of cancer who should all be screened are those patients who have had a colon cancer resected. Colonoscopy should be done either preoperatively or within a year of surgery. It should be repeated three years post surgery, and then every five years if there are no polyps or evidence of recurrent tumor. If there is any concern about complete resection of the original tumor, earlier surveillance would be recommended (less than one year after surgery).

Also at a high risk for CRC are patients with chronic ulcerative colitis (UC) for more than 8 to 10 years; this risk also appears to be present in patients with Crohn's pancolitis. The patients at highest risk are those who have had total colon involvement, as well as and those with disease up to and including the hepatic flexure (subtotal colitis). Patients with proctosigmoiditis are at least risk – probably not greater than the general population. Curiously, the risk of CRC does not correlate with the degree of disease activity. Therefore, patients with just one bout of proven subtotal ulcerative colitis would have an increased risk of CRC after 8 to 10 years of disease, and the younger the patient at the time of onset of his or her disease, the greater the cumulative risk of cancer will be for that patient. Unlike those who experience the “polyp–carcinoma sequence,” patients with UC do not develop adenomatous polyps before they develop cancer. Therefore, after the first 8-10 years of UC, they require colonoscopy about every one to two years, with multiple endoscopic biopsies of the colon performed to identify dysplasia of the mucosa. Particular attention should be paid to “elevated” or “flat” lesions seen at colonoscopy, where the incidence of early colon cancer is high. If there is dysplasia, either “high grade” or “low grade,” colectomy should be recommended to the patient.

Screening for CRC is also recommended for all “average risk” persons age 50 years or above. If a person has a first degree family member with CRC younger than age 60 years, then the person is at increased risk of colorectal cancer and imaging of the colon with colonoscopy or CT colonography should be considered. Otherwise, all individuals over age 50 should have at least stool testing for occult blood and/or flexible sigmoidoscopy.

IMAGING OF RECTAL CANCER

Current management strategies for rectal cancer include preoperative radiation and chemotherapy for patients at increased risk of local recurrence. Accurate preoperative staging helps to stratify the patient's risk. Superficial rectal cancers can be imaged with endorectal ultrasound. Larger tumours require a high spatial resolution MRI with a dedicated phased array coil. This allows evaluation of the rectal wall, the mesorectal fascia, local invasion of pelvic structures and the presence of regional adenopathy. These techniques can identify the patients who will benefit from preoperative chemotherapy or radiotherapy.



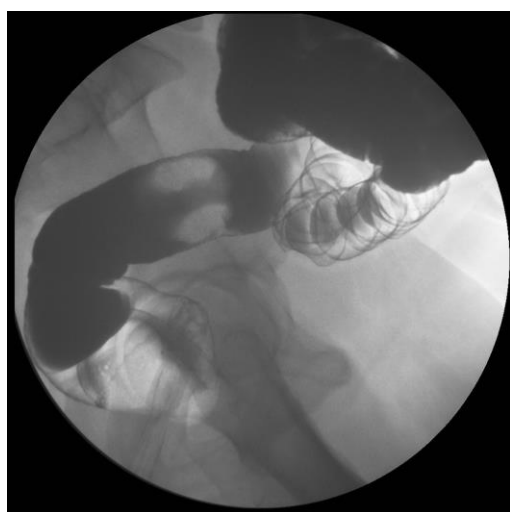


Figure 3A

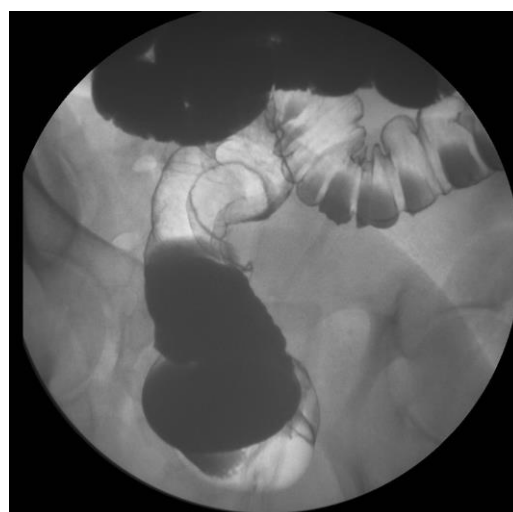
Figure 3A is an axial T2 weighted MRI image demonstrating a circumferential enhancing mass from the 5 o'clock to 1 o'clock position in the rectum (long white arrows). There is transmurial extension and local adenopathy in the mesorectal fat (short black arrows). Figure 3B is a sagittal T2 weighted MRI image which shows the craniocaudal extent of the mid to high rectal tumour (white arrows).



Figure 3B



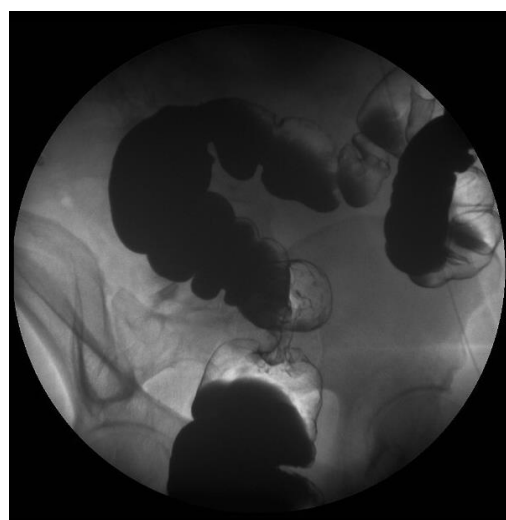
4A



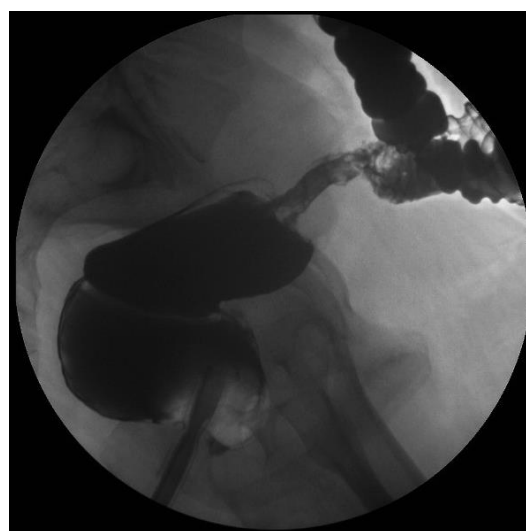
4B

Figure 4. A 5 cm broad based filling defect in the upper rectum on double contrast barium enema.

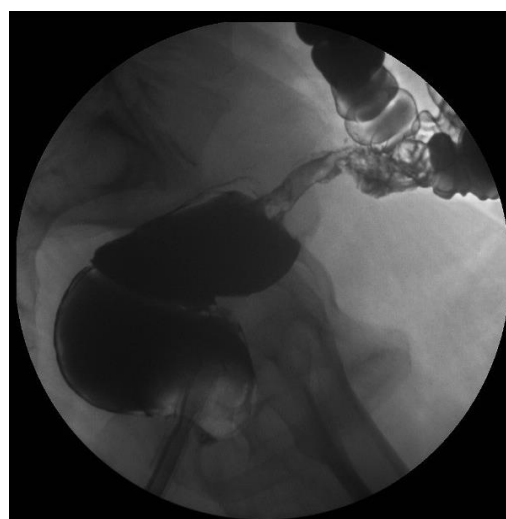




5A



5B



5C

Figure 5. Barium enema xray images of an annular lesion in the rectosigmoid colon compatible with primary carcinoma

4. Colonic Obstruction

Acute colonic obstruction is a surgical emergency that must be recognized early and dealt with expeditiously in order to avoid the high fatality rate due to colonic perforation. The highest risk patients for associated colonic perforation are those with an intact ileocecal valve (this does not allow air to reflux back into the small bowel from the obstructed colon). The cecum is the most frequent colonic site of perforation, because wall tension is highest in the bowel with the largest diameter (Laplace 's law).

Patients with more chronic colonic obstruction usually have pain as a prominent symptom, with constipation often preceding the complete obstruction. Patients may initially present with diarrhea as the bowel distal to the obstruction empties. Alternatively, the diarrhea may be persistent, especially with a partial obstruction, because of the increased intestinal secretion proximal to the obstruction, or to “overflow” diarrhea, the passage of proximally secreted fluid which leaks around an obstruction from, for example, stool or tumour.



The small intestine is the most common site of intestinal obstruction because of its narrower caliber of the bowel. Similarly the left colon is the most common site for colonic obstruction, especially since the stool is more formed in the left colon and unable to pass through a narrowed lumen.

On physical examination the general state of the patient depends upon the duration of the obstruction. With a recent sudden obstruction the patient will be in extreme pain, will often have distention of the abdomen (if the ileocecal valve is intact) and they may initially describe diarrheal stool as the bowel distal to the obstruction is emptied. Abdominal palpation may demonstrate a mass lesion at the site of the obstruction. Prompt identification of the site of obstruction is mandatory, with the use of supine and erect abdominal x-rays.

An urgent surgical consultation is required if there is a complete colonic obstruction: the rectum will be empty of air with dilation of more proximal colon. Many patients present with a more gradual history. If they have had protracted diarrhea up to the point of obstruction, the amount of abdominal pain may be less. They may have abdominal distention, but be less tender on abdominal exam. They will often show signs of dehydration. Fever and an abdominal mass is particularly common in patients with diverticulitis and a resulting colonic obstruction.

A third type of colonic obstruction can be seen that is actually a form of ileus limited to the colon, and is sometimes referred to as Ogilvie's syndrome. These patients are most often seen in intensive care units, but the condition can also occur postoperatively (even when no bowel surgery has been performed). As with a "mechanical" bowel obstruction (described above), patients with Ogilvie's syndrome may have marked abdominal distention. Frequently they have little abdominal pain, and the abdominal x-rays show a picture of dilated colon with impaired movement of air into the distal colon.

Once a diagnosis of colonic obstruction has been made, the site of obstruction should be determined by plain abdominal x-rays and/or with a water soluble contrast enema (such as iohalamate meglumine) to identify whether urgent surgery is indicated. If investigations do not confirm obstruction of the colon, colonic ileus can often be treated safely by neostigmine 2.0 to 2.5 mg IV. Bradycardia may occur with this medication, and all patients must receive cardiac monitoring.

The majority of patients respond well to neostigmine and this avoids the need for urgent colonoscopy and the increased risk of perforation of the colon due to poor visualization in the unprepared colon. However, if the endoscopist is able to decompress the lumen by suctioning the excess air, a decompression tube can sometimes be placed high in the colon to facilitate removing colonic air following the procedure.

There are many causes of colonic obstruction (Table 4). Colon cancer and diverticulitis are the most common causes. Most colon cancers that obstruct are in the left colon. They cause circumferential disease or "apple-core" lesions (so called because of the irregular mucosal appearance with luminal narrowing seen at x-ray). Diverticulitis commonly occurs in the sigmoid colon, where diverticular disease is most common. The acute abscess formation with swelling of the inflamed diverticulum compresses and obstructs the affected sigmoid colon. The person with colonic obstruction due to Ogilvie's syndrome may initially have been considered to be due to a



cancer or diverticulitis, but abdominal film and contrast x-ray demonstrates a patent lumen.

Less common causes of colonic obstruction are hernias, in which a loop of colon (usually sigmoid) becomes strangulated and the bowel is acutely obstructed. This is a much more common cause of small bowel obstruction. Strictures in the colon can also be associated with obstruction, especially when they occur in the left colon. These can occur with Crohn's colitis, after a bout of ischemic colitis or at the site of anastomosis following colonic surgery. If possible, this later cause of obstruction should always be visualized endoscopically, since most colonic resections are for cancer and the possibility of a local cancer recurrence can complicate a postsurgical stricture.

Intussusception can occur in the colon, and in adults it almost always occurs at the site of a polyp, which "leads" the intussusception. Typically, this will cause intermittent acute bowel obstruction associated with severe pain and often rectal bleeding from the vascular compromise produced in the intussuscepting bowel. Because of the intermittent nature of the obstruction, a diagnosis may not be made until after repeated attacks. A barium enema should always be considered in this setting, as it identifies the mucosal lesion "leading" the intussusception and can occasionally be used to reduce the intussusception without the need for urgent surgery. Volvulus of the colon tends to happen in the cecum and/or the sigmoid colon, because the mesentery is long and redundant in these areas and cause the bowel to rotate upon itself. This can be a surgical emergency, since the affected bowel will strangulate if the volvulus is not relieved quickly.

Table 3. Causes of colonic obstruction

➤ Common	➤ Others
○ Left-sided cancer ○ Diverticulitis ○ Ogilvie's syndrome	○ Hernia ○ Strictures ○ Crohn's ○ Postischemic ○ Postsurgical ○ Intussusception ○ Volvulus ○ Adhesions

Again, an urgent barium enema may be able to reduce the volvulus, thus allowing a more elective surgical procedure to correct the problem. A sigmoid volvulus will usually be reduced by this approach, and success with colonoscopic decompression of a sigmoid volvulus has been reported. A cecal volvulus may not be easily treatable with either a barium enema or colonoscopic therapy. Thus, surgical advice should be sought urgently if cecal volvulus is diagnosed.

Adhesions are often described as a common cause of bowel obstruction, but this is probably true only for small bowel obstruction. Since much of the colon is retroperitoneal or on a short mesentery, adhesive disease with obstruction of the colon is rare. However, it can occur, particularly in the sigmoid colon if the mesentery is quite long, particularly after pelvic operations.



4.1. Megarectum

When the rectum is enlarged, further investigations are required to exclude other causes, particularly Hirschsprung's disease. The majority of patients with constipation and a dilated rectum and/or colon at proctosigmoidoscopy or barium enema have idiopathic or acquired megarectum.

A useful guideline for the diagnosis of a "megarectum" is a rectal diameter of greater than 6 cm on a lateral film at the level of the S2 vertebral body. These patients can often present in childhood (many of them presenting with encopresis) and in the elderly with a fecal impaction. The cause of the megarectum is unknown, but if the onset is in childhood it may be the result of chronic stool holding by the child, leading to progressive distention of the rectum and eventual loss of awareness of rectal distention. Once this has occurred the child can no longer recognize when stool is present in the rectum. The distention of the rectum causes chronic inhibition of the resting tone of the internal anal sphincter. This leads to the loss of control of liquid or semisolid stool that passes by the fecal impaction without the patient being aware of it.

4.2. Hirschsprung's Disease

The majority of persons with this disorder present soon after birth or in early childhood. wherein Hirschsprung's disease, variable lengths of distal colon have no myenteric plexus neurons. The distal colon remains contracted due to this loss of neurons, and the inability to dilate, whereas the normal proximal colon dilates as it fills with stool. Most of these patients present early in life with constipation and colonic obstruction, and require surgery.

However, a few patients have a very short segment of denervated distal colon, so that they can overcome the obstruction by forcing stool out of the rectum. They usually have lifelong constipation; the normal rectum proximal to the denervated segment dilates over time so that the patient presents with constipation and a "megarectum." These patients rarely have the fecal incontinence or fecal "soiling" as seen with idiopathic megarectum, since the internal anal sphincter and denervated distal rectum maintain a high resting tone.

Anorectal manometry, will demonstrate an abnormal rectoanal inhibitory reflex (Figure 9). However, a definite diagnosis requires deep rectal biopsy from the denervated segment, which will show absence of the myenteric plexus ganglion cells and hypertrophy of nerve fiber bundles.

It should be added that an identical condition can be acquired with Chagas' disease from South America, which attacks the myenteric plexus and other autonomic ganglion cells. Persons with Chagas' disease can also present with achalasia, intestinal pseudo-obstruction, as well as cardiac arrhythmias. These patients will also have an absent rectoanal inhibitory reflex if the disease involves the rectal myenteric plexus.



Chapter 14: Evaluation of Defecation and Anorectal Complaints

M. Burnstein, G.K. Turnbull

This section will review the symptoms associated with anorectal pathology, and the techniques of anorectal examination.

1. History

As in most of medicine, taking a careful history is the most productive step in leading to a diagnosis. In the evaluation of the patient with anorectal complaints, there are a limited number of questions to be asked.

1.1. Pain

There are three common lesions that cause anorectal pain: fissure in ano, anal abscess, and thrombosed external hemorrhoid. If the pain is sharp, and occurs during and for a short time following bowel movements, a fissure is likely. Continuous pain associated with a perianal swelling usually stems from thrombosis of perianal vessels, especially when there is an antecedent history of straining, either at stool or with physical exertion. An anal abscess will also produce a continuous, often throbbing pain, which may be aggravated by the patient's coughing or sneezing. Anorectal abscesses are generally associated with local signs of inflammation. The absence of an inflammatory mass in the setting of severe local pain and tenderness is typical of an intersphincteric abscess. The degree of tenderness usually prevents adequate examination, and evaluation under anesthesia is necessary to confirm the diagnosis and to drain the pus.

Anal pain of any etiology may be aggravated by bowel movements. Tenesmus, an uncomfortable desire to defecate, is frequently associated with inflammatory conditions of the anorectum. Although anal neoplasms rarely produce pain, invasion of the sphincter mechanism may also result in tenesmus. Tenesmus with urgency of evacuation suggests proctitis.

Transient, deep-seated pain that is unrelated to defecation may be due to spasm of the levator ani muscle ("proctalgia fugax"). Anorectal pain is so frequently, and erroneously, attributed to hemorrhoids, that this point bears special mention: pain is *not* a symptom of uncomplicated hemorrhoids. If a perianal vein of the inferior rectal plexus undergoes thrombosis, or ruptures, an acutely painful and tender subcutaneous lump will appear. This is the "thrombosed external hemorrhoid." Internal hemorrhoids may prolapse and become strangulated to produce an acute problem of anorectal pain, tenderness, and mucous, bloody discharge. Gangrene and secondary infection may ensue.

1.2. Bleeding

The nature of the rectal bleeding will help determine the underlying cause. However, the clinician must remember that the historical features of the bleeding cannot be relied upon to define the problem with certainty. Bright red blood on the toilet paper or on the outside of the stool, or dripping into the bowl, suggests a local anal source, such as a fissure or internal hemorrhoids. Blood that is mixed in with the stool, or that is dark and clotted, suggests sources proximal to the anus. Melena is always due to bleeding from more proximal pathology in the colon, small intestine, duodenum, or stomach. A history of bleeding associated with painful defecation, suggests a fissure. The same bleeding pattern without pain suggests internal hemorrhoids; this may be



associated with some degree of hemorrhoidal prolapse. Bleeding and diarrhea may occur with inflammatory bowel disease.

When bleeding is associated with a painful lump and is not exclusively related to defecation, a thrombosed external hemorrhoid is likely. Bleeding associated with a mucopurulent discharge and tenesmus may be seen with proctitis, or possibly with a rectal neoplasm.

Bleeding per rectum is an important symptom of colorectal cancer, and although this is not the most common cause of hematochezia, it is the most serious and must always be considered. This does not mean that every patient who passes blood must have total colonoscopy. If the bleeding has an obvious anal source, it may be prudent not to proceed with a total colon examination, especially in a patient at low risk for colorectal neoplasms (i.e., age under 50 years; no history of Crohn's or ulcerative colitis; no family history of colon cancer; and no personal history of colorectal neoplasms). However, if bleeding persists after treatment of the anal pathology, more ominous lesions must be excluded.

1.3. Prolapse

In evaluating protrusion from the anal opening, there are several relevant questions: Is the prolapse spontaneous or exclusively with defecation? Spontaneous prolapse is usually from hypertrophied anal papillae or complete rectal prolapse, rather than from internal hemorrhoids. Does the prolapsing tissue reduce spontaneously (as with second-degree internal hemorrhoids), or does it require manual reduction (as with third-degree internal hemorrhoids or with many cases of complete rectal prolapse)? The patient may be able to describe the size of the prolapsing tissue, and this may suggest the diagnosis. Complete rectal prolapse (procidentia) must be distinguished from mucosal prolapse or prolapsing internal hemorrhoids. Procidentia occurs mainly in women (female:male = 6:1), with a peak incidence in the seventh decade. Procidentia is often associated with fecal incontinence. In later stages, protrusion occurs even with slight exertion from coughing or sneezing. The extruded rectum becomes excoriated, leading to tenesmus, mucus discharge and bleeding.

Examination of the patient with procidentia usually reveals poor anal tone, and with the tissue in a prolapsed state, the mucosal folds are seen to be concentric, whereas with prolapsed hemorrhoids there are radial folds. Rarely, a large polypoid tumor of the rectum may prolapse through the anal canal.

1.4. Perianal mass

A painful perianal lump may be an abscess, or a thrombosed external hemorrhoid.

Knowing whether there has been a discharge of blood or pus may be helpful. An intermittent mass suggests a prolapsing lesion. External or "skin" tags are very common deformities of the anal margin. They may be the result of previous or active fissure disease, or the sequelae of a thrombosed external hemorrhoid. Condylomata acuminata – or venereal warts – are caused by a sexually transmitted virus. The perianal skin is frequently affected, and the condition occurs with greatest frequency in men who have sex with men.

The differential diagnosis of a perianal mass also includes benign and malignant neoplasms.



1.5. *Pruritus ani*

Itching is commonly associated feature of many anorectal conditions, especially during the healing phase or if there is an associated discharge. Pruritus ani may also be an isolated symptom, or the patient's primary complaint. As a chief complaint, pruritus may be caused by infections (e.g., pinworms, condylomata, Candida) or skin conditions (e.g., contact dermatitis, psoriasis).

More commonly, no specific underlying pathology is identified, and the problem is idiopathic, and is treated symptomatically.

Idiopathic pruritus ani is more common in men, and is typically worse at night. When chronic, the characteristic changes of hypertrophy and lichenification, nodularity, scarring and fissuring of the skin become apparent.

1.6. *Discharge*

Although mucus is a normal product of the colorectal mucosa, it is not normally seen in the stool. Increased mucus may be the result of proctocolitis or a colorectal neoplasm, especially a villous adenoma of the rectum. Both inflammatory and neoplastic conditions may present with mucus and blood. Phosphate enemas are irritating, and often produce copious production of mucus. Patients with the irritable bowel syndrome may complain of mucous containing stools. Mucus staining of the underclothes may be associated with prolapsing rectal tissue.

When the staining has a fecal component, or when there is associated inability to control gas (the passing of flatus), or to discriminate gas from solids within the rectum, a disturbance of the continence mechanism exists. The frequency of "accidents" (from incontinence), or the need to wear pads during the day or night, will help indicate the magnitude of the problem. The discharge may arise from an obvious external lesion – e.g., blood from a thrombosed external hemorrhoid, or pus from an abscess, from the external opening of a fistula, from a pilonidal process or from perianal hidradenitis suppurativa.

Other issues that will prove helpful in coming to a diagnosis of anorectal pathology include bowel habits, associated medical conditions, medications, sexual practices, travel history and family history.

2. **Examination**

The patient about to undergo examination of the anorectum may not only be embarrassed, but also afraid of impending pain and discomfort. Explanation of the examinations to be performed, and reassurance, will lessen the patient's anxiety and contribute greatly to patient cooperation.

Some physicians prefer that the patient will have been given an enema to clear stool from the rectum.

The four steps in anorectal evaluation are inspection, palpation, anoscopy and proctosigmoidoscopy.

2.1. *Positioning*

The patient is placed either in the left lateral position, or preferably in the prone-jackknife position. The prone-jackknife position requires a special table that tilts the head down and raises the anorectal region, with the buttocks tending to fall apart. This provides the best and easiest access to the area for the examiner, although patient



comfort may be less. The left lateral (Sims') position has the advantages of patient comfort and of being suitable for any examining table, bed or stretcher. The patient's buttocks are allowed to protrude over the edge of the table, with hips flexed and knees slightly extended. The examiner may sit or stand. The patient is unable to see "what's going on back there," and it is important to continually explain what you are doing and what can be expected.

2.2. Inspection

Looking at the anal area may reveal external pathology. The resting anal aperture should be observed: a patulous opening may be seen with procidentia, sphincter injury or neurologic abnormality. Straining and squeezing by the patient may provide information about anorectal function. Gentle spreading of the buttocks may elicit pain in a patient who has an anal fissure. Asking the patient to strain down may show protruding: internal hemorrhoids or procidentia. However, if procidentia is suspected, it should be sought with the patient squatting or sitting at the toilet.

2.3. Palpation

A disposable plastic glove and water-soluble lubricant are required. The patient is told that a finger will be gently placed into the rectum. While one hand separates the buttocks, the index finger is placed on the anal verge, and with the patient bearing down, (thereby relaxing the anus), the digit is advanced into the anal canal. The patient should be cautioned that they may feel as if they need to have a bowel movement.

A methodical approach is best. Palpation anteriorly checks the prostate in males, and the cervix in females. The finger then sweeps backward and forward to palpate the rest of the circumference of the anorectum. This may be the only part of the examination that identifies submucosal lesions, which may easily go undetected by endoscopy. Resting tone, the patient's ability to squeeze, the location of tenderness, or a palpable abnormality should be precisely recorded.

2.4. Anoscopy

The anoscope is the optimal instrument for examining lesions of the anal canal. It is not a substitute for proctosigmoidoscopy, and the proctosigmoidoscope does not provide as satisfactory a view of the anal canal as does the anoscope. The best type of anoscope instrument is end-viewing, with an attached fiberoptic light source.

2.5. Proctosigmoidoscopy

The rigid 25 cm sigmoidoscope (or proctoscope) is arguably the best instrument for examining the rectum. A barium enema, because of the balloon-tipped catheter used in administering the contrast material, does not adequately evaluate the rectal ampulla, and is never a sufficient workup of a lower GI complaint. A variety of rigid sigmoidoscopes are available: disposable or reusable, in a range of diameters (1.1 cm, 1.9 cm, 2.7 cm), and with proximal or distal lighting. The 1.9 cm instrument provides good visibility with minimal patient discomfort. The instrument includes a 25 cm tube, a magnifying lens, a light source, and a bulb attachment for air insufflation. Long swabs may be helpful in maintaining visibility, but suction is best. The long swabs are also useful to determine if there is mucosal friability.



A single Fleet® enema provides excellent preparation of the distal bowel and should be used just before the examination. The Fleet® enema may produce transient mucosal changes, and if inflammatory bowel disease is suspected, it should be avoided. The digital examination has set the stage for instrumentation by permitting the sphincter to relax. With the tip well lubricated, the sigmoidoscope is inserted and passed up into the rectum. As always, the patient is informed of what is being done, and is reassured that the sensation of impending evacuation is caused by the instrument, and that the bowels are not about to move.

Air insufflation should be kept to a minimum, as it may cause discomfort, but it is of value both on entry and on withdrawal in terms of demonstrating the mucosa and lumen and in assessing rectal compliance and the presence of normal sensation of rectal distention. Advancement should occur only with the lumen, clearly in sight. When the lumen is “lost,” withdraw and redirect the sigmoidoscope in order to regain visualization of the lumen. As the rectosigmoid is reached (approximately 15 cm from the anus), the patient should be warned of possible cramping discomfort that will disappear as the scope is removed. Sometimes, even with experience, the rectosigmoid angle cannot be negotiated, and the examination should be terminated. Most importantly, the patient should not be hurt or caused significant discomfort. The scope should be withdrawn making large circular motions, carefully inspecting the circumference of the bowel wall, flattening the mucosal folds and valves of Houston. The posterior rectal wall in the sacral hollow must be specifically sought out, or it will be missed.

In most large studies, the average depth of insertion of the rigid sigmoidoscope is 18–20 cm; the full length of the instrument is inserted in less than half the patients. Perforation of the normal rectum by the sigmoidoscope is extremely rare (1 in 50,000 or less). However, advancing the instrument or insufflating air may be hazardous in settings such as inflammatory bowel disease, radiation proctitis, diverticulitis and cancer. Of course, biopsy and electrocoagulation have to be performed with care and with knowledge of the technique and equipment. The significance of bacteremia following anorectal manipulations is controversial, and has been reported in 0–25% of proctoscopies.

3. Specific Anorectal Problems

This section will briefly review some of the more common anorectal problems.

3.1. Hemorrhoids

3.1.1. Background

The upper anal canal has three sites of thickened submucosa containing arterioles, venules and arteriovenous communications. These three vascular “cushions” are in the left lateral, right anterior and right posterior positions. Minor cushions may lie between the three main ones. The cushions are held in the upper anal canal by muscular fibers from the conjoined longitudinal muscle of the intersphincteric plane. Hemorrhoids exist when the anal cushions prolapse after disruption of their suspensory mechanism, or when there is dilation of the veins and arteriovenous anastomoses within the cushions. There are various theories for the development of internal hemorrhoidal disease: raised intra-abdominal pressure, pressure on the hemorrhoidal veins by an



enlarging uterus, poor venous drainage secondary to an overactive IAS, or straining at stool with a resultant downward displacement of the cushions.

Skin tags are projections of skin at the anal verge. They may be the result of previous thrombosed external hemorrhoids, fissure-in-ano, or inflammatory bowel disease. *External hemorrhoids* are dilated veins of the inferior hemorrhoidal (rectal) plexus. This plexus lies just below the dentate line, and is covered by squamous epithelium. *Internal hemorrhoids* are the symptomatic, enlarged submucosal vascular cushions of the anal canal. The cushions are located above the dentate line, and are covered by columnar and transitional epithelium. First-degree hemorrhoids produce painless bleeding but do not protrude from the anal canal. Anoscopy, first-degree hemorrhoids are seen to bulge into the lumen. Second-degree hemorrhoids protrude with bowel movements, but reduce themselves spontaneously. Third-degree hemorrhoids prolapse outside the anal canal, either spontaneously or with bowel movements, but require digital reduction. Fourth-degree hemorrhoids are always prolapsed, and cannot be reduced.

3.1.2. Diagnosis and treatment

3.1.2.1. Thrombosed external hemorrhoids

As a rule, external hemorrhoids are asymptomatic until there is the complication of thrombosis (intravascular clot) or rupture (perianal hematoma). In either case, the presentation is severe pain with a perianal lump, often after straining.

The natural history is one of continued pain for 4 to 5 days, then slow resolution over 10 to 14 days. The treatment depends on the severity of the pain and the timing of presentation. A patient who presents within 24 to 48 hours with severe pain is best dealt with operatively. Under local anesthesia, the involved perianal vessel and clot are excised. The wound may be left open or may be closed. Simple evacuation of the thrombus is less effective.

A patient presenting later, after 3 to 4 days, is generally advised to take frequent warm baths, a bulk laxative, a surface-active wetting agent, and oral analgesics. This regimen is also prescribed post-excision.

3.1.2.2. Internal hemorrhoids

Painless, bright red rectal bleeding (usually with or following bowel movements) is the most common symptom of internal hemorrhoids. Blood appears on the toilet paper or on the outside of the stool, or drips into the bowl. It is very rare for the volume of blood lost from internal hemorrhoids to be sufficient to explain iron deficiency anemia and further workup is always indicated to ensure that a colon cancer or bowel inflammation is not missed.

Prolapse with defecation or other straining activities is also a common symptom of internal hemorrhoids. Chronic prolapse is associated with mucus discharge, fecal staining of the underclothes and pruritus. Anal sphincter spasm may result in thrombosis and strangulation of prolapsed hemorrhoids. This presents as an acute painful, discharging, edematous mass of hemorrhoids. Inspection will identify the later stages of the disease, especially when the patient is asked to bear down. Digital examination can rule out other pathology, as well as assess the strength of the sphincters. A palpable abnormality suggests some other process.



Anoscopy provides a diagnosis in first- and second-degree disease. With the anoscope in place, the patient is once again asked to strain, and the degree of prolapse observed. Proctosigmoidoscopy should always be performed to exclude other diseases, particularly rectal neoplasms and inflammatory bowel disease.

If the symptoms are at all atypical, or the physical findings leave any doubt about the source of blood, a colonoscopy should be performed to examine the entire bowel. In patients over the age of 50, it is reasonable to take the opportunity to screen (or to practice “case-finding”) for colorectal cancer by performing colonoscopy. Occasional bleeding, especially if it is related to the passage of hard stools or straining, should be managed by improving bowel habits using a high-fiber diet and bulk agents (e.g., psyllium). If bleeding persists or is frequent, intervention is indicated, and in most cases should take the form of rubber-band ligation. Prolapsing hemorrhoids that reduce spontaneously, or that can be easily reduced, are also nicely treated by rubber-band ligation. If prolapsing tissue is not easily reduced, or if there is a significant external component, surgical hemorrhoidectomy offers the best cure. Similarly, prolapsed, thrombosed internal hemorrhoids should be surgically excised. The specific operative options for internal hemorrhoidal disease, and the description of these procedures, are beyond the scope of this text.

3.1.2.3. Rubber-band ligation

In this technique, strangulating rubber bands are placed tightly at the cephalad aspect of the internal hemorrhoids. The banded tissue infarcts and sloughs over the next week, resulting in reduction of hemorrhoidal tissue, as well as fixation of the residual hemorrhoid in the upper anal canal. The absence of somatic pain fibers above the dentate line renders this a relatively painless procedure, as long as the rubber bands are properly positioned. This cuts off the blood supply. Banding is a simple office procedure requiring an anoscope and a ligator. In general, only one or two areas are banded at a time, so that several treatments are often required. Long-term success is expected in approximately 75% of patients with second degree hemorrhoids. Pain, bleeding and infection are rare complications.

3.1.2.4. Hemorrhoidectomy

Since the popularization of rubber-band ligation, excisional hemorrhoidectomy is much less frequently performed. The important principles of all excisional procedures are the removal of all external and internal hemorrhoids, protection of the internal anal sphincter from injury, and maintenance of the anoderm, so as to avoid anal stenosis.

3.2. *Fissure In Ano*

A fissure *in ano* (often simply called a “fissure”) is a linear crack in the lining of the anal canal, extending from the dentate line to the anal verge. It is seen equally in men and women, and at all ages, but is a common entity in young adults. It is encountered mainly in the posterior midline (6 o’clock position). If a fissure persists, secondary changes occur. These include the “sentinel pile” at the distal end of the fissure, the “hypertrophied anal papilla” at the proximal end, exposure of internal anal sphincter fibres at the base of the fissure, fibrotic fissure edges and widening of the fissure.



3.2.1. Pathogenesis

Fissure *in ano* is probably the result of straining to have a bowel movement, or trauma during the passage of hard stool. Not all patients with fissure in ano give a history of “constipation.” While most fissures will readily heal with an appropriate change in bowel habits, and stool composition, some fissures persist. This may be due to continued trauma or to spasm (actually, sustained hypertonicity) of the IAS.

There is an association between fissures and Crohn disease, and this association should be kept in mind.

3.2.2. Diagnosis

Pain with defecation is the chief complaint of a fissure. The pain may persist for minutes to hours. Bright red blood is often seen on the toilet paper and on the surface of the stool. The patient with an edematous, tender skin tag (sentinel pile) may complain of a painful hemorrhoid. The patient may become constipated in response to painful defecation from a fissure.

With gentle separation of the buttocks, most fissures will be visible. The sentinel pile of a chronic fissure may be the initial finding. With acute fissures, digital and anoscopic examination are usually not possible because of local tenderness. However, these examinations should be performed later to rule out other pathology. With chronic fissures, anoscopy reveals the defect in the anoderm, with exposed muscle fibers of the IAS at the fissure base. The hypertrophied anal papilla may be seen. Fissures off the midline should raise the possibility of other diseases. Crohn disease may be associated with atypical-looking fissures that are off the midline and have atypical symptoms. Anal and rectal carcinoma should be palpably different from fissures. If any doubt exists about the diagnosis, a biopsy should be performed. A syphilitic chancre may occasionally look like an idiopathic fissure.

3.2.3. Treatment

The mainstay of therapy for acute fissures is to achieve daily soft bowel movements. This will prevent further tearing, allowing most acute fissures to heal within one to two weeks. A high-fiber diet supplemented with bulk agents and surface-active wetting agents will accomplish the desired effect.

Warm tub baths are soothing and cleansing, and transiently reduce spasm. The reduction of internal anal sphincter hypertonicity (“spasm”) is associated with increased anodermal blood flow and improved rates of fissure healing. Topical calcium channel blockers and topical nitroglycerine also reduce sphincter tone, increase anodermal blood flow and encourage healing. Nitroglycerine is less popular because of side effects (headache).

If the history is longer than a few weeks and the physical findings suggest chronicity (i.e., exposed sphincter muscle fibers, hypertrophied papilla, sentinel pile, and palpable induration), this conservative therapy may not help.

If symptoms warrant, a chronic fissure may be treated by Botox injection or by operation, generally by lateral internal sphincterotomy (LIS). Botox (a total of 20-50 units injected into the sphincter or inter-sphincteric plane) transiently reduces sphincter tone. Success rates are variable, probably in the range of 50-60%, and the procedure is safe. LIS relieves the internal anal sphincter hypertonicity (“spasm”) and allows the fissure to



heal in over 90% of cases. Minor disturbances of continence, especially for flatus, may complicate LIS; the exact rate of diminished continence is controversial but may be as high as 30%.

3.3. *Fistula-Abscess Disease*

Anorectal abscess and fistula are the acute and chronic phases, respectively, of the same disease. The disease begins as an infection in the anal glands, and initially presents as an abscess. When the abscess is surgically drained, or drains spontaneously, a communication (i.e., a fistula) exists between the anal gland of origin and the perianal skin.

The infection begins in the intersphincteric plane, where many of the anal glands terminate. The infectious process may remain in this plane as an intersphincteric abscess, or, more commonly, it may track downward in the intersphincteric plane to present as a perianal abscess. Similarly, infection may penetrate the EAS to enter the ischiorectal fossa. Many complex variations are seen, and these variations are determined by the direction of spread of the abscess and sometimes by inappropriate intervention. The infection may track circumferentially from one side of the anal canal to the other to cause a “horseshoe” abscess. Perianal and ischiorectal abscesses account for at least three-quarters of anorectal abscesses.

The classical signs of inflammation are generally present, although with an intersphincteric abscess there may be nothing to see. In the case of intersphincteric abscess, the patient will be too tender for adequate examination, and examination under anesthesia will be necessary.

Management of the abscess consists of incision and drainage, and this can usually be accomplished under local anesthesia. To ensure adequate drainage, a cruciate or elliptical incision is made. For the one-half to two-thirds of patients who go on to develop a fistula in ano, a fistulotomy, or laying-open, with curettage of the track is required. The wound heals secondarily. Nonhealing or recurrence of the fistula usually indicates a failure to destroy the gland of origin. In performing fistulotomy, the utmost attention must be paid to the anatomic relationship between the fistula track and the sphincter mechanism. Excessive division of muscle contained within the fistula can lead to partial or complete fecal incontinence.

3.4. *Pilonidal Disease*

This is an acquired condition related to hair follicles in the natal cleft. Skin openings form in the midline (primary pits), from which abscesses and secondary tracks and openings may form.

Pilonidal disease is mainly seen in young, hirsute males. It commonly presents as an acute abscess, but may also present as a chronic “sinus,” usually with multiple openings. The abscess stage of pilonidal disease is treated by incision and drainage, usually under local anesthesia. A midline wound in the natal cleft should be avoided, if possible. After the abscess has healed, some of these patients will require definitive surgery to deal with the primary and secondary tracks. The optimal treatment is very controversial; a simple and effective method consists of opening the anterior wall of the tracks and suturing the edge of the track to the skin edge. This technique is called “marsupialization.”



Suggested Reading and References

For complete information on Guidelines, Meta-analyses, Systematic Reviews, Technical Reviews, General Reviews, as well as selected classical and recent references, please see the online version of this text at: www.giandhepatology.com





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