CLINICAL PHARMACOLOGY, PHYSIOLOGY and PATHOPHYSIOLOGY

Gastroenterology, Hepatology, and Pancreaticobiliary Disorders

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Alan BR Thomson

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TABLE OF CONTENTS

CANMEDS OBJECTIVES

- **Medical Expert**
  - As Medical Experts, physicians integrate all the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centred care.
  - Medical Expert is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.
- **Communicator**
  - As communicators, physician from relationships form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.
- **Collaborator**
  - Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.
- **Leaders**
  - As Leaders, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.
- **Health Advocate**
  - As Health Advocates, physicians contribute their expertise and influence as they work with communities or patient populations to improve health
  - They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect changes.
- **Scholar**
  - As Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning by teaching others, evaluating evidence, and
  - Contributing to scholarship
- **Professional**
  - As Professionals, physicians are committed to the health and well-being of individual patients and society through
  - Ethical practice
  - High personal standards of behaviour
  - Accountability to the profession and society
  - Physician-led regulation, and
  - Maintenance of personal health

"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.

ACKNOWLEDGEMENTS

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

When Rebecca, Maxwell, Megan, Henry, Felix, Toby, Grady, Jasper, and Laila, ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin and Kim to be understanding, generous, kind and forgiving. For what I was trying to say and to do was to make my professional life focused on the four Cs and an "H"; competence, caring, compassion, and composure, as well as humor - and to make my very private personal life dedicated to family – to you all.

PHARMACOLOGY, PHYSIOLOGY AND PATHOPHYSIOLOGY

The ideal treatment for any disease/ disorder is to eliminate the cause and complications, to restore the patient to a good quality of life, with as few adverse effects as possible from the treatment. With an increasing movement towards personalized/ individualized treatment, a knowledge is necessary to understand the physiology of the normal, as well as the pathophysiology of the condition, and the genetic and environmental triggers.

In this book, we present each of these, and look forward to the time when these principles may become intertwined to provide the best care possible for the patient for whom we have the privilege of caring.

DEDICATIONS

"To my children, Ava and Harrison and my mother Susan"

Aze Wilson

"To my family who have always supported me in everything I do"
"To the healthcare providers for tirelessly taking care of patients especially during the time of the pandemic"
"To Dr. Alan Thomson for his support in my career growth over the years"

"ถึงครอบครัวของฉันที่สนับสนุนฉันในทุก ๆด้านมาโดยตลอด"
"ถึงบุคลากรทางการแพทย์ที่ดูแลผู้ป่วยอย่างไม่รู้จักเหน็ดเหนื่อย โดยเฉพาะในช่วงที่มีโรคระบาด"
"ถึง ดร. อลัน ทอมสัน ที่สนับสนุนฉันในการเติบโตทางอาชีพและทางวิชาการตลอดช่วงหลายปีที่ผ่านมา"

Naiyana Gujral

"To Jeannette Mineault -Thomson"

"In Memory of Nadia Stecenko, our Baba"

Alan Thomson

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PHARMACOLOGY

- The ideal treatment for any disease/ disorder is to eliminate the cause and complications, to restore the patient to a good quality of life, with as few adverse effects as possible from the treatment.
- With an increasing movement towards personalized/ individualized treatment, a knowledge is necessary to understand the physiology of the normal, as well as the pathophysiology of the condition, and the genetic and environmental triggers.
- In this book, we present each of these, and look forward to the time when these principles may become intertwined to provide the best care possible for the patient for whom we have the privilege of caring.

General Approach to Recommend Patient Care (Sofia MA, et al. White Paper, AGA Position Statement, 2024)

➢ Monitoring

- Purpose to achieve and to maintain remission
- Fecal calprotectin (FC) target normalizes FC ↑ beneficial outcomes (Haisma S-M, et al. PLoS One 2019; 14: e0214751)
- Drug levels
  - Biologicals tailor drug dose and duration depending upon disease activity and severity
  - Antibodies to biologicals take preventative measures using biological plus low dose immunosuppressant (Singh S, et al. Gastroenterology 2023; 164: 344-372; Turner D, et al. Gastroenterology 2021; 160: 1570-1583)
- Endoscopic / histopathological scoring of activity / severity / extent and complications

➢ Holistic care

- Mental health psychotherapy
  - Improves in IBD patient's quality of life (Paulides E et al. Inflamm Bowel Dis 2021; 27; 711-724; Keefer L, et al. Gastroenterology 2018; 154: 1249-1257)
- Multidisciplinary team →
  - ↓ ER visits (Click B, et al. Inflamm Bowel Dis 2019; 25: 1881-1885)
  - ↓ hospitalization
  - ↓ disease severity scores
  - ↑ quality of life scores (Wang CP, et al. J Clin Gastroenterol 2022; 13: 1097)
  - Address
    - Social economic issues (Nguyen NV, et at. Clin Gastroenterol Hepatol 2021; 19: 1377-1385-e5)
    - Issues of possible discriminatory care in LGBTQIA+

Pharmacokinetics (PK)

- Components
  - Drug
    - Absorption
    - Distribution
    - Metabolism
    - Excretion

❖ Absorption

- The first stage of pharmacokinetics that occurs after drugs enter the body and travel from the site of administration into the body's circulation through various routes. The common routes of administration include:
  - Oral (swallowing a tablet or capsule)
  - Enteral (via a nasogastric tube)
  - Rectal (suppository)
  - Intranasal (nasal spray)
  - Inhalation (breathing inhaler)
  - Intramuscular (injecting medication into muscle)
  - Subcutaneous (injecting medication into the subcutaneous tissue)
  - Transdermal (wearing a patch absorbs through the skin)
  - Intravenous (inject medication directly into a vein)
- Depends upon the route of drug administration
  - We will consider oral intake and absorption from the gastrointestinal (GI) tract.
- Stomach
  - Gastric alcohol dehydrogenase W < M →
    - ↓ gastric metabolism of ethanol →
    - ↓ threshold for alcohol toxicity
    - ↑ rate of development of alcoholic liver disease (ALD)
  - Women have proportionally large fat stores and lower body water
  - Hydrophilic drugs like alcohol or fluoroquinolone antibiotics distribute into a small water volume in women, which produce much greater initial plasma concentration, ↑ therapeutic effects, and ↑ adverse effects
  - HCl secretion
  - ↑ pH / ↓H^+, ↓BAO / ↓MAO, W < M
  - ↓ iron absorption (F, 45%; M, 35%)
  - ↓ gastric emptying → ↓ absorption of
    - Metoprolol
    - Theophylline
    - Verapamil

- ↓ absorption in W of drugs requiring intragastric acidity, e.g., ketoconazole
  - Weak acids
  - With ↓ gastric acidity in F, there would be expected that on this basis they might have ↓ iron uptake by duodenal erythrocytes, but women incorporate more iron into their red blood cells than do women (45% of ingested iron, vs 35% in men)

- Small intestine
  - CYP3A enzymes → first-pass metabolism of some drugs e.g., corticosteroids
  - Transporters
    - Multidrug resistance transporter-1 (MDR1) gene→ encodes p-glycoprotein (PGP, a membrane ATPase transporter protein) which is an efflux transporter from enterocytes.
    - H+ - di/tripeptide transporter (PEPT1)
    - Organic anion transporting polypeptide (OATP)
  - Transit time longer (F > M), 92 h vs 45 h

- Sex differences (F vs M) in PKs of several drugs

Drug Example	PK Parameter	F	M	TEs/AEs
• ↑ PK parameter (F > M)				
○ Acebutolol	– ↑ area under the concentration time curve (AUC, ng.hr/mL)	6410	4861	↑ TEs / ↑ AEs
○ Iron	– ↑ % absorption	45	35	
• ↓ PK parameter (F < M)				
○ Ethanol	– ↓ volume of distribution (Vd, L/kg) [→↓ systemic exposure]	0.45 ↓	0.62 ↓	
	– ↑ clearance (Cl) (mg/h per kg)	89 ↓	79 ↓	↑AEs
	– ↓ 1st pass metabolism (nmol/L per h)	1.2	5.2	
○ Propranolol	– ↓ Cl (clearance)			
	▪ ↓ total	4.0	66	
	▪ ↓ glucuronidation	5.6	8.5	↑ TEs / ↑ AEs
	▪ ↓ side chain oxidation	5.1	12.1	
○ Theophylline	– ↓ T1/2			
	▪ Non-smokers	6.0	9.3	
	▪ Smokers	4.6	6.9	

Abbreviations: AEs, adverse effects; Cl, clearance; W, women; M, men; PK, pharmacokinetics; T1/2, half-life; TE, therapeutic effects; Vd, volume distribution

Adapted from: Soldin OP and Mattison DR. Clin Pharmacokinet 2009; 48: 143-57.

❖ Distribution

- Second stage of pharmacokinetics where medication is dispersed throughout the body's blood and tissues.
- After a drug is absorbed, it will pass from vascular spaces to tissues where a drug-receptor interaction will occur, creating the effect of the drug.
- Drugs are designed to primarily cause one effect, i.e., bind more strongly to one specific receptor site and predictably cause or block an action.
- However, side/adverse effects can occur when the drug binds to other sites causing an unintended action.
- The distribution of a drug throughout the body is dependent on many body-related factors including:
  - Blood flow
  - Tissue differences
  - Plasma protein-binding
  - Blood-brain barrier, and
  - Placental barrier

- Plasma proteins
  - ↑ plasma binding of a drug will ↓ free/active fraction
  - Main binding for drugs
    - Albumin
    - Alpha-1 acid glycoprotein (AAG) [AAG-glycosylations]
    - Alpha globulins
  - Effect of estrogens on binding proteins
    - Albumin no effect
    - ↓ alpha-1 acid glycoprotein (AAG) [↓ binding → ↑ free drugs]
    - ↓ serum binding globulins (SBGs, aka sex-hormone binding globulin, corticosteroid binding globulins, thyroxine binding globulin)
  - Examples of effect of sex on plasma binding free fraction of drugs (W vs M ↓binding → ↑ free drugs) many drugs have no difference in their protein binding / free fraction in women (W) or men (M).
    - The following examples are for drugs in which the plasma protein binding of the drug is less, and the free fraction is higher in women vs men.
      - W > M chlordiazepoxide, diazepam, estrogen, lidocaine, warfarin
      - W < M testosterone

- Sex Differences in Body Composition Parameters which influence Distribution

Parameter	Physiologic Differences (F < M)*	Pharmacokinetics Impact in Women vs Men (F vs. M)
– Plasma Volume (PV)	W < M < PW	↓ concentration in PW
– Body mass index (BMI)	W < M	Lower in W
– Average organ blood flow	W < M < PF	Lower in W
– Total body water (TBW)	W < PW < M	Lower in W
– Plasma protein	PW < W, M	↑ free concentration in PW
– Body fat	PW > W > M	↑ body burden of lipid-soluble drug in women
– Cardiac output (CO)*	W < PW < M	↓ rate of distribution in F

*There are also differences in W and pregnant women (PW)

- Body fat
  - Sex differences
    - F 16.5 kg
    - PF 19.8 kg (at 40 wk gestation)
    - M 13.5 kg

    ↑ body burden of lipid-soluble, slowly metabolized drugs

- Regional blood flow higher in women
  - Sex differences

W > M		W < M	
▪ Adipose tissue	8.5% vs 5%	Kidney	17% vs 19%
▪ Heart*	5% vs 4%	Muscle	12% vs 17%
▪ Liver	27% vs 25%		

Adapted from: Soldin OP and Mattison DR. Clin Pharmacokinet 2009; 48: 143-57.

❖ Drug Metabolism

- Third stage of pharmacokinetics.
- After a drug has been absorbed and distributed throughout the body, it is broken down by a process known as metabolism so that it can be excreted from the body.
- Drugs undergo chemical alteration by various body systems to create compounds that are readily excreted.
- Metabolism occurs mainly in the liver by chemical structure breakdown and coupling with another molecule (conjugation) followed by metabolites and conjugates being excreted from the cells.

- The most important enzymes involved are monoamine oxidase and cytochrome P450.
- Biotransformation of drug
  - Occurs mostly in the liver
  - Potentially altered by drug
    - Lipid solubility
    - Protein binding
    - Route/dose
  - Altered by disease
    - Sex
    - Pregnancy
  - Altered by patient characteristics
    - Height
    - Weight
    - BMI
    - Body composition
- Phase I
  - CYP450 system
    - Metabolize drugs
    - Oxidizes
    - Reduces
    - hydroxylates
- Phase II
  - Production of polar conjugate of
    - Parent drugs, or
    - Phase I metabolites
  - Metabolites
    - Glucuronidation
    - Sulfation
    - Acetylation
    - Methylation
  - Reactions are slower in women → slower metabolism → slower elimination (and possibly lower doses):
    - Acetaminophen
    - Caffeine
    - Digoxin
    - Doxorubicin
    - Fluorouracil
    - Levodopa
    - Mercaptopurine
    - Propranolol

MCQ Trick Question

- There is a large variation in drug metabolism between
  - Individuals
  - The sexes
- Often correcting for patient differences (height, weight, BMI, body composition), the "sex-dependent" differences in the biotransformation of drugs is removed.

- Give examples where the biotransformation of drugs is influenced by the patient's sex, even after adjustment for the above patient characteristics.
  - Acetylsalicylic acid
  - Chlordiazepoxide
  - Flurazepam
  - Heparin
  - Nicotine

- The major reason for sex-related differences in hepatic metabolism of drugs is related to sequential hepatic enzymatic reactions.
- Lipophilic drugs are more likely to be affected by phase ± types of metabolism, involving the cytochrome (CYP) 450 enzymes.
- Women have ↑ specific activity of CYP2D6 as compared with men and will have greater metabolism of drugs such as codeine, hydrocodone, propranolol, imipramine.
- F have ↓ specific activity (vs M) for drugs metabolized by CYP1A and 2E, with W = M for CYP 2C9, 2C19, 3A.
- Women should be given smaller doses when given loading/bolus doses of drugs with altered body distribution in women vs men such as
  - Antiarrhythmics, class I/III
  - Aminoglycosides
  - Chemotherapy
  - Digoxin
  - Heparin
  - Lidocaine
  - Thrombotic
- Women suffer QT syndrome adverse effects from antiarrhythmic and antipsychotic drugs more than do men.
- Women require lower doses of warfarin (2.5 to 4.5 mg less warfarin per week than men) to achieve the same level of therapeutic anti-coagulation.

❖ Elimination/excretion

- Final stage of pharmacokinetics where drug byproducts and metabolites are eliminated from the body.
- Remaining parent drugs and metabolites in the bloodstream are often filtered by the kidney, where a portion undergoes reabsorption back into the bloodstream, and the remainder is excreted in the urine.
- The liver also excretes byproducts and waste into the bile.
- Other potential route of excretion is the lungs. Sweat, tears, reproductive fluids, and breast milk can also contain drugs and byproducts/metabolites of drugs. This can pose a toxic threat, such as the exposure of an infant to breast milk containing drugs or byproducts of drugs ingested by the mother.

- Sites
  - Urine
  - Feces
  - Breath
  - Kidney
  - Liver
  - Lung
- Renal excretion
  - Glomerular filtration
    - ↑ renal blood flow → ↑ GFR
  - Tubular secretion
  - Tubular reabsorption
  - Some drugs are excreted unchanged in the urine → these unchanged drugs are excreted slower in women (but not in men)
    - E.g., slower excretion
      - Digoxin, ↓ 13%
      - Methotrexate, ↓ 17%
- Drug pregnancy (PF, pregnant female)
  - There is ↓ elimination because of ↓ plasma protein binding / ↑ free drug, but in PF vs F, there is
    - ↑ RBF (renal blood flow)
    - ↑ GFR (glomerular filtration rate) / ↑ Tubular secretion/reabsorption
    - ↑ HBF (hepatic blood flow)
    - ↑ BF (bile flow)
    - ↑ PF (pulmonary function → ↑ pulmonary elimination)
  - In PF there is ↑ estrogen / progesterone → ↑ hepatic enzyme activity →
    - ↑ accumulation
    - ↓ elimination

- Physiologic changes during pregnancy that affect the PK of drugs (PF vs F)

	F	PF
○ ↑ Vd (volume of distribution)		
– ↑ PV (plasma volume)		
– ↑ ECW (extracellular water, L)	11.6	15
– ↑ TBW (total body water)	29	33

  - ○ Lung
    - Respiratory alkalosis
    - ↓ $PaCo_2$
    - ↑ pulmonary function
  - ○ Binding proteins
    - ↓ plasma albumin concentration
  - ○ Kidney
    - ↑ RBF (renal blood flow)
    - ↑ GFR (glomerular filtration rate)
  - ○ GI
    - Stomach
      - ↓ rate of gastric emptying / ↑ retention
      - ↓ pH / ↑ H → ↓ absorption of weak acids
    - Small intestine
      - ↓ rate of transit
  - ○ CVS
    - ↑ PV
    - ↑ CO (cardiac output)
      - CO and regional distribution of flow are important for pharmacokinetics
      - CO is commonly standardized and reported as the cardiac index (CI)
      - When standardized for body surface area (BSA), CI is nearly identical for both sexes.
    - ↑ SV (stroke volume, T1)
    - ↑ HR (heart rate, T3)↑ regional blood flow (skin, kidney, mammary glands, uterus)
  - ○ Skin
    - ↑ blood flow
    - ↑ body surface area

  - ○ Depending on whether a drug is metabolized and eliminated by the kidneys or liver, impairment in either of these systems can significantly alter medication dosing, frequency of doses, anticipated therapeutic effect, and even whether a particular medication can be administered at all.

Glossary

○ Adverse effect	Unintended/dangerous pharmacological effect that occurs when a medication is administered correctly.
○ Affinity	Strength of binding between drug and receptor.
○ Agonist	Drug that binds to a “receptor” and produces its effect.
○ Antagonist (opposite of agonist)	Molecule that prevents action of other molecules, often by competing for a cellular receptor.
○ Bioavailability	Fraction (%) of an administered drug that reaches the systemic circulation. when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via routes other than intravenous, its bioavailability is lower due to intestinal epithelium absorption and first-pass metabolism.
○ Blood brain barrier	A nearly impenetrable barricade that protects the brain from dangerous substances such as poisons or viruses.
○ Duration	Length of time that a medication is producing its desired therapeutic effect.
○ Efficacy	Maximum effect of which the drug is capable.
○ First-pass effect	Inactivation of oral/enteral drugs in the liver and intestines.
○ Half-life	The amount of time that it takes for half of the drug to be eliminated from the body. It determines the length of drug effect and indicates whether accumulation of the drug will occur under a multiple dosage regimen. It is essential to decide on the appropriate dosing interval.
○ Mechanism of action	How a medication works at a cellular level within the body.
○ Onset	Time it takes for a medication to first begin to exerts its therapeutic effect.
○ Peak concentration (Cmax)	Maximum serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and before the administration of a second dose. Tmax (time) is defined as the time at which Cmax is attained.
○ Pharmacodynamics	Effects of drugs in the body and the mechanism of their action.

○	Pharmacogenetics	Study on the effect of a person's genetic makeup on response to medicines.
○	Pharmacokinetics	Study of how body absorbs, distributes, metabolizes, and eliminates drugs.
○	Pharmacology	Science dealing with actions of drugs on the body.
○	Potency	Drug dose required to produce a specific intensity of effect.
○	Selectivity	Proportion between the desired and undesired effects of a drug.
○	Side effect	Effect of a drug other than the desired effect (may be on other organs).
○	Therapeutic index	Relative safety of a drug that compares the amount of drug that produces a therapeutic effect versus the amount of drug that produces a toxic effect.
○	Volume of distribution (Vd)	Ratio of amount of drug in a body (dose) to concentration of the drug that is measured in blood, plasma, and un-bound in interstitial fluid. Volume of Distribution (L) = Drug dose (mg) / Plasma concentration of drug (mg/L) ↑ Vd → ↑ distribution to other tissue → ↑ drug dose required to achieve plasma concentration ↓ Vd → ↓ distribution to other tissue → ↓ drug dose required to achieve plasma concentration)

Pharmacodynamics (PD)

- The alteration in the number of receptors, their binding properties for the drug, and the response of the signal transduction pathway after bind of the drug to the receptor will alter the pharmacodynamics, the response of the target organ.
- Drug interaction may result from alterations in PDs as well as PK properties of the drug.

➢ Recommendations for prescribing drugs for women.

- ↓ dose
  - Antipsychotic medication doses (use lower does to control symptoms)
  - Opioid does (women have a greater response and require ~33% less than do men.
  - Beta blockers (women have ↑ response)
  - Digoxin (women have ↑ rate of death when on digoxin therapy and target dose to 1.02 Nmol/L (0.8 ng/mL)
- Change medication
  - SSRIs better for women being treated for depression (TCAs better for men)
  - Aspirin more efficacious for prophylaxis against stroke in women (against myocardial infarction in men).
  - Consider using high doses in women for secondary prophylaxis after a cardiac event.

Please also see section on pharmacokinetics/pharmacodynamics of drugs used to treat patients with inflammatory bowel disease (IBD), under Therapeutics in IBD, Chapter on Small Bowel

Abbreviations: AAG, alpha-1 acid glycoprotein; ALD, alcoholic liver disease; AUC, area under the curve; BAO, basal acid output; BF, blood flow; BMI, body mass index; Cl, clearance; CO, cardiac output; CYP, cytochrome P450 enzymes; F, female; FF, free fraction; GFR, glomerular filtration; HBF, hepatic blood flow; h, hour; L, litre; M, male; MDR, multidrug resistance; OATP, organic anion polypeptide; PD, pharmacodynamic; PEPT, H+ di/tripeptide transporter; PF, pregnant female; PF, pulmonary function; PK, pharmacokinetic; PV, plasma volume; QT, ECG (electrocardiogram) interval; RBF, renal blood flow; SBG, serum binding globulins (sex-hormones binding globulin); T1/2, half life; TBW, total body weight; TR, tubular reabsorption; TS, tubular secretion; Vd, volume of distribution

Sex Differences in Pharmacodynamics (PD) **and Pharmacokinetics** (PK)

* "Sex" is ……the property or quality by which organisms are classified as female (F) and male (M) on the basis of their reproductive organs and functions.

Soldin OP and Mattison DR. Clin Pharmacokinet 2009; 48: 143-57.

- Men (M) and women (W) differ in their responses to drug treatment, and their likelihood of developing adverse effects.
  - Understanding their phenomenon requires an appreciation of the sex-based variations in the pharmacokinetics (PK) and the pharmacodynamic (PD) properties of each drug.
  - For example, the number and seriousness of adverse effects to drugs in general is W >> M.

➢ Some differences between men and women which influence their response to drugs

- Physiological (differences in W vs. M)

Parameter	Adult Men (M)	Adult Women (W)	Pregnant Women (PW)
Body			
– Weight (kg)	78	68	72.5
– Length (cm)	176	162	162
– Surface area (cm^2)	18,000	16,000	16,500
Total water (L)	42.0	29.0	33.0
– Extracellular water (L)	18.2	11.6	15.0
– Intracellular water (L)	23.8	17.4	18.8

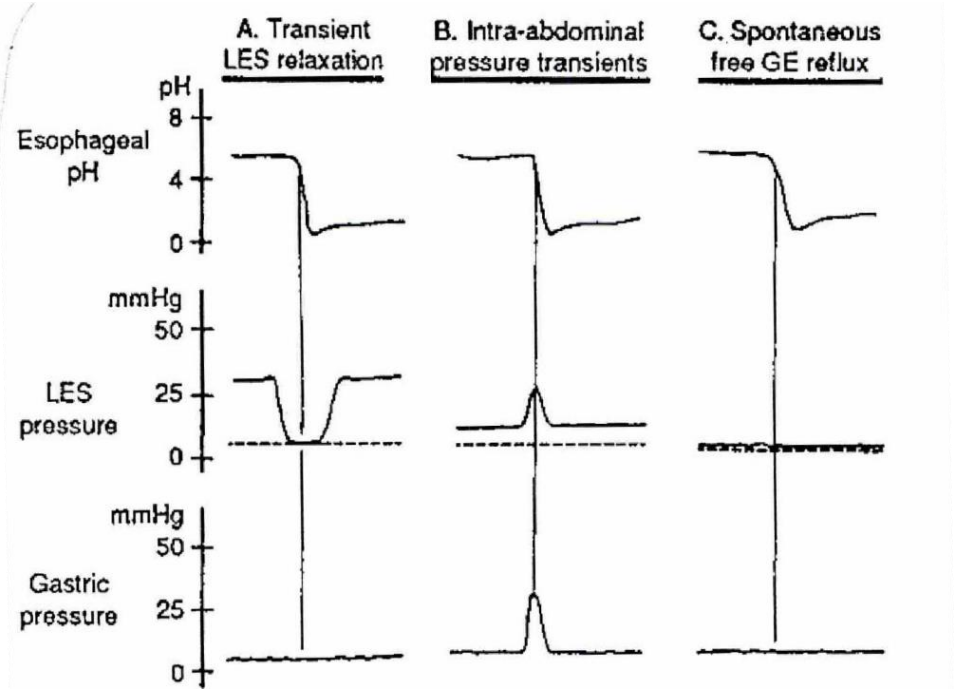
- Pharmacological (differences in W vs M)
  - PK
    - ↓ Vd (↓ volume of distribution of drug)
    - ↑ FF (↑ free fraction)
    - ↓ Cl (↓ clearance) rate
  - PD
    - ↓ receptor
      - Number
      - Binding
      - Signal transduction for binding to receptor
  - PK/PD
    - ↑ frequency / ↑ severity of drug interactions

ESOPHAGUS

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

- Pathophysiology
  - The commonest disorder of the esophagus is GERD (gastroesophageal reflux disease).
  - GERD is caused by regurgitation of gastric acid into the esophagus for intervals which are longer than normal ('physiological").
  - The mechanism of GERD includes excessive TLESR (transient lower esophageal sphincter relaxation, intraabdominal transients, and spontaneous GE reflux. In many GERD patients, the baseline LES pressure is reduced.

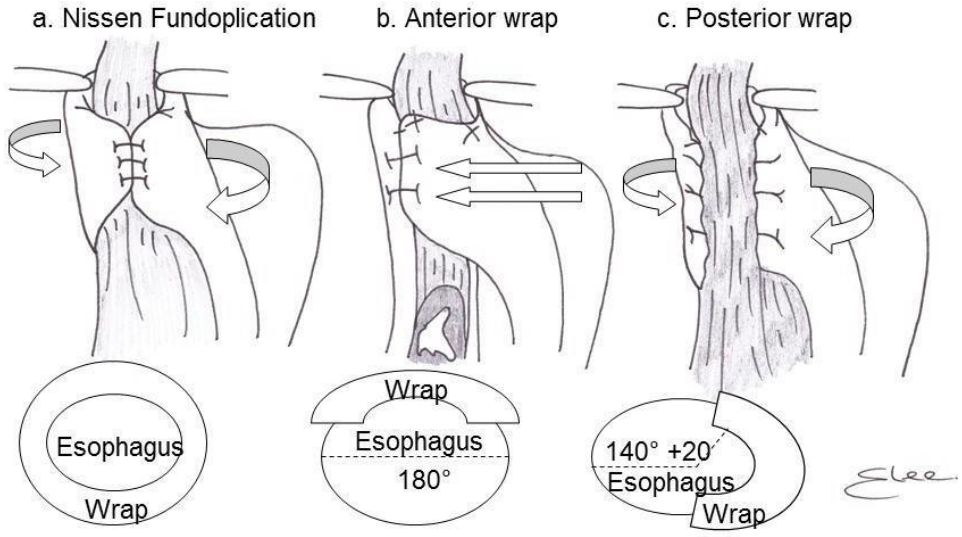
MECHANISMS OF GERD



Abbreviations: LES, lower esophageal sphincter; GE, gastroesophageal

  - In some patients with GERD, when life-style changes (such as weight loss in the setting of increased BMI [obesity]) and medical therapeutics fail, the surgical enhancement of LES pressure and surgical correction of an associated hiatus hernia may be considered.

SURGICAL TREATMENTS FOR GERD



Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Figure 43-15, page 723, Ninth Edition, 2010.

❖ Pharmaceutical measures

➢ Classes of drugs used to treat GERD.

- Sensation – Tricyclic antidepressants (TCA), selected serotonin receptor inhibitors (SSRIs)
- ↑ saliva – chewing gum
- ↑ lower esophageal sphincter pressure (LESP) cholinergic (bethanechol)
- ↓ transient lower esophageal sphincter pressure (TLESP) – (GABA receptor agonist [baclofen])
- ↑ coating – alginate
- ↓ acid – proton pump inhibitor (PPI), histamine 2 receptor antagonist (H_2RA), antacids, anti-cholinergic
- ↑ gastric emptying – prokinetics (e.g., domperidone)
- ↓ bile acids
  - Cholestyramine
  - Sucralfate

Abbreviations: GABA, gamma butyric acid; H2RA, H2 receptor antagonist; PPI, proton pump inhibitor; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic anti-depressants

- The smooth muscle receptors and affecting drugs which act on these receptors to treat patients with GERD.

Receptor		Drug
○ α-adrenergic antagonists		▪ Clonidine
○ Ach (acetylcholine)	– Muscarinic	▪ Cisapride ▪ Bethanechol
	– Anticholinesterase	▪ Buscopan ▪ Botulinum toxin
○ D2 (antagonist)	– Peripheral – Peripheral and central	▪ Domperidone ▪ Metoclopramide
○ GABA agonist, type B receptor		▪ Baclofen
○ 5-hydroxytryptamine receptor (5HT)	– 5HT3 receptor antagonist	▪ Metoclopramide ▪ Cisapride ▪ Ondansetron
	– 5HT4 receptor agonist	▪ Metoclopramide ▪ Cisapride ▪ Tegaserod
○ Motilin		▪ Erythromycin
○ Phosphodiesterase		▪ Viagra
○ Somatostatin		▪ Octreotide

Drug	Receptor
○ Cisapride	– Muscarinic (acetylcholine) receptor agonist – 5-HT3 receptor antagonist – -5-HT4 receptor agonist
○ Domperidone	– Peripheral D2 antagonist
○ Metoclopramide	– Central/peripheral dopamine receptor antagonist (D2) – 5-HT3 receptor antagonist – 5-HT4 receptor agonist

❖ Acute therapy

Please see chapter on stomach for the physiology of gastric acid secretion and gastric motility for an understanding of the basis for the targeted pharmacology and physiology of this therapy.

- Used in addition to tailored lifestyle changes:
- ↓ **acid secretion** (in GERD, target to achieve intragastric pH > 4 for ~ 14 h per day)
  - PPI > H2RA > antacids
    - Therapeutic gain (TG) 57% to 74% versus placebo for PPI, 10% to 24% for H2RA relief of heartburn / esophageal mucosal healing
    - Complete relief of heartburn, per week of treatment
  - Start with standard dose of PPI, taken 30-60 min before the first meal of the day, for 8 wks (~12% healing per week, but LA grade C or D severe esophagitis may take longer to heal).
    - Lower response of symptom of regurgitation to PPIs/H2RAs
      - PPIs ~12%
      - H2RA ~6%
    - If symptom response to PPI po is incomplete after 8 wks of od therapy, increase PPI to b.i.d. therapy, standard dose and 30 min before breakfast and supper.
    - The ↑ therapeutic gain (TG) for doubling the dose of PPI is small,
      - Symptom improvement, 4%
      - Healing, 6%
    - In some persons, who fail to benefit from PPI therapy, switching to another brand of PPI may prove to be useful; the explanation for this phenomenon is not clear, since all the PPIs have approximately similar inhibition of H^+ secretion.
- **Prokinetics** (↑ rate of gastric emptying / ↑ LES pressure)
  - Use as adjunctive therapy of incomplete response to PPI b.i.d. for patients with possible delayed gastric emptying contributing to their poor therapeutic response.
  - Some prokinetics cause ventricular arrhythmia and sudden cardiac death (SCD)
  - Any drug potent enough to alter GI motility will affect the heart – same effects onsmooth muscle.
    - Avoid in patients with heart failure (HF) or history of arrhythmias
    - QTC (corrected QT) must be normal on ECG (no QT conduction defect) when using prokinetics.
  - Don't combine erythromycin and domperidone for gastroparesis (both CYP 3A4 inhibitors, leading to further ↑ risk of arrythmias).
- ↓ TLESR (transient lower esophageal relaxation)
  - Baclofen (gamma-aminobutyric acid [GABA] agonist for the type B receptors) may be used in patients with refractory GERD.
  - Start with 10 mg b.i.d., ↑ slowly to 20 mg t.i.d., or maximum benefit obtained without the development of CNS-related adverse effects.

The H_2RA (H2 receptor antagonists) are ~60% as effective as the PPIs in the ↓ gastric acid secretion, the ↓ acid-related symptoms, and the healing of acid- induced mucosal damage.

- Histamine is considered to be the most dominant amongst the other main stimuli of gastric acid secretion, acetylcholine and gastrin, because
    - Histamine is released from the ECL (enterochromaffin-like) cells close to the parietal cells, and in response to food in the stomach.
        - The release of histamine is ↑ by gastrin, which also acts on the ECL cells.

- Mechanisms of action of GABA β receptor agonists (e.g., baclofen) on the physiologyof the esophagus and stomach, which make this class of drugs useful in persons with refractory GERD:
    - GABA β receptor agonists have the following physiological effects
        - ↓ TLESR (~50%)
        - ↑ LESP (basal)
        - ↑ rate of gastric emptying
        - ↓ reflux episodes (~40%)
    - ↓ H. pylori infection
        - Some algorithms for the management of uninvestigated dyspepsia support a therapeutic trial of empiric PPI therapy, or empiric anti-pylori therapy, or “test-and-treat” H. pylori infection.
        - Without EGD plus biopsy or intragastric pH studies, it is not possible to determine if the H. pylori-associated gastritis
            - ↑ intragastric pH (↓ secretion of H^+ as a result of pangastritis), or
            - ↓ intragastric pH (↑ secretion of H^+ as a result of antral gastritis)
        - Note
            - There is a negative association between GERD and H. pylori infection
            - There is a concern that the rate of H. pylori-associated progression of chronic gastritis to gastric metaplasia atrophic gastritis and dysplasia may be accelerated by the chronic use of PPIs, such as used in persons on long-term PPI maintenance therapy for GERD.

❖ Maintenance therapy

- Rational: recurrence of dyspepsia occurs within 1 yr of stopping therapy, it will likely occur in the first 3 mon.

- Options
    - Continuous
        - If recurrent typical symptoms in < 3 mon
        - Use half the standard dose if a PPI was effective for acute treatment
            - Use full single standard dose if b.i.d. PPI was necessary

- Repeat full dose acute therapy
  - If recurrent typical symptoms in 3 mon
  - This provides for a trial off medications to determine each person's individual natural history of possible recurrence.
- Intermittent
  - Only for mild to moderate heartburn in the patient having had an EGD showing only mild or no esophagitis.

- Special considerations
  - Pregnancy and lactation
    - PPIs and H_2RAs should only be used when lifestyle changes fail to relieve symptoms.
    - These drugs have category 'B' in the former FDA classification and are
      - Considered to be safe to use during pregnancy and lactation.
  - Surgery
    - Surgery is an effective option for the management of GERD, but only in highly selected patients
    - The general standard of care is for the person with GERD who is being considered for a surgical procedure (e.g., fundoplication) to
      - Have had at least a partial response of their GERD symptoms with a PPI used for 4-8 wks.
      - Have preoperatively at least a normal esophageal manometry study, and preferentially esophageal pH and multichannel intraluminal impedance testing.

Abbreviations: CNS, central nervous system; ECG, electrocardiogram; EGD, esophago-gastroduodenoscopy; FDA, Food and Drug Administration; GABA, gamma amino butyric acid; GERD, gastroesophageal reflux disease; H2RA, H2 receptor antagonist; HF, heart failure; LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure; mon, month; PPI, proton pump inhibitor; SCD, sudden cardiac death; TG, therapeutic gain; t.i.d., three times a day; TLESR, transient lower esophageal sphincter relaxation

DYSPEPSIA AND PREGNANCY

- Upper GI symptoms are common in pregnant women
  - Esophagogastroduodenoscopy (EGD) not usually required
  - When EGD performed, the findings are esophagitis (~35%) and gastritis (25%), with the greatest proportion of EGDs being normal (as in non-pregnant women).
- Predictors of heartburn during pregnancy include the mother is parity,↑gestational age, and the presence of heartburn before pregnancy (which occurs in ~15% of mothers).

➢ Factors to carefully consider when performing EGD in pregnant women.

- The procedure
  - A strong indication is always needed, particularly in high-risk pregnancies
  - Whenever possible, EGD should be deferred until the second trimester (T2)
  - The lowest possible dose of sedative medication should be used(wherever possible only ↓ FDA category A or B drugs)
  - Procedure time should be short, and the endoscopist should be experienced.
  - The patient should be positioned in the left pelvic tilt or left lateral position to avoid compression on the inferior venal cava or aorta
- No endoscopy should be performed in patients with obstetric complications (placental rupture, imminent delivery, ruptured membranes, or pre-eclampsia)
- The patient and fetus
  - Confirm the presence of fetal heart sounds before sedation and after the procedure.
  - An obstetrical consultation in advance of the procedure is helpful
  - Obstetric and fetal support should be immediately available, if necessary.

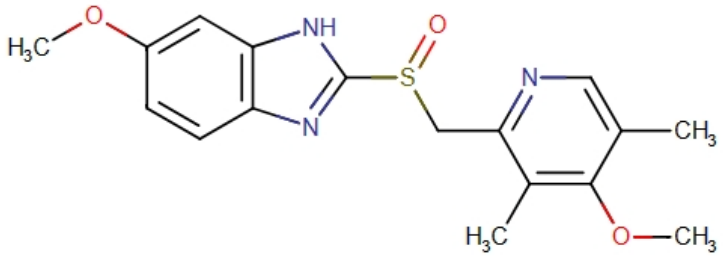
Adapted from: Keller J, et al. Nat Clin Pract Gastroenterol Hepatol 2008; 5(8): 435.

❖ **PROTON PUMP INHIBITORS** (PPI)

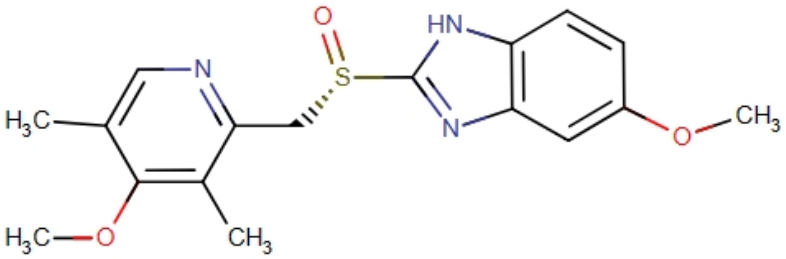
➢ Mechanism of action of PPIs

- A benzimidazole which non-competitively ↓ activity of H^+/K^+ of gastric canaliculi in food-activated parietal cells

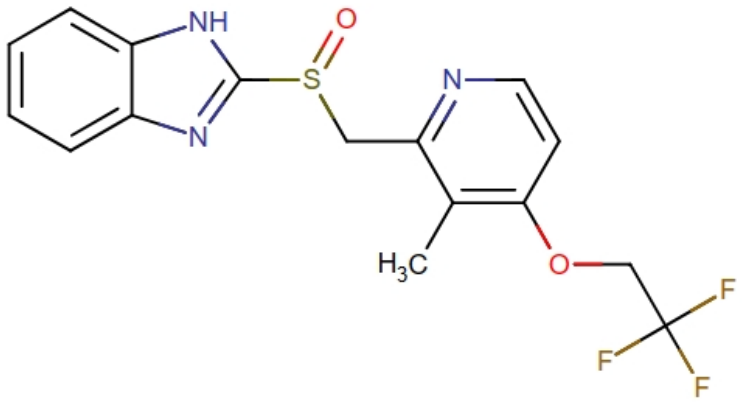
- Omeprazole



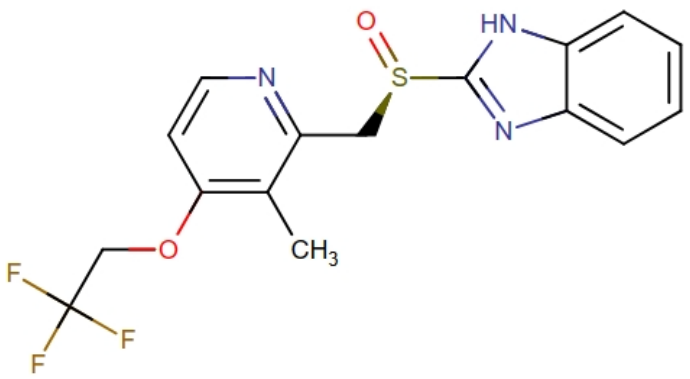
- Esomeprazole (s-isomer of omeprazole)



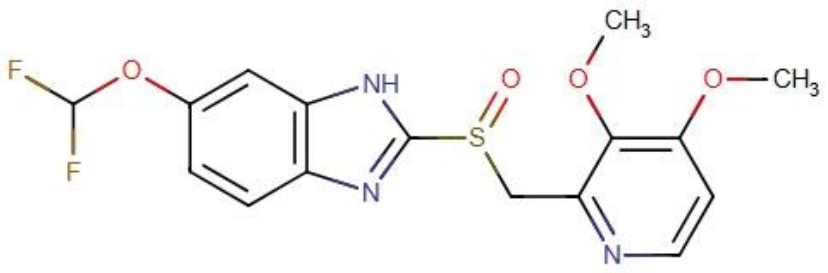
- Lansoprazole



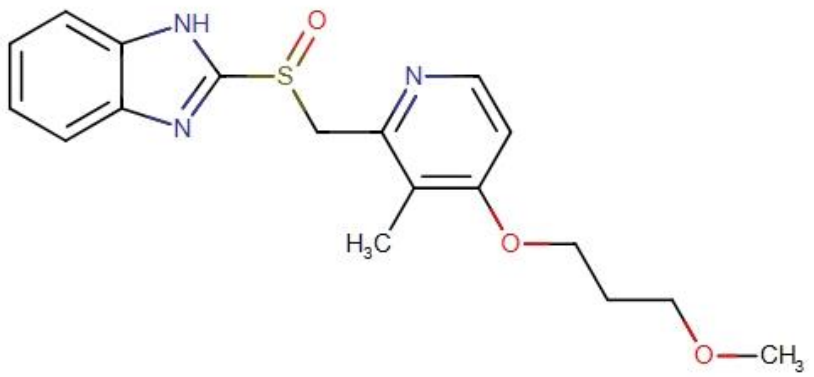
- Dexlansoprazole



- Pantoprazole



- Rabeprazole



- Indications for the use of PPIs
  - Esophagus
    - Normal endoscopy reflux disease (NERD)
    - GERD (symptoms and/or signs on EGD of damage from acid-related disorders), including BE
    - Barrett epithelium (BE)
    - Eosinophilic esophagitis (EoE)
    - Bronchopulmonary disorders associated with GERD, especially when associated with dyspeptic symptoms /GERD
    - Motility disorders
      - Achalasia
      - Scleroderma
      - Distal esophageal spasm (DES) /hypertensive esophagus
    - ↓ # of esophageal dilations needed to relieve dysphagia from benign (peptic) stricture
    - ↓ recurrence of esophageal strictures
    - Healing after
      - Endoscopic mucosal resection (EMR) of BE
      - Post-banding or post-sclerotherapy of esophageal varices
  - Stomach
    - Nocturnal acid breakthrough (NAB)
    - Prevention of drug-induced damage to stomach, e.g.
      - Aspirin (ASA)
      - Non-steroidal anti-inflammatory drugs (NSAIDs)
      - COX_2 inhibitors (COXIBs)
    - Upper GI bleeding
    - H. pylori eradication
    - Gastroparesis (with prokinetics)
    - Hypersecretory states (e.g., ZES [Zollinger Ellison Syndrome] / MEN-1 [multiple endocrine neoplasia type 1] syndrome)
    - Prevention/treatment of gastric stress ulceration
    - ↓ drainage of gastric fistula
  - Small bowel
    - Duodenal Crohn disease
    - ↓ small bowel fistulae drainage
    - Short bowel syndrome (↓ small bowel output, and ↓ post-resection hypersecretion of HCl)
    - Early post-ileal resection hypergastrinemia and diarrhea
  - Pancreas
    - Pancreatic insufficiency
      - Non-coated pancreatic replacement treatment
      - Pain control from chronic pancreatitis

Food and Drug Administration Approved Indications for Proton Pump Inhibitors

Indication	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Gastro esophageal reflux disease						
Erosive esophagitis healing	✓	✓	✓	✓	✓	✓
Erosive esophagitis–maintenance	✓	✓	✓	✓	✓	✓
Nonerosive reflux disease	✓	✓	✓	✓		✓
Peptic ulcer disease						
Duodenal ulcer–healing	✓		✓			✓
Duodenal ulcer–maintenance			✓			
Gastric ulcer–healing	✓		✓			
NSAID induced ulcers–healing			✓			
NSAID induced ulcers–prophylaxis		✓	✓			
Zollinger-Ellison syndrome	✓	✓	✓		✓	✓
Treatment of Helicobacter pylori						
Dual therapy	✓		✓			
Triple therapy	✓	✓	✓			✓
Pediatric population						
Any age (weight-based dosing)	✓	✓	✓			✓
Age greater than 5 years old					✓	
Special & off label uses						
Nonvariceal acute GI bleeding (IV)		✓	✓		✓	
Administration via NG tube		✓	✓	X		

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal; IV, intravenous; NG, nasogastric

Source: Strand DS, et al. Gut Liver 2017;11(1):27-37

➢ Pharmacokinetics

	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
○ Bioavailability, %	30–40	64–90	80–85	-	77	52
○ Time to peak plasma level (Tmax, h)	0.5–3.5	1.5	1.7	1–2, 4–5	2–3	2–5
○ Protein binding, %	95	97	97	96	98	96.3
○ Half-life, h	0.5–1	1–1.5	1.6	1–2	1–1.9	1–2
○ Primary excretion	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
○ Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19 CYP3A4	CYP2C19 CYP3A4	CYP2C19

Source: Strand DS, et al. Gut Liver 2017;11(1):27-37

➢ Metabolism

- Gastric and duodenal lumen
  - The PPI is coated to protect it from gastric HCl.
  - The PPI is pumped by the gastric antrum through the relaxed pylorus into the duodenum.
  - In the duodenum the alkaline pancreatic juice allows coating to come off PPI.
  - The PPIs are absorbed passively across the upper intestinal brush border membrane,
  - The H^+ - K^+ - ATPase is a member of the P2 family of ion motive transport enzymes.
  - The proton pump is comprised by the H^+ - K^+ - ATPase in the canalicular membrane of the parietal cell.
  - The secretory canaliculus is an acidic space in a slightly invaginated area of the apical membrane of the parietal cell.
  - The absorbed PPIs accumulate in this acidic space in the secretory canaliculus.

- Liver
  - The PPIs are weakly protonatable pyridines, with values of pKa ~4, depending on the individual PPI.
  - The PPI is acted upon by hepatic cytochrome P450 (CYP2C19) enzyme to form the active sulfonamide.
  - With the intake of food, the canaliculi undergo a structural change, exposing the cysteine binding site for the active sulfonamide PPI.
  - The higher the value of the pKa, the faster the PPI undergoes an acid-catalyzed conversion to the active agent, a thiophilic sulfonamide.
  - The thiophilic sulfonamide diffuses into the parietal cell and up to the secretory canaliculus.

- Parietal cell secretory canaliculus
  - The thiophilic sulfonamide forms a non-reversible disulfide bond with cysteine 813 in the activated H^+ - K^+ - ATPase in the canaliculus.
  - Cysteine 813 is in the catalytic alpha-subunit of the H^+ - K^+ - ATPase.
  - While all PPIs bind to cysteine 813, some PPIs may bind to additional cysteine molecules (e.g., pantoprazole also binds to cysteine 822).
  - The activated canaliculi with the H^+ - K^+ ATPase inhibited by PPI is inserted into apical membrane of the parietal cell.
  - The H+ pump is inhibited.
  - The resulting non-competitive inhibition is the final common pathway of the parietal secretion of HCl lasts until new pumps are produced in new parietal cells.
  - In the fasting stomach, the canaliculus and lasts in the parietal cells are distal to the apical membrane, and the cysteine binding area for the activated are not exposed.

- There are differences between PPIs in terms of their pKa, as well as their rate of absorption and metabolism,including differences in PK (pharmacokinetics) and PD (pharmacodynamics) properties.
- This explains why the biological and pharmacodynamics T½ differ
  - T½ ~60 min for pharmacokinetics, and T½ of $H^+\downarrow$~ 14 h.

➢ Contraindication/precautions

- Known hypersensitivity
- Electrolyte disorders
  - ↓ Ca^{2+}_s (serum calcium)
  - ↑ HCO_3^- (metabolic / respiratory alkalosis)
  - ↓ K_s^+ (serum potassium)
  - ↓ Mg^{2+}_s (serum magnesium)
  - Bartter syndrome

➢ Special Considerations

- Dosing
  - PPIs do **not** require either hepatic or renal dosing
  - PPIs ↓ absorption of some HIV protease inhibitors, requiring dose-adjustment
- Timing
  - PPIs must be taken 30 to 60 minutes before 1st meal of the day in order to achieve their maximal effect on inhibition of acid secretion.
    - PPIs takes time to
      - Become decoated in the stomach and absorbed in the duodenum
      - The metabolised, and diffuse into parietal cells and up to the secretary canaliculi
  - Food must be taken to open the canaliculi, and for the PPIs to be bound to the appropriate cysteine molecules.
  - The secretory canaliculus with the inhibited H^+/K^+- ATPase must then diffuse to the apical membrane of the parietal cell.
    - This process takes 30-60 min, and food is required for the insertion of PPIs into the opened channels in the canalicular, and
      - For the canaliculi to diffuse to and be inserted into the apical membrane of the parietal cells.
- Competitive inhibitors of H^+/K^+ ATPase

➢ Target pH

- The target pH for PPI therapy depends upon the indication for its use
  - It does **not** matter how high the pH goes on PPIs, but rather the target level
  - For example, it is not important if PPI_2 achieves peak pH level of 3.5, and PPI_1 a pH level of pH 3.1, a long as each achieves their target pH value for the same duration, i.e., > 18 h per day.

- Optimal intragastric pH (> 14 h per day) for upper GI disorders
  - ≥ 3 Duodenal ulcer (DU)
  - 4 Gastroesophageal reflux disease (GERD)
  - 5 H. pylori eradication
  - 6 Non-variceal upper GI bleeding
- This means that the usual pharmacokinetic parameters of C max (maximum drug concentration), t1/2 (half-life) and AUC (area under the curve), are less important in the comparison of two PPIs, than are
  - The targets optimal intragastric (OIG) pH values and the area under the blood concentration vs. pH values up to the target pH.
- The best value to use to compare two different PPIs is their ~10% of time pH ≥ 3, 4.5 or 6, depending upon the indication for the use of the PPI.

- Give the explanation why the PPIs rabeprazole and pantoprazole have fewer adverse effects than omeprazole.
  - Omeprazole is metabolized by CYP2C19, and depending upon whether the patient has a mutation, the PPI may interfere with the metabolism of many drugs which are also metabolized by CYP2C19 (please see examples above).
  - Rabeprazole has affinity for CYP2C19 plus CYP3A4
    - The risk of adverse effects from drug interactions with drugs metabolized by CYP 2C19 is less.
  - Pantoprazole is rapidly sulphated after CYP2C19 methylation
    - It does **not** induce other CYP450 metabolized drugs (e.g., CYP3A4 or CYP1A), so has less drug interaction.
- The acid inhibitory effect of a single dose of PPI is less than the inhibitory effect which occurs after multiple dosing. Give the explanation for this steady-state phenomenon.
  - When food enters the stomach, not all the parietal cells become active.
  - PPIs only bind to cysteine 813 of H^+ - K^+ - ATPase when the H^+ - K^+ - ATPase is active.
  - Over several days, more and more parietal cells will have been stimulated, resulting in more and more proton pump being activated and subsequently inhibited by the PPI.
  - In the same manner, with the progressively increased recruitment of H^+ - K^+ - ATPase and its inhibition by PPIs, the acid inhibitory effect of the PPIs may last 1 to 2 days after the PPI has been stopped.

- In the context of PPIs, give the advantages and disadvantages of polymorphisms for a mutation in CYP2C19.

		Clinical Advantage	
	Duration of ↓H+	Eradication H. pylori	↓GERD symptoms / ↑healing
○ Homozygous CYP2C19 mutation (slow metabolizers; about 5% of Caucasians; inactivating mutation)	Long	~85%	85%
○ Heterozygotes	Inter-mediate	60%	68%
○ Homozygous, wild type (rapid metabolizers; ~65% of Caucasians)	Short	29%	16% (severe)

- Give commonly used drugs,which interact with PPIs through their CYP2C19 metabolism to cause drug-drug interactions.
  - ○ CNS
    - − Diazepam
    - − Phenytoin
  - ○ Heart
    - − Warfarin
    - − Clopidogrel (minimal)
    - − Digoxin
  - ○ Lung
    - − Theophylline
  - ○ Immune system
    - − Cyclosporine

➢ Adverse Effects of PPIs

- Long term adverse effects of PPI therapy.

	Risk Possible/Magnitude Consequence
❖ Associated with hypergastrinemia	
○ Hypergastrinemia-induced carcinoid tumours	− Not demonstrated in humans
○ Accelerated progression of atrophic gastritis/gastric metaplasia with concomitant *H. pylori* gastritis	− No documentation of ↑ in atrophic gastritis − No basis to recommend testing or treatment for *H. Pylori* before long-term PPI use
○ Formation of gastric fundic gland polyps	− Odds ratio of 2.2 for developing fundic gland polyps within 1-5 yr use of PPIs ▪ Negligible if any, risk of dysplasia

	Risk Possible/Magnitude Consequence
○ Acid rebound	– Consider slowly tapering dose when PPI is being stopped – Suddenly stopping PPIs taken for > 6 mon results in temporary hyperacidemia/symptoms

❖ Malabsorption

○ Vitamin B12 (cobalamin) malabsorption	– ↓ peptic release of B12 from protein – ↓ alkalinity of duodenal contents → ↓ R-factor plus B12 dissociation → ↓ binding of B12 to intrinsic factor (IF) → ↓ ileal absorption of IF-B12 complex → B12 deficiency

○ The relative risk of the above adverse effects is low. ~1.3

○ Calcium malabsorption

– In patients > 50 yr; adjusted odds ratio of 1.44 (95% confidence interval, 1.30-1.59) of hip fracture with PPI used longer than 1 yr
– While there is an ↑ relative risk of metabolic bone disease in persons who used PPI > 2 yr, the ↑ absolute risk of hip fractures per 1000 person-year is low

PPI Non-Users	PPI Users
	HR
Fractures	
▪ Hip*	1.30
▪ Spine	1.56
▪ All sites	1.16

* Hazard ratio was higher in current and than no former smokers, 1.51

○ Iron malabsorption

– Poor response to ↓ solubilization of oral iron supplement with PPIs absorption
  ▪ Improves after cessation of PPI
  ▪ No clear clinical relevance

○ Central nervous system (CNS)

– Headache
– Fatigue
– Dementia (poor evidence)

○ Respiratory
  – ↑ risk of community-acquired (CAP) as well as hospital acquired pneumonia (HCAP; presumably aspiration)

– Community / nosocomial infections
  ▪ Nested case-control analysis, adjusted odds ratio for pneumonia with PPI use of 1.73 (95% confidence interval, 1.33-2.25)

Abbreviations: CAP, community acquired pneumonia; HCAP, healthcare associated pneumonia

○ Gastrointestinal system (GI)
  – Abdominal pain
  – Diarrhea
    ▪ PPI-related
    ▪ Associated with enteric infection
  – ↑ LEs (mild ↑ALT/ ↑AST, reversible when PPI stopped)
  – Pancreatitis
  – Collagenous colitis (especially with lansoprazole)

– ↑ risk of C. difficile infection / Traveler's diarrhea
  - PPI use is an independent risk of *C difficile* diarrhea in antibiotic users, odds ratio of 2.1 (95% confidence interval,1.2-3.5)
  - Association with the use if PPIs occurs even in persons who have not previously taken antibiotics
  - Use of PPIs (or odds ratio)

	OR
– C. difficile infection	
▪ Incident	1.7
▪ Recurrent	2.5

- Genitourinary system (GU) – Interstitial nephritis
- Skin – Rash
- Musculoskeletal system (MSK) – Osteoporosis; – Hip fracture
- Endocrine – Hyperglycemia; – Hypergastrinemia
- Immune – Anaphylaxis

➢ Drug-drug Interactions

- Drug-drug interactions; PPIs metabolized by cytochrome P450 and may induce or inhibit metabolism of other drugs (drug-drug interaction)
  - Clinically significant PPI drug-drug interactions are rare (<1/million prescriptions)
  - Clinical significance of some PPIs reducing effectiveness of Plavix (clopidogrel) is uncertain.

- Concentration ↑ – Cyclosporine; – Digoxin; – Phenytoin; – Warfarin
- Concentration ↓ – Atazanavir; – Cefuroxime; – Itraconazole; – Ketoconazole

❖ Individual PPIs – Skin; – Epidermal necrolysis (Rabeprazole, R); – Erythema multiforme (R); – Stevens Johnson syndrome (R)

- Esomeprazole – Rhabdomyolysis
- Pantoprazole – Hyperglycemia
- Lansoprazole – Microscopic colitis; – Do **not** use in phenylketonuria (PCU; contains phenylalanine

❖ Infection
- ↑ risk of enteric infections in persons on PPI, including C. difficile, Campylobacter, Salmonella, and Travelers' Diarrhea
- ↑ risk of development of SBP (spontaneous bacterial peritonitis) in patients with ascites

❖ Cancer
- Data on PPI use and increased gastric *N*- nitrosamine remain uncertain, and the risk of cancer is speculative
- ↑ risk of colorectal cancer is speculative

❖ Safety in pregnancy
- FDA category B (safe in pregnancy and during lactation)
- No observed ↑ teratogenicity

- Possible ↑ risk of gastric cancer is a theoretical consideration:
  - Gastric colonization with bacteria that convert nitrates to carcinogenic *N*-nitroso compounds
- Interaction with H. pylori infection
  - The progression from gastritis from H. pylori infection → metaplasia/atrophic gastritis → dysplasia is accelerated by PPIs

- Comparison of the Metabolism, Pharmacokinetics (PK) and Pharmacodynamics (PD) of the Proton Pump Inhibitor (PPI) Lansoprazole and the Potassium-competitive Acid Blocker (PCAB, Vonoprazan)

Feature	Lansoprazole	Vonoprazan
○ Metabolism	Proton Pump Inhibitors (PPIs)	Potassium competitive acid blockers (PCABs)
− Prodrugs	+	-
− Converted to sulfonamide	+	-
− Stored in tuberculosis in inactive state	+	-
− Require acidic pH for activation in extracytoplasmic secretory vesicle in apical membrane of parietal cell	+	-
− Binding to		
▪ Active pumps (vesicles)	+	+
▪ Inactive pumps (cytoplasm)	-	+
▪ Cysteine (irreversible, non-competitive)	+	-
▪ Ionic (reversible competitive)	-	+
− Block		
▪ H^+ binding site	+	-
▪ K^+ binding site	-	+

Feature	Lansoprazole	Vonoprazan
○ Pharmacokinetics (PK)		
− Tmax, h	2	2
− T1/2, h	1.4	7.9
○ Pharmacodynamic (PD)		
− Day 7		
▪ Mean intragastric pH		
0-2 h	2.1	2.2
12-24 h	2.5	4.6
▪ % 24 h		
pH > 4	42%	88%

Adapted from Laine L, et al. Am J Gastroenterol 2022; 117: 1158-61)

- Concept of optimal PR in patients on PPIs; targeting duration of achieving

The area-under-the-curve (AUC) of the time-versus concentration of a drug may be the major factor for the efficacy of some drugs, others the Cmax, T1/2, volume of distribution, lipids solubility, or metabolism/excretion. For proton pump inhibitions (PPIs), their efficacy depends mainly on the achievement of an intragastric pH > 4 for the longest period (usually about 14-18 h). Higher class of PPI have only a small ↑ rate of healing of duodenogastric ulcers, but any change in the PPI to prolong the time to intragastric pH is > 4 (such as Tecta, where essentially a magnesium [Mg^{2+}] id added to pantoprazole) to extend the duration of the pH being > 4. For the treatment of patients with gastroesophageal reflux disease (GERD), reduction of morbidity and mortality rates in persons with upper GI bleeding from peptic ulcers, or the use of PPIs with selected antibiotics to eradicate infection with H. pylori, the target pH will be higher. Yet again, it is the duration that the pH is above a clinical level.

❖ **Histamine H_2 Antagonists** (aka H2RA [histamine 2 receptor antagonists])

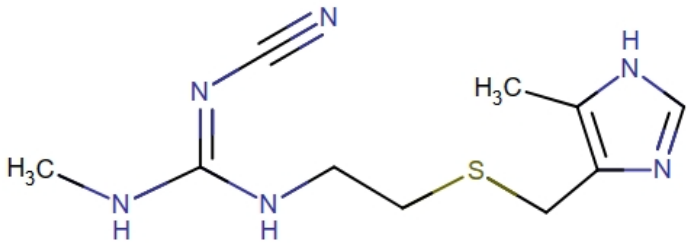
➢ Mechanism of action

- Occupies H_2-receptor on basolateral portion of parietal cell to ↓ HCl secretion arising from the gastric stimulus effect of histamine from enterochromaffin cells

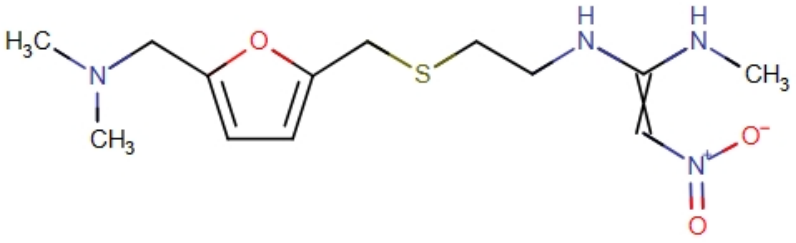
➢ Nocturnal Acid Breakthrough (NAB)

- Patients with dyspepsia at bedtime despite PPI therapy, and who have pH > 4 for ≥ 1 h at night, have “nocturnal acid breakthrough”.
- This often fails to respond to adequately higher doses of PPI
  - Give why this benefit of H2RA in patients with nocturnal acid breakthrough is often lost within 2 wk.
    - There is tachyphylaxis due of the H2 receptors.
    - If the patient takes a “drug holiday” from H2RA, their inhibition effect of nocturnal intragastric acid may be restored.
  - Give why the weaker H2RA (receptor antagonist) when added to the PPI may give symptomatic relief.
    - PPIs require food to be activated and to ↓ H^+ secretion.
    - At night when the patient is fasting, there is basal acid secretion, which is not affected by PPI.
    - H2RA block the histamine site on the parietal cell regardless of the intake of food.
    - This nighttime fasting inhibition of H^+ may be sufficient to ↓ nocturnal symptoms.

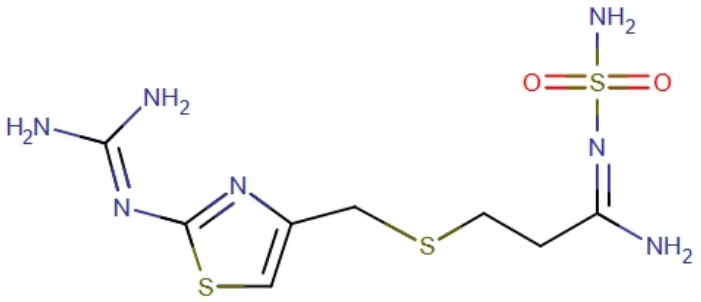
- **Cimetidine**



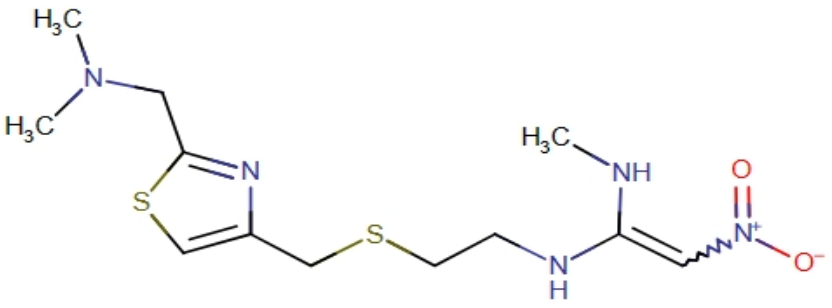
- **Ranitidine**



- **Famotidine**



- Nizatidine



- Pharmacokinetics

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Bioavailability	80	50	40	>90
Relative potency	1	5-10	32	5-10
Half-life (h)	1.5-2.3	1.6-2.4	2.5-4	1.1-1.6
Duration of action (h)	6	8	12	8
Inhibition of CYP450	1	0.1	-	-
Dose (mg) bd	400	150	20	150

- Contraindications/precautions
  - Hypersensitivity to the H2RA or any of its components
- Adverse effects (AEs)
  - CNS
    - Agitation
    - Headache/dizziness
    - Insomnia/somnolence
    - Fatigue
  - CVS
    - Bradycardia/bradyarrhythmia
  - GI
    - Nausea/vomiting
    - Diarrhea/constipation
    - Abdominal pain
    - Pancreatitis
    - Necrotizing enterocolitis in children
- Drug-drug interactions
  - Blood levels
    - ↓ atazanavir
    - ↓ iron
    - ↑ fluvastatin (→ ↑ risk of rhabdomyolysis)
  - Tenofovir
    - ↑ blood levels of ranitidine
- Pregnancy/lactation
  - Individual H2-RA
    - –Famotidine
      - ↑ liver enzymes (LEs)
      - ↓ blood Harvoni® (when famotidine given in high dose)
    - –Rabeprazole
      - Skin
        - Stevens-Johnson syndrome
      - Musculoskeletal (MSK)
        - Hip fracture
        - Rhabdomyolysis

- Food Drug Administration (USFDA**)** category for the safety of drugs used to treat GERD in pregnancy andrecommendations for breastfeeding.

Drugs	Recommendations for Breastfeeding
○ Antacids	
– Aluminum-, calcium or most magnesium-containing antacids	▪ Only calcium-containing antacids should be used for GERD symptoms in pregnancy. ▪ Avoid long-term, high-dose therapy with antacids in pregnancy ▪ Composition – Aluminum-containing antacids may cause **fetal neurotoxicity**, – Alginic acid (Gaviscon, sucralfate) may cause **fetal distress** – Magnesium-containing antacids may cause renal stones, respiratory distress, and cardiovascular impairment, and hypothermia.
– Magnesium trisilicates	▪ Do **not** use in pregnancy (causes fluid overload and metabolic alkalosis)
– Sodium bicarbonates	▪ Acceptable for human use because of minimal absorption
○ Mucosal protectant – Sucralfate	▪ Safe in pregnancy
○ Histamine2-receptor antagonist (H2RA) – Cimetidine, Ranitidine, Famotidine,Nizatidine	▪ Safe in pregnancy
○ Proton-pump inhibitors	▪ Safe in pregnancy
○ Promotility agents – Cisapride	▪ Embryotoxic and fetotoxic in animals. ▪ Prospective controlled study in human suggests acceptable in pregnancy, but was removed from general use because of reports of fatal cardiac arrhythmias
– Metoclopramide	▪ Do **not** use in pregnancy (Embryotoxic and fetotoxic) ▪ Possible cardiac damage

* The FDA category has been officially disbanded, but remains clinically useful for the cautious clinician

Printed with permission: Ali RAR, and Egan LJ. Best Pract Res Clin Gastroenterol 2007;21(5):793-806 (Table 1).

EOSINOPHILIC ESOPHAGITIS (EoE)

- Definition
  - Idiopathic but likely immune–condition causing inflammatory infiltration of eosinophils into the mucosa of all portions of the esophagus
    - ≥ 15 eosinophils in ≥ 2 hpf, ≥ 25 eosinophils in ≥ 1 hpf, 2-4 biopsies from the distal and proximal esophagus
      - Eosinophilic microabscesses, ≥ 4 eosinophils in aggregation

- Endoscopy
  - Corrugation (multiple rings)
  - Longitudinal furrows
  - Mucosa — featureless, fragile (crepe paper–like)
  - White surface vesicles (eosin microabscesses)
  - Proximal or mid–esophageal stenosis and strictures
  - Small caliber esophagus
  - Shortening of esophagus
  - Food impaction

- Clinical
  - Dysphagia
  - Dyspepsia
  - Solid food bolus impaction
  - Reactive airway disease
  - Atopy to skin conditions
  - Typical presentations of eosinophilic esophagitis.
    - Young adult
    - Male to women ration of 3:1
    - Intermittent dysphagia, sometimes severe; food impaction
    - Chest pain with odynophagia
    - Peripheral eosinophilia is common
    - Atopic diseases

- Causes / Associations

- Eosinophilic gastrointestinal diseases (EGIDs)
  - Idiopathic
    - Eosinophilic syndromes
  - Infection
    - Fungal, parasitic and non–parasitic

- Inflammation
  - Gastroesophageal reflux disease (GERD)
  - Gluten sensitive enteropathy [celiac disease] (GSE)
  - Inflammatory bowel disease (IBD)
  - Microscopic colitis (MC)
- Neoplasia
  - Hodgkin lymphoma
  - Leiomyomatosis
- Immune
  - Allergic vasculitis
  - Allergy (i.e., foods)
  - Autoimmune
    - Connective tissue disease (i.e. scleroderma)
    - Graft-versus-host (GVH) diseases
    - Hypersensitivity
    - Post–transplantation
- Iatrogenic
  - Drugs (i.e. gold, azathioprine)

➢ Treatment

- Advantage and disadvantages of current medical and nutritional treatment strategies for eosinophilic esophagitis.

Treatment	Advantages	Disadvantages
❖ Pharmacology		
○ Proton pump inhibitors, standard dose, 30-60 min before first meal of the day		
○ Viscous budesonide (<10 yr, 1 mg daily; >10 yr, 2 mg daily)	– Easier to swallow – Theoretically can reach more distal areas of esophagus – ↓ symptomsand heals esophageal mucosa	▪ Cumbersome to mix ▪ Risk of candida esophagitis ▪ Long-term efficacy unknown
○ Prednisone* (1-2 mg/kg/day: maximum 60 mg)	– Rapid ↓ symptoms	▪ Significant systemic side effects ▪ Prompt recurrence when discontinued

Treatment	Advantages	Disadvantages
○ Swallowed fluticasone (children, 440-880 µg/day; adolescents/adults, 880-1769 µg/day)	− Minimal systemic steroid absorption − ↓ symptoms − Heals esophageal mucosa	▪ Risk of candida esophagitis ▪ Small amount is systemically absorbed ▪ Long term efficacy unknown, but prompt recurrence when discontinued ▪ Difficult for small children and developmentally delayed patients to swallow ▪ Not for maintenance
○ Elemental diet	− 92%-98% effective − Resolution of symptoms in7-10 d − Histologic remission within 4-5 wks	▪ Poor palatability ▪ Usually requires nasogastric or gastrostomy tube ▪ Very expensive ▪ Socially isolating
○ Montelukast (20- 40 mg daily) (leukotriene D4 receptor inhibitor)	− Symptomatic relief has been shown at high doses(100 mg) − No significant adverse effects	▪ **Not** recommended because of − Lack of reduction of eosinophilic infiltration in the esophageal mucosa − Inadequate studies

- Mechanism of action
  - Proton pump inhibitors
    - Block gastric acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump
  - Corticosteroids
    - Controls the rate of protein synthesis
    - Depresses the migration of polymorphonuclear leukocytes, fibroblasts
    - Reverses capillary permeability
    - Lysosomal stabilization at the cellular level to prevent or control inflammation.
  - Montelukast
    - Binds with high affinity and selectivity to the CysLT type 1 receptor, which consequently assists in inhibiting any physiological actions of CysLTs like LTC4, LTD4, and LTE4 at the receptor

❖ Non-pharmacological

- Elimination diet
  - Evidence for benefit in adults, similar to benefit in children
  - Commonest food allergies are dairy, eggs, wheat, soy, peanuts, fish/shellfish
  - Do **not** use skin prick testing in patients with EoE (poor correlation between symptoms / eosinophilic condition and results of skin testing) to diagnose Type 1 IgE-mediated sensitivity, and skin patch testing forType IV Th-2 delayed hypersensitivity reactions

INFECTIOUS ESOPHAGITIS

- **Candidiasis, and other fungal infections**

➢ Causes/associations

❖ Fungal
  - Aspergillosis
  - Blastomycosis
  - Candida Albicans
  - Cryptococcosis
  - Histoplasmosis

  – Recommended antimicrobial therapy, fluconazole or itraconazole

➢ Risk factors
  - Iatrogenic
    - Drugs
      - Antibiotics, broad spectrum
      - Chemotherapy
      - Corticosteroids
      - Immunosuppressives
    - Catheters
      - Hemodialysis
      - Total parenteral nutrition (TPN)
    - Hospitalizations
    - Transplantation
    - Recent surgery
  - Infection
    - Pancreatitis
    - HIV-infection, CD4 < 100 cells/μL
  - Infiltration
    - Malignancy
  - Kidney
    - Acute kidney injury (AKI)
  - Blood
    - Neutropenia

- Clinical
  - Microabscesses in virtually any organ, but especially in
    - Eye
      - White exudates
    - Skin
      - Painless papules/pustules on red base
    - MSK
      - Bone
      - Joints
    - GI
      - Peritoneum
    - GU
      - Urinary tract infection (UTI)

- Diagnosis
  - Culture
    - Tissue from skin lesion, or any involved organ, or blood
      - Since candida pneumonia is very rare, sputum culture is not usually performed.
    - Blood culture is the "gold standard"
    - Negative blood culture does not exclude systemic candidiasis
    - Candidiasis obtained from a blood culture should never be considered a contaminant, but instead should initiate investigation for a cause/source.

- Treatment

Drugs	Mechanism of action
Azole – Fluconazole – Voriconazole	– Selective inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-α-demethylase (This enzyme normally works to convert lanosterol to ergosterol, which is necessary for fungal cell wall synthesis)
Caspofungin IV	– Inhibiting the synthesis of β (1,3)-D-glucan, an essential component of the fungal cell wall. This disrupts the growth of the fungi and causes them to die.
Clotrimazole troche	– Inhibition of ergosterol biosynthesis, an essential constituent of fungal cell membranes.

- Non-immunocompromised
  - Spontaneous remission is usual before 2 wks;
  - Acyclovir 200 mg po 5x/day, or 400 mg po t.i.d. for 7 to 14 days for faster symptom relief

- Non-neutropenic
  - Fluconazole
    - First choice for C. parapsilosis
    - If no/poor response, switch to echinocandin
  - Caspofungin

- Anidulafungin
  - Micafungin
  - If echinocandin response is poor, switch to Fluconazole if patient is stable
    - First choice empiric therapy for Candida glabrata
    - If echinocandin fails when used for C. glabrata, perform susceptibility testing before using
      - Fluconazole, or step-down
      - Voriconazole
- Treat for 2 wks after
  - Loss of symptoms
  - Clearance of fungemia
- Remove possibly causative catheters, central lines

Therapeutic Alert

- Do **not** use echinocandins for meningitis or endophthalmitis

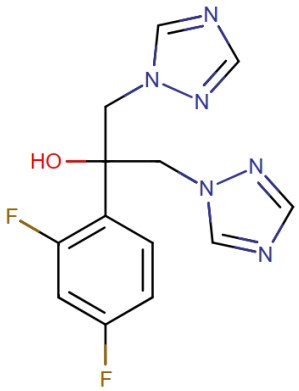
- Neutropenic
  - Echinocandin, or
  - Voriconazole, or
  - Amphotericin B, echinocandin

- Immunocompromised
  - HIV-seropositive
    - HAART therapy
      - Restoration of CD4 counts > 100 cells/μL helps to ↓ risk of recurrent disease
      - Recurrent disease, moderate-to-severe infection, or CD4 < 100 cells/μL (at risk for esophageal candidiasis)
        - Fluconazole po 200 mg loading dose, followed by 100 mg to 200 mg a day for 7 to 14 days.
  - Symptom relief: viscous xylocaine/lidocaine, gargle/swallow ~ 300 mg/dose, ≤ 8x/day
  - For severe disease (odynophagia, dysphagia, or unable to swallow):
    - Acyclovir, 5 mg/kg IV q8h for 7 to 14 days
    - Acyclovir-resistant (cross-resistance of valacyclovir and famciclovir due to mutation of thymidine kinase or DNA polymerase): use foscarnet
  - Asymptomatic cystitis
    - Treat with fluconazole, if patient
      - Neutropenic
      - Having urologic surgery
  - Focal infections
    - Meningitis
    - Endophthalmitis

    } ▪ Do **not** use echinocandins

- Systemic/Invasive Candidiasis
  - Candidemia
  - Disseminate candidiasis
  - Focal organ involvement
  - Hepatosplenic (chronic disseminated)

❖ **Fluconazole**



➢ Pharmacokinetics

- Absorption
  - > 90%, po in healthy volunteers
  - Oral absorption is not affected by food intake but may increase the time until the maximum concentration is reached
  - Tmax 3 h, in healthy patients receiving 50 mg/kg fluconazole
  - Cmax in fasting and healthy volunteers occur between 1-2 h post-dose
  - Steady-state concentrations are achieved within 5-10 days 50-400 mg po od
  - Loading dose on the first day, or twice the usual daily dose → plasma concentrations close to steady-state by the second day
- Volume of distribution
  - Similar to the volume of distribution of total body water
  - Substantial penetration in many body fluids, stratum corneum, dermis-epidermis of skin, eccrine sweat and can cross the blood-brain barrier
- Metabolism
  - Metabolized minimally in the liver
  - Inhibitor of CYP2C9, CYP3A4 and CYP2C19
- Route of elimination
  - In healthy subjects, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose measured in the urine as unchanged drug.
  - About 11% of the dose is excreted in the urine as metabolites.
  - Dose of fluconazole may need to be reduced in patients with decreased renal function.

- Half-life
  - Elimination half-life in the plasma is approximately 30 h after oral administration.
  - ↑ T1/2 supports a single-dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.
  - Patients with renal failure may require dosage adjustment, and half-life can be significantly increased in these patients.
- Clearance
  - Mainly eliminated by the kidney
  - Mean body clearance in adults is 0.23 mL/min/kg
  - Clearance in the pediatric population varies according to age, as does clearance in patients with renal failure

➢ Contraindication/precautions

- Known hypersensitivity to fluconazole or any component in their formulation
- Adverse effects / drug-drug interaction

CVS	– QT prolongation – Pre-existing heart disease / arrythmias
↓ liver/renal function	– Electrolyte disturbances
Blood	– Hematologic malignancy
Endocrine	– Galactose intolerance – Lactose deficiency

➢ Adverse effects

CNS	– Headache/dizziness – Seizures
CVS	– QT prolongation / torsade de pointes – Arrythmias
GI	– Nausea/vomiting – Altered taste – Abdominal pain
Blood	– Agranulocytosis/leucopenia – Thrombocytopenia
Skin	– Angioedema – Rash – Stevens-Johnson syndrome (SJS)

➢ Drug-drug interaction

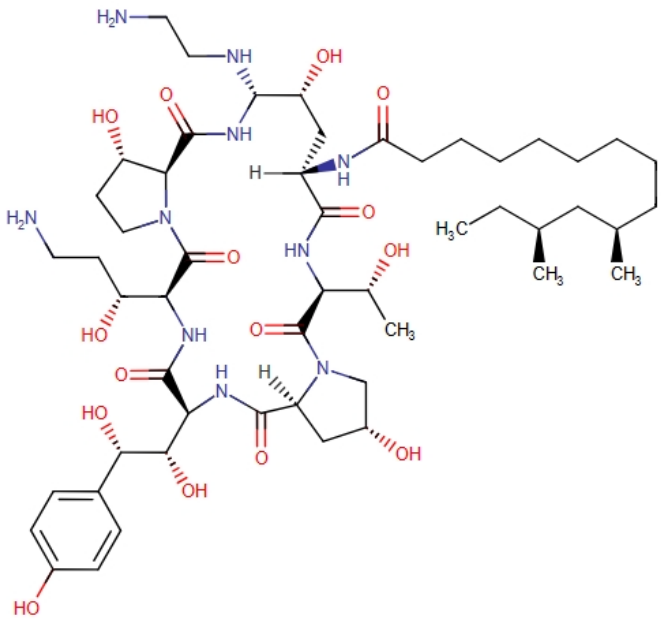
↑ blood concentrations / ↑ toxicity of	– Barbiturates – Carbamazepine – Rifabutin – Rifampin

- ↑ QT prolongation when used with
  - Amiodarone
  - Cisapride
  - Droperidol
  - Phenothiazines
  - Pimozide
  - Quinidine
  - Ranolazine

➢ Peripartum

- Pregnancy – Safe
- Lactation – Safety uncertain

❖ **Caspofungin**



➢ Pharmacokinetics

- Absorption
  - 92% tissue distribution within 36-48 h after IV infusion
- Volume of distribution
  - NA
- Metabolism
  - Metabolized slowly by hydrolysis and N-acetylation
- Route of elimination
  - After single IV administration of [3H] caspofungin acetate, excreted 35% in feces and 41% in urine.

- Half-life
  - 9-11 h
- Clearance
  - 12 mL/min (after single IV administration)

➢ Contraindication/precautions

- Known hypersensitivity to caspofungin, or any component in their formulation
- Adverse effects / drug-drug interaction, e.g., hepatotoxicity

➢ Adverse effects

GEN	– Fever/chills – Flushing
Lungs	– Adult respiratory disease syndrome (ARDS) – Pulmonary edema
GI	– Nausea/vomiting – Abdominal pain – Diarrhea – Hepatotoxicity
Blood	– Eosinophilia
Endocrine	– ↑ Ca^{2+}_s (hypercalcemia) – ↓ K^{+}_s (hypokalemia)

Abbreviations: GEN, general; GI, gastrointestinal

➢ Drug-drug interaction

- Cyclosporine → ↑ caspofungin blood concentration → ↑ risk of toxicity
- Caspofungin → ↓ blood levels / ↓ efficiency of
  - Dexamethasone
  - Efavirenz
  - Nevirapine
  - Phenytoin
  - Rifabutin
  - Rifampin
  - Sirolimus
  - Tacrolimus

❖ Oropharyngeal candidiasis

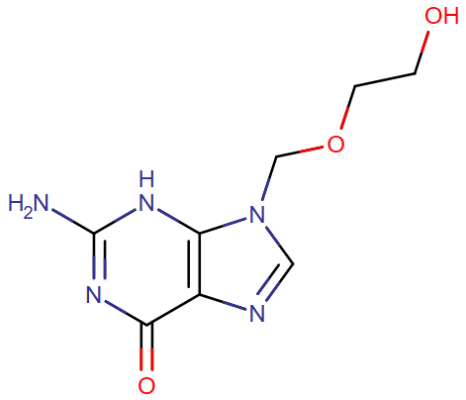
Clinical Gems and Pearls

- The presence of oropharyngeal candidiasis ↑ likelihood of esophageal infection, but Candida esophagitis may occur in the absence of oropharyngeal disease.
- An immunosuppressed patient who develops odynophagia/dysphagia, with or without oropharyngeal candidiasis, may be treated empirically with fluconazole.
- If a 3 day course of fluconazole does not relieve the esophageal symptoms,perform EGD to diagnose
  - Other causes of esophagitis e.g.,
    - Pill esophagitis
    - Herpes simplex virus (HSV) infection
    - Cytomegaloviral (CMV) esophagitis
    - Gastroesophageal reflux disease (GERD)
  - Fluconazole-resistant strains
- When esophageal candidiasis is associated with HIV-seropositivity with CD4 <100 cells/μL
  - Don't forget to mention the use of HAART therapy to restore CD4 levels to ↓ risk of recurrent disease.

- Risk factors for oropharyngeal candidiasis
  - CD4 < 200 cells/μL
  - Prior colonization or infection with C. albicans
- Local
  - Nystatin swish and swallow, 400,000 to 600,000 units q.i.d. for 7 to 14 days (only for mild disease)
  - Clotrimazole: one 10 mg troche dissolved slowly taken, 5 times a day
    - May be first-line therapy, or when there are risk factors (e.g., steroids, chemotherapy), or when there is no/poor response to nystatin
- Systemic
  - Fluconazole
    - 200 mg loading dose, followed by 100 mg to 200 mg a day for 7 to 14 days
    - Prophylaxis: 100 mg po od

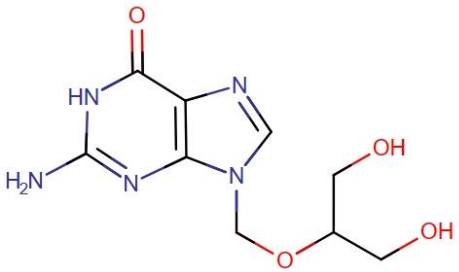
- Adverse drug effects
  - Azoles
    - All equally effective
    - Hepatotoxic
    - Teratogenic in pregnancy
    - Multiple drug interactions (CYP450)
    - ↑ risk of drug resistance
  - Fluconazole
    - Secondary prophylaxis, 100 mg to 200 mg per week, for
      - Risk of cryptococcosis
      - No immune reconstitution on HAART Rx – frequent/severe candidiasis
    - Same dose as for oropharyngeal candidiasis, but treatment duration 7 to 14 days
    - May be given IV
  - Itraconazole oral solution
    - 10 mg/mL, 200 mg daily for 7 to 14 days
    - Nausea in > 10% of patients
  - Posaconazole
    - 200 mg b.i.d.
    - Transient visual disturbance in 25% of users
  - Echinocandins are given IV for esophageal candidiasis refractory to azoles
    - Anidulafungin
      - 100 mg IV per day
    - Caspofungin
      - 50 mg IV per day for 7 to 21 days
    - Micafungin
      - 100 mg to 150 mg IV per day
  - Amphotericin B
    - Indications
      - Treatment of candidiasis during pregnancy (azoles are teratogenic)
      - Resistance to azoles or echinocandins
    - Dosage
      - 0.3 to 0.7 mg/kg per day

- **Herpes Simplex Virus** (HSV) **Infection**
  - Acyclovir



- **Cytomegalovirus** (CMV) **Infection**

❖ **Ganciclovir**



Similar profile for valganciclovir, but varying dosage

➢ Mechanism of action

- Inhibition of the replication of viral DNA by ganciclovir-5'-triphosphate (ganciclovir-TP) →
  - Selective and potent inhibition of the viral DNA polymerase.

➢ Pharmacokinetics

- Absorption
  - Poorly absorbed following oral administration.
  - Bioavailability under fasting conditions is approximately 5%, and when administered with food, 6 to 9% (about 30% with a fatty meal).
- Volume of distribution
  - 0.74 ± 0.15 L/kg
- Metabolism
  - Little to no metabolism
    - ~ 90% plasma ganciclovir eliminated unchanged in the urine
- Route of elimination
  - Renal excretion of unchanged drug by glomerular filtration
  - Active tubular secretion is the major route of elimination of ganciclovir

- Half-life
  - 2.5 to 3.6 h (mean 2.9 h) (IV in adults)
  - 3.1 to 5.5 h (po in adults)
  - ↑ T1/2 in renal impairment in half life (9 to 30 h IV, 15.7 to 18.2 h po)
- Clearance
  - 128 ± 63 mL/min (patients with CrCl 50-79 mL/min)
  - 57 ± 8 mL/min (patients with CrCl 25-49 mL/min)
  - 30 ± 13 mL/min (patients with CrCl <25 mL/min)
  - 4.7 ± 2.2 mL/min/kg (pediatric patients, aged 9 mon to 12 yr)

➢ Indication

- CMV colitis / esophagitis
- CMV prophylaxis

➢ Contraindication/precautions

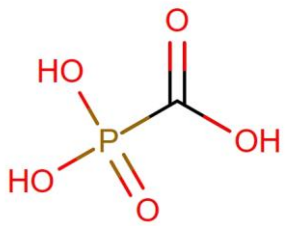
- Known hypersensitivity to ganciclovir, acyclovir, or any component in their formulation
- Adverse effects / drug-drug interaction
- Neutropenia (<500) / thrombocytopenia (<25,000) / myelosuppression
- ↓ renal function
- Chemotherapy

➢ Adverse effects

- General
  - Fever
- CNS
  - Depression
  - Seizures
  - Psychosis
  - Neuropathy
  - Retinal detachment
- CVS
  - Hypertension
- GI
  - Nausea/vomiting
  - Diarrhea
  - Bowel perforation
  - Hepatotoxicity (↑ ALT / ↑ AST)
  - Pancreatitis
- GU
  - Nephrotoxicity
  - Infertility
- Blood
  - Anemia
  - Aplastic anemia
  - Leucopenia
  - Myelosuppression
  - Pancytopenia/thrombocytopenia

- Drug-drug interaction
  - CNS – ↑ risk of seizures with imipenem
  - GU – ↑ risk of nephrotoxicity when given with
    - Aminoglycosides
    - Carboplatin
    - Cisplatin
    - Clofarabine
    - Efavirenz
    - Emtricitabine
    - Tacrolimus
    - Tenofovir
  - Blood – ↑ risk of myelosuppression when given with
    - Azathioprine
    - Cisplatin
    - Clozapine
    - Methotrexate
- Peripartum
  - Pregnancy – Safe
  - Lactation – Do **not** use

❖ **Foscarnet**



Similar profile as for valganciclovir, but varying dosage

- Mechanism of action
  - Binds reversibly near the pyrophosphate-binding site of DNA polymerase (or reverse transcriptase) without requiring further modification.
  - After binding, the drug blocks the cleavage of the pyrophosphate moiety from deoxynucleotide triphosphates, thereby halting DNA chain elongation.
- Pharmacokinetics
  - Absorption
    - Poorly absorbed after oral administration
    - Bioavailability from 12 to 22%

- Volume of distribution
  - NA
- Metabolism
  - Not metabolized
- Route of elimination
  - Not Available
- Half-life
  - 3.3-6.8 h
- Clearance
  - 2.13 ± 0.71 mL/min/kg (patients with normal renal function, CrCl > 80 mL/min)
  - 68 ± 8 mL/min/kg (CrCl 50-80 mL/min)
  - 34 ± 9 mL/min/kg (CrCl 25-49 mL/min)
  - 20 ± 4 mL/min/kg (CrCl 10-24 mL/min)

➢ Contraindication/precautions

- Known hypersensitivity to foscarnet, or any component in their formulation
- Adverse effects / drug-drug interaction
  - CNS – Seizures
  - GU – Electrolyte disturbances
    – Nephrotoxicity
  - Blood – Myelosuppression

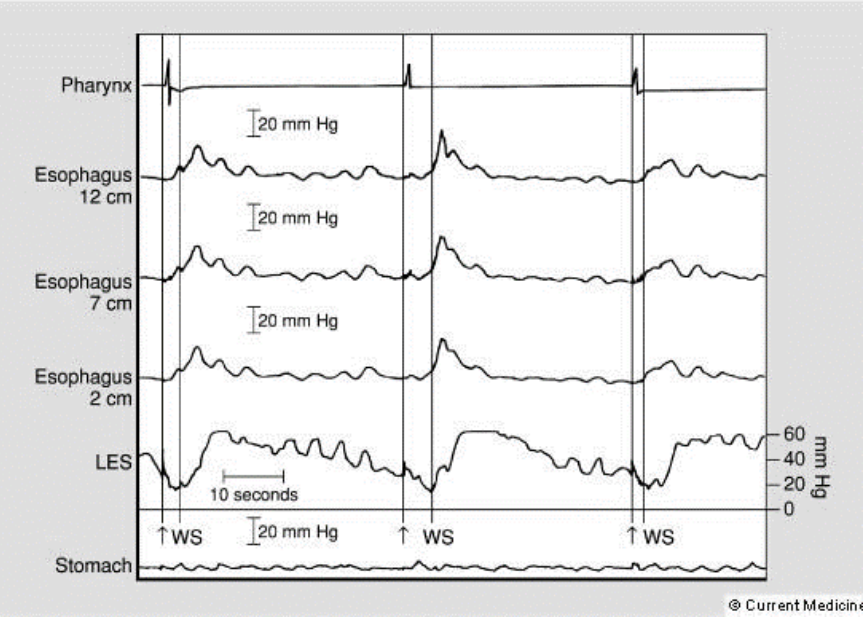
➢ Adverse effects

- GEN – Fever
- CNS – Paresthesia
- GI – Nausea/vomiting
  – Diarrhea
  – Pancreatitis
- GU – Nephrotoxicity
  – Electrolyte disturbance
    - ↓ Ca^{2+}_s (hypocalcemia)
    - ↓ K^{+}_s (hypokalemia)
    - ↓ Mg^{2+}_s (hypomagnesemia)
- Blood – Anemia
  – Granulocytopenia/leukopenia
  – Thrombocytopenia

- Drug-drug interaction
  - CVS – ↑ QT prolongation
    - Amiodarone
    - Droperidol
    - Erythromycin
  - GU – Nephrotoxicity with
    - Aminoglycosides
    - Carboplatin
    - Cidofovir
    - Cisplatin
    - Clofarabine
    - Efavirenz
    - Emtricitabine
- Peripartum
  - Pregnancy – Safe
  - Lactation – Safety not known

ACHALASIA

- Conventional Manometry
  - ↓ LES relaxation ± ↑ resting LES pressure
  - Absent peristalsis (but can have spasm or pressurization)
  - ↑ baseline intraesophageal pressure
  - Normal values



Lower esophageal sphincter (Normal values in brackets)	Esophageal body: (Normal values in brackets)
○ Resting pressure: 23 mmHg (16-30) ○ Relaxation duration: 6 seconds (> 2) ○ % relaxation: 58.5% (80-100%) ○ Residual pressure: 9.3 mmHg (< 8)	– Peristaltic contractions: 0% (> 80%) – Simultaneous contractions: 100% (< 20%) – Mean contraction amplitude: 16 mmHg (30 – 180) – Mean contraction duration: 2.7 seconds (< 5.8) – Low amplitude contractions: 100% (< 30%) – Spontaneous activity between swallows: none

- Acid Infusion test: not done

- Pharyngoesophageal sphincter (PE): not done
  - Resting Pressure: mm Hg (40-150 mm Hg)
  - Pharyngeal contraction pressure: mm Hg (40-150 mm Hg)
  - Coordination:

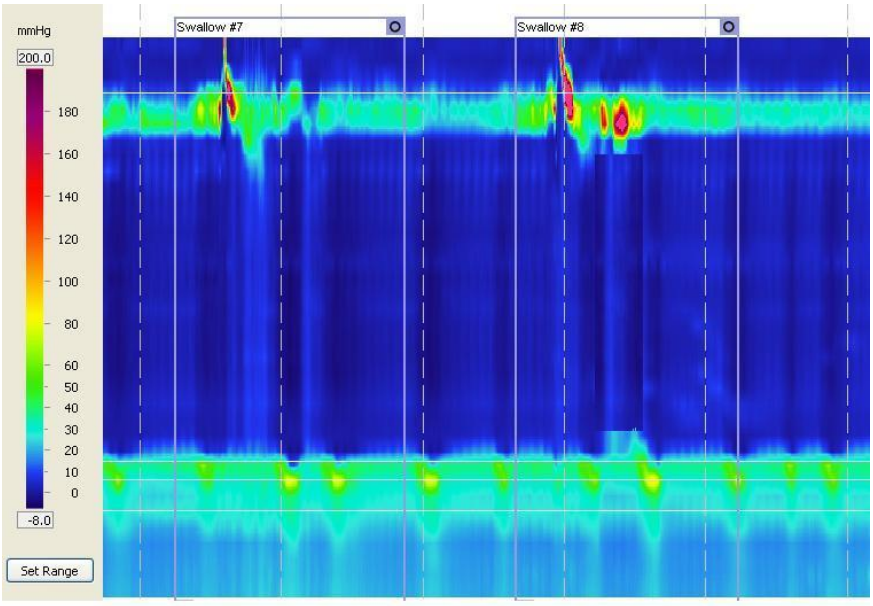
Summary and Conclusions: Normal LES pressure. Relaxations are incomplete and esophageal retention is evident. Marked motor abnormality of the body of the esophagus. No peristalsis is seen. All waves are simultaneous and of decreased amplitude, diagnostic of achalasia.

➢ High Resolution Esophageal Manometry (HREM)

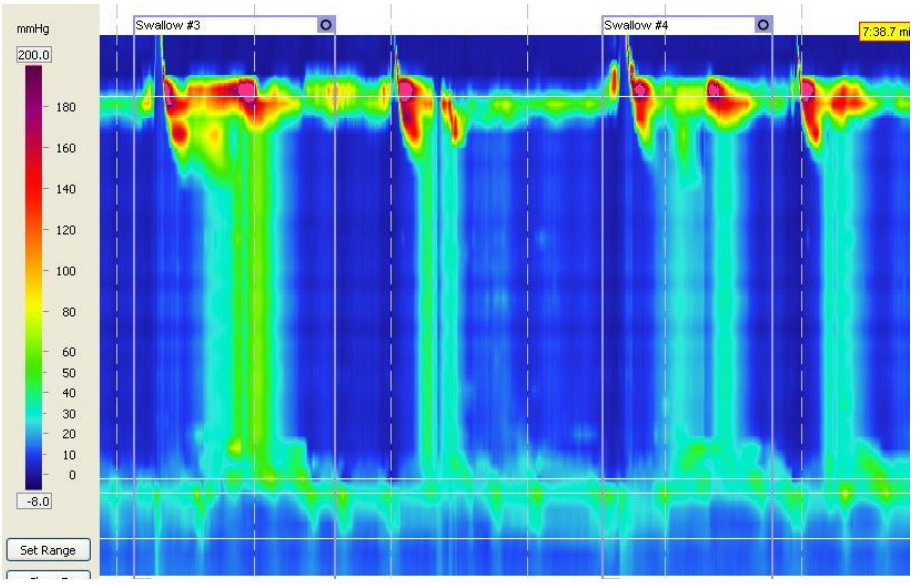
- Subtypes of Achalasia on HREM

Subtypes	IRP > ULN	No Peristalsis	Normal	Additional Features
Type I	+		+	
Type II	+		+	▪ Panesophageal pressurization > 20%
Type III	+		+	▪ Premature contractions of distal esophagus > 20%

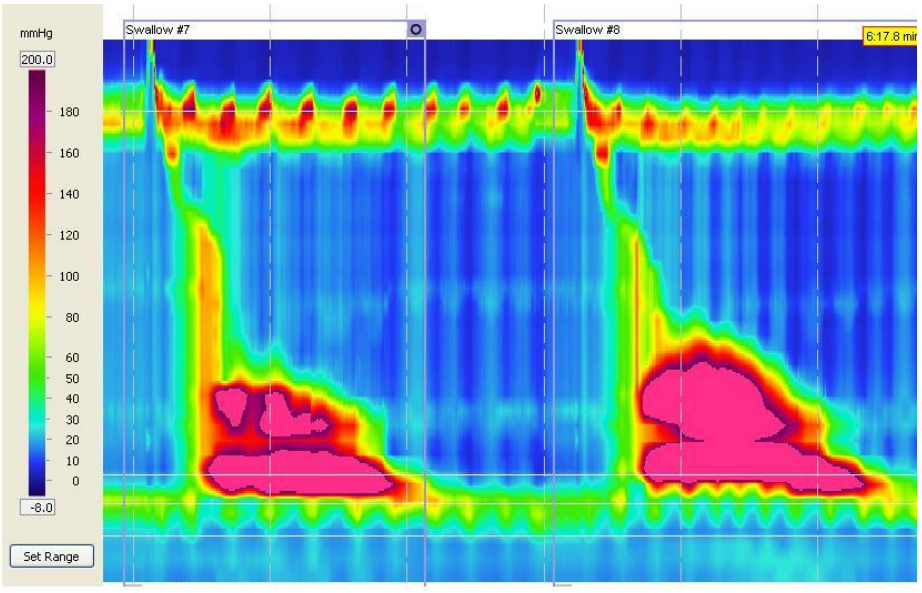
Type I IRP > ULN, 100% failed peristalsis



Type II IRP > ULN, no normal peristalsis, panesophageal pressurization > 20%



Type III IRP > ULN, no normal peristalsis, premature contractions distal esophagus >20%



- Causes of secondary achalasia (pseudoachalasia)

❖ Infection and infiltration
  - Amyloidosis
  - Chagas disease (*Trypanosoma cruzi*)
  - Fabry disease
  - Sarcoidosis
  - Sjögren syndrome

❖ Cancer (GI)
  - Squamous cell carcinoma of the esophagus
  - Adenocarcinoma
    - Esophagus
    - Gastric cardia
  - Hepatocellular carcinoma
  - Pancreatic adenocarcinoma

❖ Cancer (Non–GI) (Paraneoplastic syndrome)
  - Breast adenocarcinoma
  - Leiomyoma
  - Lung carcinoma (non–small cell)
  - Lymphangioma
  - Lymphoma
  - Mesothelioma
  - Metastatic prostate carcinoma
  - Metastatic renal cell carcinoma
  - Reticulum cell sarcoma

❖ Motility abnormalities
  - Achalasia with associated Hirschsprung disease
  - Familial achalasia
  - Fundoplication
  - Hereditary hollow visceral myopathy
  - Parkinson disease

❖ Surgical

- Post–fundoplication
- Post–vagotomy

❖ Miscellaneous

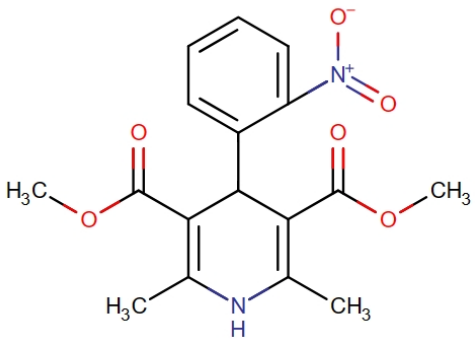
- Allgrove syndrome (AAA [triple A] syndrome)
  - Mutation in AAAs gene encoding the protein ALADIN (alacrima-achalasia-adrenal insufficiency neurological disorder
  - Clinical features:
    - Achalasia
    - Addison
    - Alacrima
    - Autonomic dysfunction
    - Nasal voice
    - Neuromuscular disease
- Autoimmune polyglandular syndrome type II
- Hereditary cerebellar ataxia
- MEN IIb (Sipple Syndrome)

Adapted from: Clouse, R. E. and Diamant, N. E. Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology / Diagnosis / Management 2006:871.

➢ Treatment

❖ **Smooth Muscle Relaxation**

- **Nifedipine**



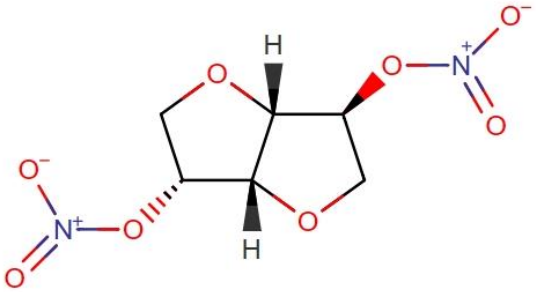
➢ Indication

- Esophagus
  - Achalasia
  - Distal esophageal spasm (DES)
- Stomach
  - Dumping syndrome
  - Tachygastria

- Mechanism of action
  - Calcium channel blocker
- Pharmacokinetics
  - Absorption
    - Sublingual (Cmax 10ng/mL, Tmax 50 min, and AUC 25ng*h/mL)
    - Oral (Cmax of 82 ng/mL, Tmax 28min, and AUC 152ng*h/mL)
    - ↓ solubility and ↑ intestinal permeability
      - Almost completely absorbed in the GI tract but has a bioavailability of 45-68%, partly due to first pass metabolism
  - Volume of distribution
    - At steady state, 0.62-0.77 L/kg
    - Central compartment, 0.25-0.29 L/kg
  - Metabolism
    - Predominantly metabolized by CYP3A4 to 2,6-dimethyl-4-(2-nitrophenyl)-5-methoxycarbonyl-pyridine-3-carboxylic acid, and then to 2-hydroxymethyl-pyridine carboxylic acid.
  - Route of elimination
    - 60-80% in urine as inactive water-soluble metabolites, and the rest in the feces as metabolites.
  - Half-life
    - ~2 h
- Contraindication/precautions
  - Known hypersensitivity to nifedipine or its components
  - CVS
    - Heart failure / edema
    - Hypotension
    - Myocardial infarction (within 4 wks) / angina pectoris (unstable)
- Dosing
  - Nifedipine po 10-30 mg od, then
    - Continue long term if benefit achieved
- Adverse effects (AEs)
  - CNS
    - Headache/dizziness
  - CVS
    - ↑ risk of angina/myocardial infarction
    - Heart failure / edema
    - Palpitation/edema
  - Skin
    - Flushing

- Drug-drug interactions
  - ↑ risk of CVS AEs with
    - Nitrates
    - B-blockers (octreotide, amiodarone)
      - ↑ risk of hypotension
      - ↑ risk of
        - AV block
        - Bradycardia
        - Hypotension
- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Safety not certain

- **Isosorbide Dinitrate (Isordil®)**



- Indication
  - Distal esophageal spasm (DES)
- Mechanism of action
  - Chemically related to glyceryl trinitrate, and has a similar mechanism of action
  - Directly relaxes the arterial smooth muscle at the postcapillary sphincter (dilation of the venous capacitance bed)
    - ↓ venous return
    - ↓ preload, and to a lesser extent at the arterial resistance vessels → ↓ afterload
  - ↓ myocardial oxygen requirements.
  - The epicardial coronary arteries are dilated even in stenotically altered vessel parts.
- Pharmacokinetics
  - Absorption
    - Po absorption is nearly complete, but bioavailability is highly variable (10% to 90%, average ~25%), with extensive first-pass metabolism in the liver
  - Volume of distribution
    - 2 to 4 L/kg
  - Metabolism
    - Hepatic

- Half-life
  - 1 h

➢ Dose

- Isosorbide dinitrate
  - 5-10 mg po q AC, or prn for chest pain

➢ Contraindication/precautions

- CNS
  - Headache/dizziness
- CVS
  - Hypotension
- GI
  - Nausea/vomiting
  - Fecal incontinence
- MSK
  - Weakness

➢ Drug-drug interactions

- ↑ risk of AEs when given with
  - Phosphodiesterase-5 inhibitors (e.g., Viagra®)

➢ Peripartum

- Pregnancy
  - Safe
- Lactation
  - Safety not known

- **Botulinum Toxin** (Botox®, $C_{6760}H_{10447}N_{1743}O_{2010}S_{32}$)

➢ Indication

- Achalasia (EGD injection into muscle of lower esophageal sphincter [LES])

➢ Mechanism of action

- Binds presynaptically to high-affinity recognition sites on the cholinergic nerve terminals
  - ↓ release of acetylcholine
    - Neuromuscular blocking effect

➢ Pharmacokinetics

- Human pharmacokinetic studies have not been performed due to its chemical molecule complexity and extreme potency.
- Animal studies using radio labeled botulinum toxin suggest it is absorbed systemically after subcutaneous and intranasal administration.
- Clinical relevance is unknown.

- Contraindication/precautions
  - Known hypersensitivity to Botulinum Toxin (Onabotulinum Toxin A)
  - Note adverse effects (for drug-drug interactions, please see below)

- Dosing
  - Botulinum toxin 80-100 U injected into distal esophageal mucosa, by way of EGD catheter, divided dose into 4 quadrants, then
  - Maintenance with repeated EGD plus injections into esophagus

- Adverse effects (AEs)
  - General
    - Anaphylaxis
    - Tachyphylaxis, with requirement for repeated injections
  - CNS
    - Headache
    - Speech impairment
  - Eyes
    - Ptosis
    - Sicca (dryness)
    - Glaucoma, acute angle
    - Keratitis, punctate
  - CVS
    - Angina / myocardial infarction
    - Arrhythmia/syncope
    - Hypertension
    -
  - Lung
    - Shortness of breath (SOB [dyspnea])
    - Upper respiratory infection (URI)
  - GI
    - Dyspepsia/dysphagia
  - MSK
    - Muscle weakness/pain
  - Skin
    - Erythema multiforme (EM)
    - Pain, injection site

- Drug-drug interactions
  - ↑ risk of AEs (neuromuscular weakness/pain) with
    - Aminoglycosides
    - Clindamycin
    - Succinylcholine

- Peripartum
  - Pregnancy − Safe
  - Lactation − Safety not known

SWALLOWING

➢ Physiology

- Physiological mechanisms involved in swallowing

- Mouth/tongue
  - The tongue, like the face and palate, has a bilateral upper motor neuron innervation in most people, so a unilateral upper motor neuron (UMN) lesion often causes no deviation.
  - A clinically obvious UMN lesion of the twelfth cranial nerve (CN) is usually bilateral and results in a small (atrophic) immobile tongue.
  - The combination of bilateral upper motor neuron lesions of the ninth, tenth and twelfth nerves is called pseudobulbar palsy.
  - A lower motor neuron lesion of the twelfth CN causes fasciculation, wasting and weakness.
    - If the lesion is bilateral, it causes dysarthria.
  - Movement disorders may affect the tongue.
  - Muscles of soft palate, tongue and pharynx shorten the lumen of the pharynx.

- Oropharynx
  - Complex coordinated transfer of bolus from mouth to upper esophagus
  - Affected by neurological disease affecting cranial nerves
  - Pharyngeal swallow
    - Coordination of patterned activation of motor neurons and muscles to transform the oropharynx from a respiratory pathway into an esophageal transfer pathway
    - From VFSA (video fluoroscopy swallowing assessment), there are several mechanical steps:
      - Nasopharynx-soft palate elevation and retraction
      - UES – opens
      - Larynx – closes
      - Tongue – becomes filled with food & fluid
    - Propulsion of bolus
      - Pharynx – constrictors clear the pharynx
      - UES pressure rises after bolus enters upper portion of esophagus.

- UES (upper esophageal sphincter)
  - Cricopharyngeus forms the 1 cm area of ↑ pressure of the UES (upper esophageal sphincter)
  - UES pressure maintenance and coordination of relaxation of swallowing is achieved by vagal trunks from the nucleus ambiguous
  - ↑ UES pressure
    - Distention of esophagus
    - Inspiration swallowing
    - Stress

- ↓ UES pressure
  - Anesthesia
  - Belching (causes relaxation of UES and closure of the glottis)
  - Sleep
- GER (gastroesophageal reflex) – no effect on UES pressure

- Larynx
  - Inlet to the larynx closes

- Esophagus

Muscle	Site	Efferent Nerves (Motor)
Striated	Proximal 5% Middle 35%	– Lower motor neurons cell bodies in nucleus ambiguous – Excitatory vagal innervations – Activation of motor units in a craniocaudal sequence through the release of Ach and stimulation of nicotinic cholinergic receptors on motor endplates of striated muscle cells – Peristalsis of striated muscle of esophagus is controlled by the medullary swallowing centre
Smooth	Middle 35% Lower 60%	– Dorsal motor nucleus of the vagus – Excitatory ganglionic neurons predominate proximally, inhibitory ganglionic neurons dominate distally

Muscle	Afferent (sensory)
High resolution esophageal pressure topography shows a transition zone between the skeletal and smooth muscle, characterized by – ↓ amplitude contractions – ↓ progression of peristalsis – ↑ likelihood of failed transmission	– Superior laryngeal nerve, cell bodies in nodose ganglion – Recurrent laryngeal nerve, esophageal branches of vagus nerve
ANS (autonomic nerve system)	– Myenteric plexus between longitudinal and circular muscle layers – Meissner plexus between muscularis mucosa and circular muscle

- **Peristalsis**
  - Primary (1º) wave – initiated by swallow 1º >2º wave pressure
  - Secondary (2º) wave – initiated by distention of esophagus (food, fluid, air; balloon)
  - A "milking" wave clears the esophagus from the top to the bottom
  - When the pressure of the 1º/ 2º peristaltic milking wave is low (<30 mm Hg), the esophagus is less likely to be completely cleared
  - If there are two swallows made in rapid succession, in such a way that the first peristaltic wave is still in the esophagus, the inhibitory ganglionic neurons in the myenteric plexus rapidly cause hyperpolarization of the circular smooth muscle in the lower third of the esophagus
  - This hyperpolarization of the circular smooth muscle inhibits the peristaltic contraction of the first swallow (deglutitive inhibition)
  - There is no deglutitive inhibition in the longitudinal muscle layer
  - With contraction of the outer longitudinal and inner circular smooth muscle, the esophagus may shorten (about 1 inch, 2.5 cm)
  - There may be a central origin to deglutitive inhibition
  - Thus, the esophageal clearance is less efficient with low pressure esophageal peristaltic waves, on with rapid swallowing causing deglutitive inhibition
- Skeletal muscle
  - From the swallowing centre in the medulla, vagal efferent fibers are excited, and discharge in spike bursts during 1º/ 2º peristalsis
  - Ach stimulates nicotinic cholinergic receptors on the motor end plates of the striated muscle cells
  - The medullary swallowing centre vagal efferent fibers discharge first the vagal fibers in the upper and then the middle of the esophagus
  - This sequential firing of skeletal muscle first in the proximal and then in the middle esophagus leads to peristalsis
  - These discharges leading to peristaltic muscle contraction are enhanced when the afferent sensory fibers are activated by the bolus passing along the esophagus
  - These vagal motor efferents are inhibited during the pharyngeal component of swallowing, or when the proximal esophagus is distended (deglutitive inhibition)
- Smooth muscle
  - Vagus nerve also controls 1º peristalsis in lower esophagus (smooth muscle)
  - Stimulation of the vagal efferent (motor) may ↑ or ↓ the smooth muscle activity:
  - Control of peristalsis by smooth muscle – medullary swallowing centre
  - Stimulation by swallowing (vagus):
    - Longitudinal muscle
    - Depolarization with superimposed spike bursts
  - Circular muscle: hyperpolarization, then depolarization and spike bursts
    - Myenteric plexus – necessary for peristaltic propagation
  - Smooth muscle contraction caused by ganglionic cholinergic neurons in response to swallowing
  - This vagal nerve stimulation simultaneously reaches the ganglionic neurons in the middle and distal third of the esophagus
  - There is a short (2 sec) latency in the proximal smooth muscle in terms of the time of the arrival of the nerve stimulation and muscle contraction
  - There is a longer (5 to 7 sec latent period in the distal esophagus)

- This latent period may result "...from a neural gradient along the esophagus, where in excitatory ganglionic neurons dominate proximally and NO&VIP-releasing inhibitory ganglionic neurons dominate distally" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Saunders/Elsevier, Philadelphia, 2020).

➢ **Lower esophageal sphincter** (LES)

- The high pressure at the esophagogastric junction (EGJ) is caused by
  - LES (lower esophageal sphincter) pressure
    - 3-4 cm in length
    - Tonically contracted
  - Crural diaphragm
    - 2 cm length
    - ↑ in crural diaphragm contraction, with ↑ EGJ pressure
    - Inspiration (abolished by mechanical ventilation)
  - ↓ crural contraction, ↓ EGJ pressure
    - Distention of esophagus
    - Belching air, vomiting
  - Sling and clasp fibers of the middle layer of the musculature of the gastric cardia (including the angle of His)
- The high pressure in EGJ goes form 1-1.5 cm proximal and 2 cm distal to the SCJ (squamocolumnar junction)
- The LES is tonically contracted
- This myotonic LES tone"... varies directly with membrane potential and superimposed electrical spike activity that leads to an influx of Ca^{2+}." (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Saunders/Elsevier, Philadelphia, 2020).
- The spike activity which influences Ca^{2+} flux is itself regulated by K^+ - and Ca^{2+} - activated Cl^- channels
- Vagal (cholinergic) input partially determines LES basal tone
- Adrenergic (sympathetic, acting through the myenteric neurons)
  - Stellate and proximal thoracic ganglia – with
    - Splanchnic nerve
    - celiac ganglion
    - α – adrenergic receptors on myenteric neurons (excitatory, as well as inhibitory)
- Sympathetic (adrenergic, α – adrenergic receptors) activity
  - ↑ excitatory neurons activity
  - ↓ inhibitory neuron activity
  - The net effect of α – adrenergic stimulation is
    - ↑ LES pressure
    - ↓ body muscle (relaxation)
- Hormonal factors
- Mechanical factors

- Relaxation of LES
  - An intramural process
  - Mediated by post ganglionic nerves and by vagus
  - Caused by swallowing or distention of esophagus
  - Post-ganglionic transmission is by way of nicotinic and muscarinic receptors
  - Transmitters of post ganglionic neurons causing LES relaxation and ↓ LES pressure is mediated by NO (nitric oxide, produced from the amino acid L-arginine, by way of the enzyme NO synthase)
  - Postganglionic deglutitive relaxation of the LES may also occur with other peptides such as VIP (prejunctional neurotransmitter acting on nerves containing NO synthase), as well as possibly PHI (peptide histidine isoleucine), CGRP (calcitonin gene-related peptide), galanin, and PACAP pituitary adenylate cyclase activation peptide)

- Myogenic factors which physiologically modulate LES pressure
  - Membrane potential
  - K^+ and Ca^{2+} - activated Cl^- channels
  - Spike activity
  - Ca^{2+} flux
  - Pressure
    - Gastric distention
    - Intra-abdominal pressure (e.g., obesity, ascites)
  - Food
  - Peptides
  - Hormones
  - Medications
  - MMC (migrating motor complex (MMC phase III ↑ LES to 80 mmHg [NORM] resting LES pressure/ tone is 10 – 30 mmHg)
  - Neurogenic factors
    - Vagal (cholinergic input partially determines LES basal tone
    - Adrenergic (sympathetic, acting through the myenteric neurons)

- Transient lower esophageal sphincter relaxation (tLESR)
- Differences in the physiology of tLESR and swallow-associated declines in sLES pressure (sLESP).

	tLESR	sLESR
○ Stimulus	− Distention of gastric cardia/fundus, even without swallowing or peristalsis	▪ Swallowing, or peristalsis
○ Association with pharyngeal swallowing	**No**	Yes
○ Associated with synchronized peristalsis	**No**	Yes
○ Post-prandial	Yes	**No**
○ Inhibition of crural diaphragm	Yes	**No**
○ Contraction of distal esophageal longitudinal muscle	Yes	**No**
○ Shortening of esophagus	Yes	**No**
○ Afferent neural pathway	− Gastric afferents in the subdiaphragmatic vagus	▪ Pharyngeal and superior ▪ Laryngeal nerves
○ Central neural circuit	− Caudal dorsal motor nucleus	▪ Subnuclei of the medulla
○ Efferent limb in the preganglionic vagal inhibitory pathway to LES	Yes	Yes

Abbreviations: tLESRs, Transient lower esophageal sphincter relaxations; sLESR, swallow-associated lower esophageal sphincter relaxations

STOMACH

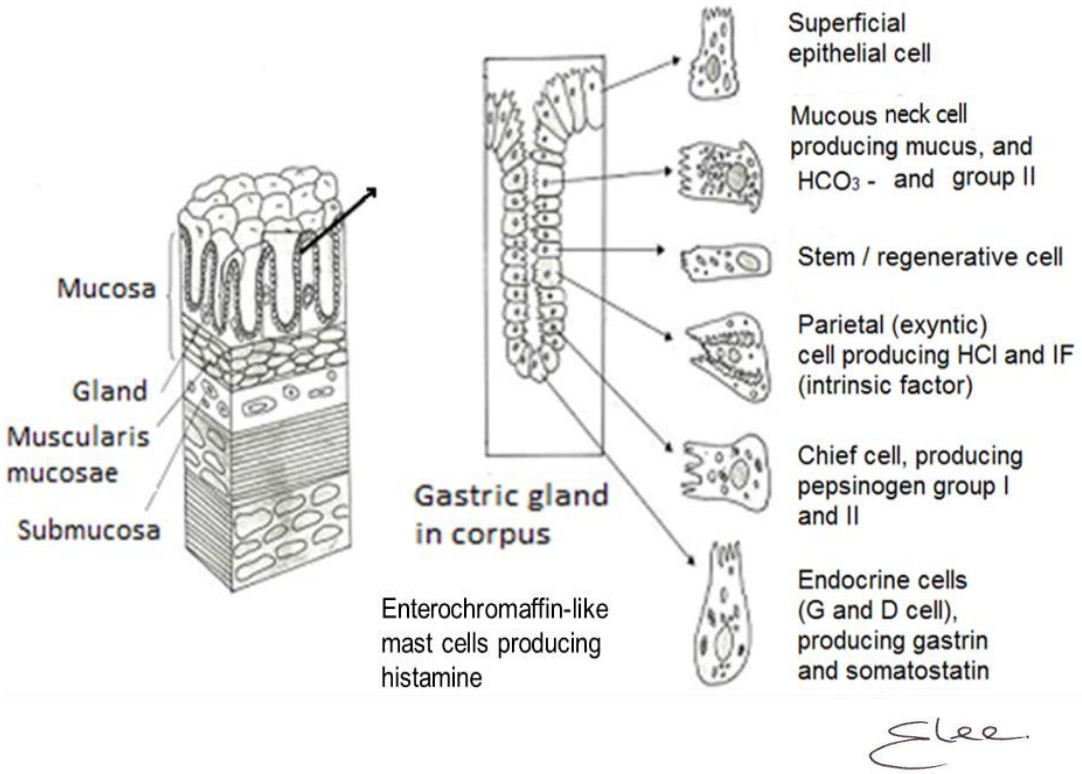
DYSPEPSIA (Please see previous chapter on Esophagus)

An understanding of the physiology of gastric acid secretion forms the basis for the understanding of targeted pharmacology and the pathophysiology of GERD and peptic ulcer disease.

- Functions
  - Receive
  - Digest
  - Empty

  } Food
  - − Receptive relaxation
  - − HCl, intrinsic factor (IF), pepsinogen
  - − Trituration, mixing, controlled emptying

- Cells of the Stomach and their Function



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 42-1, page 896.

➢ Secretory Gastric Cells

- Secretory cells of the stomach, and chemical / peptide / hormone which the cell secretes.
  - Goblet cell – mucus
  - Parietal cell – HCl, intrinsic factor
  - Chief cell – pepsinogen, gastric lipase
  - D cell – somatostatin
  - G cell – gastrin
  - Mast cell – histamine
  - Enterochromaffin-like cells – histamine

➢ Parietal (oxyntic) Cells

Products	Function
○ Hydrochloric acid	– ↑ pepsinogen activation and gastric lipase – ↑ duodenal inorganic iron absorption (reduction of food Fe^{3+} to Fe^{2+}) – Negative feedback of gastrin release (↑ H^+→ ↓ gastrin → ↓H^+) – Stimulation of pancreatic secretion of secretin → HCO_3- – ↓ growth of microorganisms ingested in food – ↑ release of vitamin B12 from food
○ Intrinsic factor (IF)	– Dietary animal protein contains vitamin B12 – Gastric acid activates pepsinogen → pepsin – H+ / pepsin begin digestion of protein → releasing vitamin B12 – Vitamin B12 in stomach binds to R factor in swallowed saliva – Vitamin B12 – R complex mixes with gastric juice → empties into duodenum – Duodenal contents of gastric juice → stimulate release of secretin from duodenal S cell → ↑ pancreatic secretion of HCO_3 → ↑ pH of duodenal contents – ↑ duodenal AA → ↑ release of vitamin B12 from R-factor, and vit B12 binds to intrinsic factor (IF) – Food releases CCK (cholecystokinin) → release/activation of trypsinogen → breakdown of protein → release of vitamin B12

  - The parietal cell is stimulated by the cephalic, gastric and intestinal phases of H^+ secretion, with activation occurring through
    - ↑ Ca_i^{2+} (intracellular Ca^{2+})
    - ↑ cAMP → cAMP-dependent PK (protein kinase) cascade
  - When activation of the parietal cell ceases, or inhibition increases, the H^+-K^+ ATPase in the parietal cell membrane moves back (reinternationalization) into the cytoplasmic side of the cell.

- Reinternalization of the H^+ - K^+ ATPase occurs by way of the cytoplasmic tail of the beta subunit of the enzyme.

➢ Chief Cells

Cell / Products	Function
Pepsinogens	– Pepsinogen secretion → hydrolyzed to pepsin in gastric lumen in presence of H^+ – Liberation of vitamin B_{12} and Fe^{3+} from dietary protein – Initial hydrolysis of dietary proteins to amino acids (AA) – AA directly stimulate G cells to ↑ gastrin, and indirectly activate Ach neurons as well as gastrin releasing peptide (GRP) containing neurons.
Gastric Secretion of Pepsin	– This ↑ gastrin leads to ↑ histamine released from ECL cells, activate the H2 receptors on the parietal cell to stimulate secretion of H^+. – Pepsins become inactive at pH > 4, so the low intragastric pH (↑H^+) maintains pepsins in an active form, which then maintains the AA-stimulation of release of gastrin from G cells, as well as release of Ach and GRP from neurons.

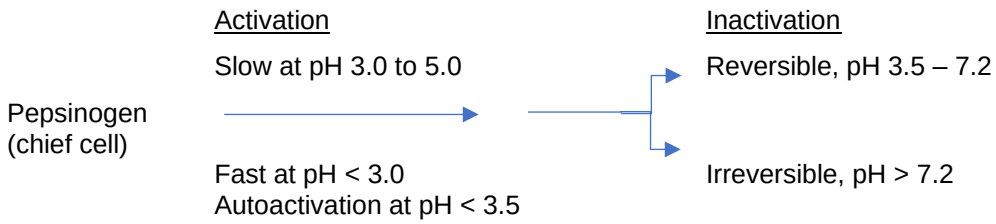
Abbreviations: Ach, acetylcholine; GRP, gastrin-releasing peptide; H2, histamine 2; ECL, enterochromaffin-like

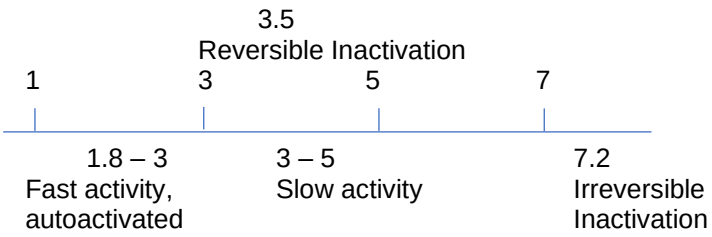
- Pepsinogens
  - Pepsinogens are a group of proteolytic proenzymes, (aka “zymogens”).
    - Group I pepsinogens (the main pepsinogens) secreted from the gastric chief cells located in the body of the stomach.
    - Group II pepsinogens
      - Also secreted from chief cells as well as from mucous neck cells in the gastric cardia, body and antrum.
    - Group III, aka cathepsin E
  - The pepsinogen secretory granules fuse with other secretory granules in the chief cells, and then diffuse across the outer plasma membrane of the chief cells.
    - Both preformed and newly synthesized pepsinogen are secreted into the gastric lumen by the process of compound exocytosis.
  - Agonists of Chief Cells and Pepsinogen Secretion
    - Ach
    - β2–adrenergic
    - CCK
    - PG_2
    - Secretin
    - VIP

    → ↑ Ca_i^{2+} → ▪ ↑ chief cell pepsinogen secretion

Abbreviations: Ca_i^{2+} intracellular calcium concentration; CCK, cholecystokinin; PG2, prostaglandin E2; VIP, vasoactive intestinal peptide

- Pepsin and Gastric Protein Digestion
  - The pepsinogen secreted into the gastric lumen is an inactive enzyme precursor, which must be activated by H^+ before it has proteolytic activity and can begin to digest protein.





  - The endopeptidase pepsin breaks down dietary protein.
  - These nitrogenous proteolytic breakdown products of pepsin also stimulate the secretion of
    - Gastrin from antral G cells
    - CCK from I cells in the duodenum
    - Binding affinity
      - CCK_A CCK > G
      - CCK_B G > CCK

➢ Endocrine Cells & Mucous Neck Cell

Cell / Products	Function
Endocrine Cells	
Gastrin secreting G- cells	▪ ↑ acid (HCl) secretion from parietal cells
Somatostatin (SST) secreting D-cells	▪ ↓ gastrin release → ↓ H^+ secretion
Superficial epithelial cells	
Maintain barrier function of gastric membrane	
Mucous Neck cells	
Mucin/HCO_3-	▪ Protect against noxious agents, including HCl and pepsins

- Gastrin, CCK, and Receptors
  - Gastrin is released from G cells in the gastric antrum as a result of
    - Amino acids (AA)
    - Peptides and protein and) in the stomach
    - Distention of the stomach
    - ↓ H^+ present in lumen
  - Gastrin binds to G-protein receptor for
    - CCK2 (aka CCK-B) receptors on
      - Parietal cells
      - ECL cells in body of stomach
      - Adjacent to parietal cells
    - CCK1 (aka CCK-A) receptors are on D cells, pancreas, gallbladder and brain

- ECL Cells
  - Physiology
    - Acutely: stimulation of ECL (gastric mucosal mast) cells → release histamine
      - ↑ histamine releases from ECL
        → Histamine → stimulates H2 receptor
        → somatostatin → ↓ histamine release
  - Note paradoxical effect of gastrin
    - ↑ histamine release from ECL cells
      - ↑ HCl secretion
    - ↑ somatostatin release from D cells
      - ↓ G release
      - ↓ HCl secretion
  - Inhibitors of ECL Cells
    - Other peptides → ↓ ECL histamine release → ↓ acid secretion by way of
      - Inhibitors of ECL cell release of histamine → ↓ H^+ output
      - Calcitonin gene-related peptide (CGRP)
      - CCK2 and CCK2 receptors
      - Galanin
      - Peptide YY (PYY)
      - Prostaglandins
      - Agonist stimulation of receptors

Abbreviations: CCK, cholecystokinin; CGRP, calcitonin gene-related peptide; ECL, enterochromaffin-like; PYY, peptide YY

- Somatostatin (SST)
  - ↑ SST
    - Minor distention of stomach (acting through VIP neurons) →
      → ↑ SST → ↓ histamine
      → ↓ gastrin → ↓ H^+ (major inhibitory mechanism of somatostatin release)
  - ↑ H^+
    - ↓ SST
  - ↓ SST
    - Distention of stomach
    - Gastrin-stimulated release of histamine from ECL cells

- Prostaglandins (PGs)
  - Produced and stored in gastric macrophages and capillary endothelial cells
  - PGs → ↓acid secretion by way of inhibiting
    - ↓gastrin-stimulated histamine release
    - ↓histamine → ↓parietal cell acid secretion

- Gastric Distention
  - Initially, little distention
    - VIP neurons are activated to release somatostatin → ↓antral G cells → ↓gastrin → ↓H+
  - Then, more distention
    - Stimulation of release of acetylcholine (Ach; cholinergic)
      - Ach directly stimulates M3 receptors on parietal cell → ↑gastrin
        → ↓somatostatin
        → ↓H+

- Amino Acids (AA) in Stomach
  - Direct effect of AA → stimulate G cells → ↑gastrin → ↑H^+
  - Indirect effect of AA
    - Activate Ach neurons
    - Activate GRP (gastrin related peptide) neurons → G cells → ↑ gastrin → ↑H^+

➢ Gastrointestinal (GI) Peptide Hormones

Hormone	Source	Action
Gastrin (G)	G cells, antrum of stomach and duodenum	↑ H^+ secretion
Gastrin-releasing peptide (GRP)	K cells in duodenum, jejunum	↑ Gastrin (G) release → ↑H^+
Somatostatin (SST)	D cells of stomach and duodenum, islet cells of pancreas	↓ Gastrin (G) release, ↓ H+ secretion
Acetylcholine (Ach)	Vagal nerve endings	↑ H^+ secretion
Histamine (HIS)	ECL cells	↑ G from G cells, ↓ SST from D cells
Secretin	S cells in small intestine ↑ secretin as a result of H+ in duodenal lumen	↑ HCO_3- and fluid secretion by pancreatic duct cells
Motilin	ECL cells in upper GI tract	↑ Smooth muscle contraction

Abbreviations: Ach, acetylcholine; G, gastrin; GRP, gastrin releasing peptide; HIS, histamine; SST, somatostatin; ECL, enterochromaffin-like

➢ Gastric Acid Secretion

- Turning on (Stimulating) Gastric Parietal Secretion of Acid (HCl)
  - Acetylcholine (Ach)
  - Ca_i^{2+}
  - Gastrin (G)
  - Histamine (HIS)
  - Phospholipase C (PLC)

Contribution of Secretory Components

- Cephalic 30%
- Gastric 60%
- Intestinal 10%

- Acetylcholine (Ach)
  - The site, smell and taste of food or distention of the stomach stimulates vagal afferents acting on the DMN (dorsal motor nucleus) in the medulla

    Site / Smell / Taste → Vagal Afferents → DMN (medulla) → Vagal Efferents (postganglionic intramural neurons in the mucosa of the fundus) → Ach, GRP, VIP
  - Note: VIP is important for the taste of food, and is only indirectly part of the process of acid secretion
    - These signals are
      - Ach (acetylcholine)
      - GRP (gastrin releasing peptide)
      - VIP (vasoactive intestinal peptide)
    - Ach binds to
      - The M3 receptor on the basal membrane (BM) of the parietal cell → activates a Ca^{2+} channel → ↑Ca_i^{2+} (intracellular Ca^{2+}) →
      - ↑ post-translational modification of G_{101} in ER (endoplasmic reticulum) of G-cells → ↑ G_{17} and G_{34} (active components of G_{101})
      - The fundic ECL cell → ↑ histamine (HIS) → ↑G / ↓SST → ↑H^+ secretion by parietal cell

- Histamine (HIS)
  - Ach and gastrin act on the M3 and CCK receptors, respectfully of the ECL cells → ↑ HIS
  - Histamine (HIS)
    - Acts on PPP and ENS neurons → ↑ GRP on G-cells → ↑ gastrin
    - Couples to G1 binding protein → ↑ AC → ↑ cAMP → ↑ PKA

  - HIS → HIS-G_1 – AC* → cAMP → PKA (activated) → neurons PPP / ENS → ↑ GRP → ↑ G

Abbreviations: AC, adenyl cyclase; ENS, enteric nervous system; G1, GTP-binding proteins; PPP, post-ganglionic parasympathetic peptide

- Food and Gastrin
  - Dietary peptides, amino acids, alcohol and coffee
  - Dietary fat, glucose
    - ↑ GRP from K cells in duodenum / jejunum
    - GRP binds to receptor (GRPR) →
    - Act on G-cells

    } ▪ ↑ gastrin release from G cells

  - G_{17} and G_{34} bind to CCK2 receptor on basal membrane (BM) of parietal cells
    - ↑ PLC (phospholipase C)
    - ↑ Ca^{2+}_i
    - ↑ bind to GTP-binding protein
    - G_{17} is very active, but is quickly degraded
    - G_{34} (sulphated gastrin II) is less active, but slowly degraded
    - Mole per mole, G_{17} and G_{34} have similar potency

- Ca_i^{2+} and Phospholipase C (PLC)
  - PIP2 (phosphatidyl inositol 4, 5 – biphosphate) —— PLC
    - DAG (diacylglycerol)
    - IP3 (inositol 1,4,5 Triphosphate)

    → ↑Ca_i^{2+}
    → Activate parietal cell Ca^{2+} channel → ↑H^+

- Turning Off (Inhibitory) Gastric Parietal Secretion of Acid (HCl)
  - Somatostatin (SST)
  - Gastric inhibitory Peptide (GIP)
  - Secretin

- Somatostatin (SST)
  - H^+ in lumen → ↑ CGRP (calcitonin gene-related peptide) – released from extrinsic sensory neurons → ↑ SST (SST-28 > SST-14) from D cells in stomach and duodenum
  - SST tonically
    - ↓ ECL cell secretion of HIS
    - ↓ G cell secretion of gastrin
    - ↓ parietal cell secretion of H^+
  - Somatostatin Receptor ($SSTR_2$)
    - SST binds SSTR2 (SST receptor) on
      - Parietal cells
      - G cells
      - ECL cells

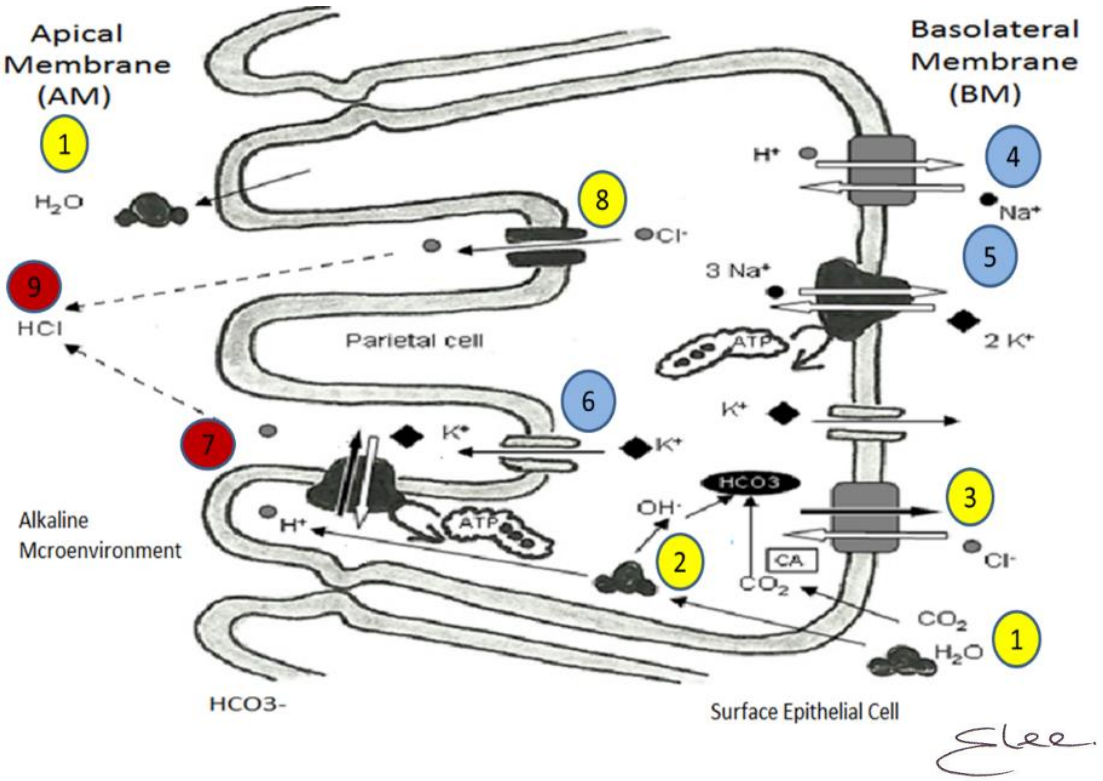
    Overview
    H^+ → ↑ CGRP → ↑ SST → ↓ H^+, G, HIS

    - SSTR2 and PGE2-EP3 → ↓activity of GTP-binding protein → ↓H^+, K^+-ATPase.

- Gastric Inhibitory Peptide (GIP)
  - Duodenal / jejunal GIP released from K cells in the duodenum and jejunum as the result of fat and glucose in the lumen.
  - GIP → ↓G → Directly ↓H^+ secretion by the parietal cell.

- Secretin (S)
  - Duodenal/jejunal secretin released from S cells in duodenum/jejunum as the result of H^+ in the duodenum (gastric emptying of HCl)
  - Secretin
    → Directly ↓gastric parietal cell acid secretion
    → ↑Ca_i^{2+} → ↑pepsinogen secretion by chief cells

- Gastric Hydrochloric Acid Secretion at Micro' (Cellular) Level of Parietal Cell



(1) CO_2 and water diffuse across the BM.

(2) Carbonic anhydrase (CA) in the cytosol of the parietal cell forms H^+ plus HCO_3^- (from OH^- plus CO_2).

(3) Cl^- enters across the BM by the Cl^- / HCO_3^- exchanger.

- The cytosolic HCO_3^- formed from the CA effect on CO_2 + H_2O exits across the BM by the Cl^- / HCO_3^- exchanger.

(4) Na^+ enters the parietal cell across the BM by way of the Na^+ / H^+ exchanger.

- Parietal cells in the gastric body have numerous tubulovesicles (TVs) which contain inactive, H^+, K^+ -ATPase (aka "the acid [or proton] pump".
- The beta subunit of the H^+, K^+ - ATPase is the actual H^+ pump or catalytic unit.

(5) Na^+ exits across the BM by the Na^+ / K^+ ATPase. K^+ enters the parietal cell across the BM by the Na^+ / K^+ ATPase.

(6) To avoid accumulation of K^+ in the parietal cell, K^+ may exit the parietal cell through the AM or BM K^+ channel.

(7) The H^+ in the cytosol of the parietal cell is removed by the proton pump on the luminal canalicular membrane.

- With stimulation of the parietal cell (neural, hormonal and paracrine factors), the activated PKA, PCA, Ca^{2+} activate H^+, K^+, - ATPase.
- The tubulovesicles (TVs) which now contain activated H^+, K^+ - ATPase are inserted into the canalicular membrane.
- Upon stimulation of the parietal cells, and with the inserting of the TVs with their active proton pumps (H^+, K^+ - ATPase) into the canalicular membrane, the H^+ is actively secreted into the gastric lumen, in exchange for K^+ in the lumen.
- Together the activated PKA, PKC and Ca^{2+} phosphorylate and activate the previously inactive H^+, K^+ -ATPase.
- The secretion of gastric hydrochloric acid, HCl, begins.

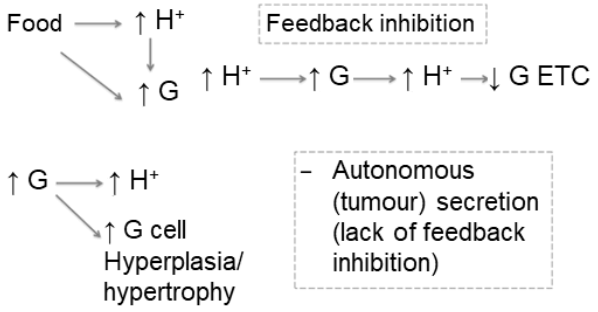
(8) The Cl^- needed to form HCl in the lumen moves from the cytosol of the parietal cell across a Cl^- channel in the AM.

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 42-4, page. 898.

- Parietal Cellular HCl Secretion
  - H^+
    - H^+/K^+ ATPase
    - Na^+/H^+ exchanger (NaHEx)
    - Carbonic anhydrase (CA)
  - Cl
    - Cl-/HCO_3- exchanger (Cl/HCO_3 Ex)
    - Cl Channel
  - K
    - H^+/K^+ ATPase
    - K Ch
    - Na^+/K^+ ATPase
  - Na
    - Na^+/K^+ ATPase
    - Na^+/H^+ Exchanger
  - HCO_3
    - CA
    - Cl
    - HCO_3

Abbreviations: H^+, hydrogen ion; K^+, potassium ion; HCO_3^-, bicarbonate ion; ClCh, chloride channel; KCh, potassium channel; NaHEx, Na^+/K^+ exchanger; $Cl^-HCO_3^-$ Ex, Cl^-/HCO_3^- exchanger

Clinical Applications



- PPIs, atrophic gastritis →↓H+ →↑G
  - Physiological feedback intact
    - Loss of H+ -related inhibition of G release (no parietal cell loss of parietal cell feedback
- Gastrinoma →↑↑G → ↑↑ H+
  - Unregulated release of g from gastrinoma → loss of H+-related inhibition of G release
- Renal failure
  - ↓ metabolism/excretion of g in urine → ↑ serum g

- Acid Rebound

➢ Definition

- ↑ acid secretion to above pretreatment values when an anti-secretory drug (e.g., PPI, H2RA) is suddenly discontinued.
- The magnitude of the acid rebound, which is usually ~15%, may be sufficient to cause a post-treatment recurrence of symptoms.

➢ Pathophysiological Mechanism

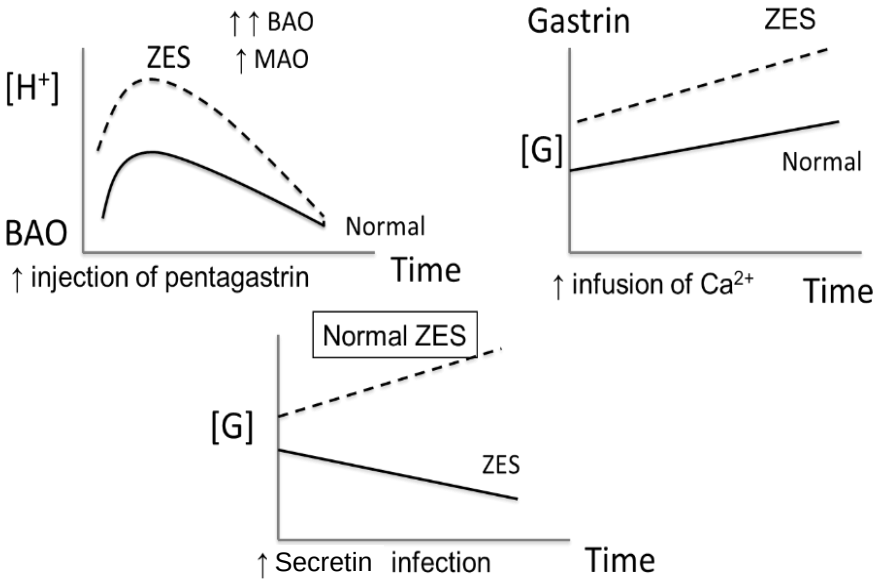
- Phenomenon of acid rebound when anti-secretory treatment is suddenly stopped
  - Acid secretion inhibition → ↑gastrin → up-regulation of parietal and G cells →↓SST → down-regulation of D cells
  - A given stimulus causes ↑ release of stimulatory G and Ach and less release of inhibitory SST from the increased number of parietal cells

- Hypergastrinemia: Suspicion of Zollinger Ellison Syndrome (ZES): Diagnostic Testing
  - Clinical suspicion of ZES
    - Severe / non-responsive PUD
    - Multiple DU / GU in unusual sites
    - Diarrhea not explained by PPIs / H_2RAs, Mg^{2+} AA
    - MEN-1 parathyroid adenoma ↑ serum Ca^{2+}, renal calculi

  ↑ fasting gastrin

  - Is there a tumour?
    - CT/MRI Scan, EUS
  - Is there ↑ gastric H^+ secretion?
    - Sham meal
    - Pentagastrin stimulation
  - Is there normal gastrin secretion?
    - Ca^{2+} or secretin infusion to ↑ gastrin

- Diagnostic Biochemical Testing for ZES



Explanation

- Effect of secretin infusion
  - Normal → ↓ gastrin
  - ZES → ↑ gastrin

- Differential diagnosis
  - ↑ serum gastrin to < 1000 pg/mL, plus fasting gastric pH < 2
  - Stomach
    - Antral G cell hyperplasia/hyperfunction
    - Gastric outlet obstruction GOO)
    - H. pylori infection
    - Retained gastric antrum
  - Duodenum/pancreas
    - Zollinger-Ellison syndrome (ZES)
  - Small bowel
    - Short bowel syndrome (SBS)
  - Kidney
    - Chronic renal failure (CRF)

UPPER GI BLEEDING (UGIB)

- Peptic Ulcer Disease
  - Target PPIs to achieve pH > 6 for 72 h after patient is admitted to hospital for UGIB.
  - Provide IV dosing for high-risk lesions (Forrest I, IIa)
    - Quickly achieves/maintains intragastric pH ≥ 6 to ↓ risk of rebleeding by 50% (combine with endoscopic hemostatic therapy [EHT])
    - After esophagogastroduodenoscopy (EGD), continue IV PPI for 3 d if EGD shows high risk bleeding cause
    - Pantoprazole sodium
      - 80 mg IV bolus, then
      - 8 mg/h 3 d after endoscopic hemostatic therapy (EHT)
  - If IV dosing not available, take PPI e.g., omeprazole 20 mg po q1h (take about 3 days to achieve steady state and optimal ↓ H^+)
  - Mechanism of action of IV PPI
    - ↓ H^+ / ↑ pH →
      - Stabilizes platelets
    - ↓ conversion of gastric pepsinogen to active pepsin → ↑ maintenance of clot formation
    - Begins process of ulcer healing
  - Esophageal variceal hemorrhage (EVH)
    - PPI IV given before/after EGD
    - If upper GI bleeding due to esophageal varices, perform endoscopic band ligation, continue PPI, and add
  - Ceftriaxone to ↓ development of spontaneous bacterial peritonitis
  - Add octreotide

- **Octreotide** (Sandostatin®)

➢ Mechanism of action
  - Analog of somatostatin → ↓ portal pressure → ↓ EVH (also ↓ bleeding peptic ulcers)

➢ Pharmacokinetics
  - Absorption
    - SC dose is absorbed completely upon administration
    - Cmax of delayed-release capsule po is 33% lower than SC
    - Tmax 1.67–2.5 h after po vs. 30 min after SC administrations.
  - Volume of distribution
    - 13.6 L after delayed-release capsule po in healthy volunteers
    - 18.1-30.4 L after IV administration in healthy volunteers
  - Metabolism
    - Heavily metabolized in the liver
  - Route of elimination
    - ~32% po dose excreted into the urine and 30-40% by the liver into the feces.
    - ~11% of the unchanged parent drug is found in the urine, and 2% in the feces

- Half-life
  - SC plasma T1/2 ~0.2 h
  - SC and po elimination T1/2, 2.3 - 2.7 h (did not differ significantly).
- Clearance
  - Total body clearance of octreotide is 7-10 L/h

➢ Dose
- Indication
  - Acute variceal bleeding (occasionally also given for unknown/severe peptic ulcer bleeding)
    - 50 µg IV bolus, then 50 µg/h
  - Diarrhea, secretory
    - Octreotide 50-500 mcg (µg) SC/IV t.i.d./q.i.d.; titrate dose to outcome
  - VIPoma (neuroendocrine tumour)
    - Octreotide 150-700 µg SC/IV per day in divided doses; titrate dose to outcome
    - Carcinoid acute crisis
      - 50-500 mcg (µg) IV prn for 8-24 h, or
      - 50 mcg (µg)/h IV for 8-24 h
    - Crisis prophylaxis
      - 250-500 mcg (µg) IV x1 given 1-2 h preoperatively
  - Dumping syndrome
    - Octreotide 50-100 mcg (µg) SC AC
  - Neuroendocrine tumours (NET)

➢ Contraindications/precautions
- Sensitivity to octreotide or its components
- Cardiac complications
  - Do **not** use with calcium channel blocker (CCBs) due to ↑ risks of bradycardia/bradyarrhythmia

➢ Adverse effects (AEs)
- General
  - Fever
  - Fatigue/malaise
- CNS
  - Confusion
  - Headache/dizziness
  - ↓ memory
  - Somnolence
  - Vertigo
- CVS
  - Bradycardia
  - Chest pain (angina)
  - Heart failure
  - Hypertension
  - Peripheral edema
  - ↑ QT interval

- GI
  - Nausea/vomiting
  - Abdominal pain
  - Diarrhea/constipation/steatorrhea
  - ↑ Flatus
  - Acute pancreatitis
  - Biliary tree
    - Cholelithiasis
    - Cholecystitis
    - Cholangitis
  - Endocrine
    - Blood sugar ↑/↓ (hyper-/hypoglycemia)
    - Hypothyroidism
- GU
  - Renal calculi
- Endocrine
  - Hyperglycemia
- MSK
  - Arthropathy myalgias
- Skin
  - Alopecia
  - Pain at injection
  - Pruritis
  - Rash
- Endocrine/ metabolic
  - Hyperglycemia
  - Hypothyroidism/goiter
  - Hypokalemia

For a list of less common adverse effects, please see Wu GY. Pocket Handbook of GI Pharmacotherapeutics. Second Edition 2016; pages 179-180.

➢ Drug interactions

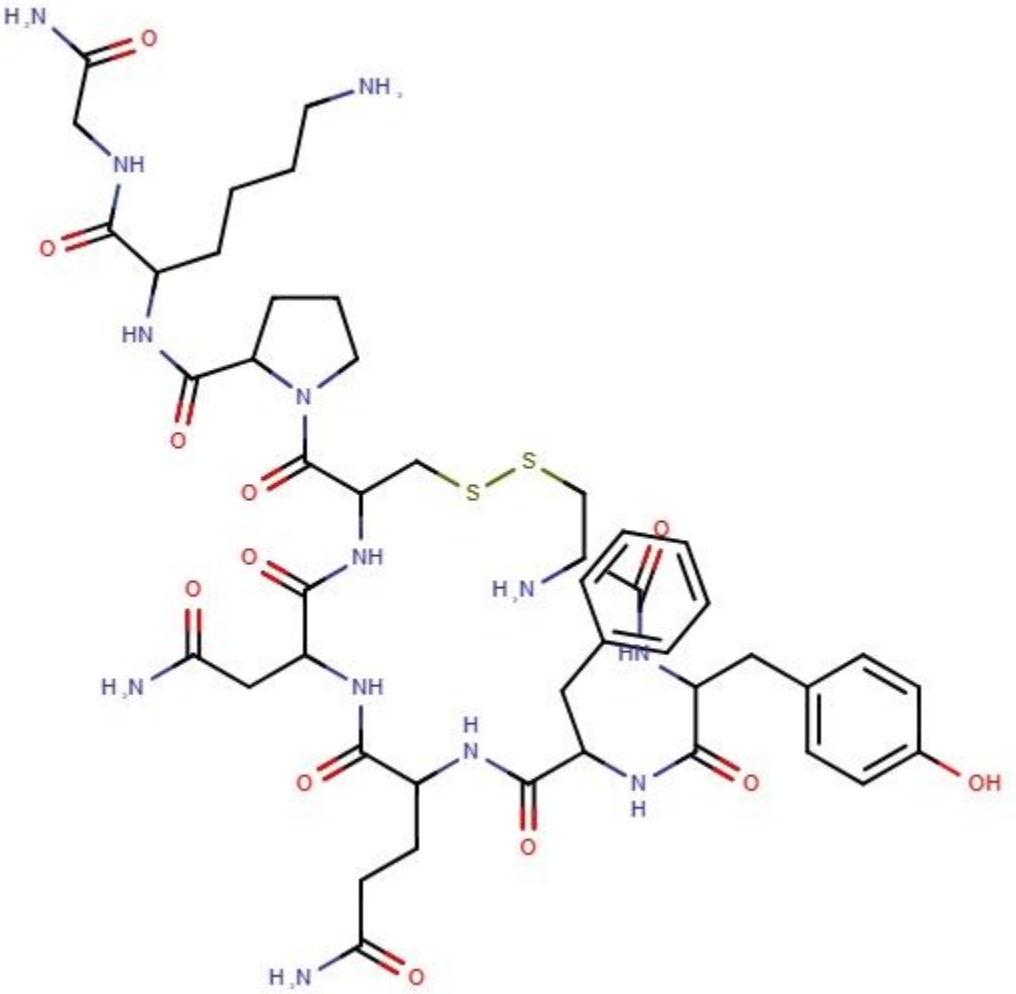
- CNS
  - ↑ QTc prolongation with
    - Alfuzosin
    - Artemether
    - Chloroquine
    - Ciprofloxacin
    - Dronedarone
    - Gadobutrol
    - Lumefantrine
    - Nilotinib
    - Pimozide
    - Quinine
    - Tetrabenazine
    - Thioridazine
    - Ziprasidone

- Endocrine – ↑ hypoglycemia and hypoglycemic agent
- ↓ serum concentration – Cyclosporin
- ↓ metabolism – Codeine

➢ Peripartum

- Pregnancy
  - Do **not** use
    - Causes uterine ischemia
- Lactation
  - Not known

❖ **Vasopressin (Pitressin®)** (use if octreotide not available)



- Mechanism of action
  - Potent vasoconstrictor which greatly reduces mesenteric blood flow results in decreased portal venous flow and portal pressure.
  - Control the hemorrhage by lowering the portal pressure
- Pharmacokinetics
  - Metabolism
    - Animal studies suggest that vasopressin is metabolized into inactive metabolite by serine proteases, carboxypeptidases, and disulphide oxidoreductases, primarily in the liver and kidneys.
  - Route of elimination
    - Primarily eliminated in the urine
    - ~6% excreted unchanged
  - Half-life
    - 0.01-0.1 U/min administered has an apparent T1/2 of ≤10 min
  - Clearance
    - 9-25 mL/min/kg in vasodilatory shock patients receiving 0.01-0.1 U/min vasopressin
- Dose
  - Upper GI bleeding (due to esophageal/gastric varices)
    - Vasopressin
      - 20 U IV over 20 min, then
      - 0.2-0.4 U/min, plus
    - Nitroglycerin (to ↓ risk of vasoconstriction, ↑ dose by 5-10 µg/min q5 min prn, to maximum dose of 50-180 µg/min
  - Post-operative prophylaxis
    - Vasopressin 5 U IM post-operatively, then
      - 5-10 U IM q3-4 h prn
- Contraindications/precautions
  - Hypersensitivity to vasopressin or its components
  - Disease
    - CNS
      - Seizure disorder
    - CVS
      - Arrhythmias
      - Heart failure
      - Hypertension
      - Ischemic heart disease
    - Respiratory
      - Bronchospasm (asthma)
- Adverse effects
  - CNS
    - Headache
    - Tremor/seizure
    - Vertigo

- CVS
  - Angina/myocardial infection
  - Arrhythmia
  - Hypertension
- Respiratory
  - Bronchospasm
- Endocrine
  - Water retention
    - Edema
    - Water intoxication syndrome
- Skin
  - Sweating/urticaria
  - Ischemia/gangrene
- Anaphylaxis

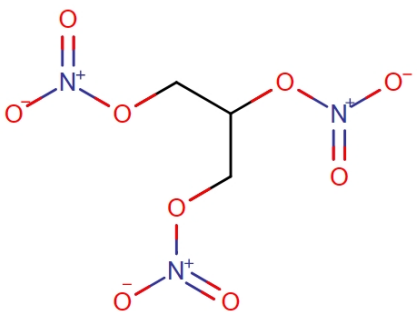
➢ Drug-drug interactions

- Antidiuretic effect
  - ↑ (hyponatremia, seizures)
    - Carbamazepine
    - Fludrocortisone
    - Polyethylene glycol (PEG)
    - Sodium phosphate
  - ↓
    - Demeclocycline
    - Lithium

➢ Peripartum

- Pregnancy
  - Uterine ischemia; **avoid**
- Lactation
  - Probably safe

❖ **Nitroglycerin (Nitrostat®)**



- Mechanism of action
  - Relaxation of vascular smooth muscle
    - Venous effects predominate
    - Dilates both arterial and venous beds
      - Dose-related manner
- Pharmacokinetics
  - Absorption
    - Sublingual Nitroglycerin 0.6 mg
      - Cmax 2.1 ng/mL
      - Tmax 7.2 minutes
    - Bioavailability of sublingual administration ~40%.
      - Depends on several factors, such as mucosal metabolism and hydration status, which affect the absorption of sublingual drugs
  - Volume of distribution
    - 3 L/kg
  - Metabolism
    - Mitochondrial aldehyde dehydrogenase 2 promotes the bioactivation of nitroglycerin.
    - Nitroglycerin is metabolized to nitrite; 1,2-glyceryl dinitrate; and 1,3 glyceryl dinitrate which are less biologically active than nitroglycerin has ↑ T1/2 (explains some prolonged effects of nitrates).
    - Nitrite is further metabolized to nitric oxide. 1,2- and 1,3-dinitroglycerols
    - Both dinitrates are finally metabolized to glycerol, carbon dioxide, and mononitrates with no vasodilatory actions.
  - Route of elimination
    - Metabolism is the main route by which nitroglycerin is eliminated from the body.
  - Half-life
    - Plasma T1/2 of
      - IV form, ~ 3 min
      - Sublingual form, ~ 6 min
    - Elimination T1/2 of metabolites 1,2-dinitroglycerin and 1,3-dinitroglycerin, 26-32 min
  - Clearance
    - IV administration, 1 L/kg/min
    - Sublingual administration, 21.9 L/min

➢ Contraindication/precautions

- IV vasopressin to ↓ risk of vasoconstriction and ischemia e.g., myocardial infection
  - CNS – ↑ intracranial pressure (ICP)
  - CVS – Cardiomyopathy, restrictive
    – Hypotension, systemic
    – Pericarditis
      - Constrictive
      - Tamponade
  - Blood – Methemoglobinemia
  - Skin – Flushing

➢ Adverse effects (AEs)

- CNS – Headache/dizziness
- CVS – Hypotension
  – Tachycardia, reflex
- Blood – Methemoglobinemia
- Skin – Flushing

➢ Drug-drug interactions

- ↑ risk of AEs (severe hypotension) when given with phosphodiesterase inhibitors (PDEs)

➢ Peripartum

- Pregnancy
  – Safe
- Lactation
  – Safety not known

➢ Please note

- Non-specific β-blockers (NSBB) are used to reduce the risk of bleeding from esophageal varices (primary and secondary prophylaxis, but are **not** used to ↓ acute bleeding
  - They will be discussed in the Liver section in portal hypertension.

- Drugs that may be used safely for nausea and vomiting in pregnancy; and their usual dose.

Drug	Usual Dosage
○ Domperidone, cisapride	1-20 mg t.i.d. or q.i.d.
○ Doxylamine	12.5 mg twice daily
○ Metoclopramide	10-20 mg four times daily (q.i.d.)
○ Ondansetron	4-8 mg t.i.d.
○ Prochlorperazine	5-10 mg t.i.d.
○ Promethazine	12.5-25.0 mg q.i.d.
○ Thiamine (vit B_6)	10-25 mg three times daily

❖ Management of antithrombotic agents in the setting of acute GI bleed

- Vitamin K antagonist reversal
  - Do **not** give FFP for patients on warfarin (conditional recommendation, very low certainty of evidence).
  - No recommendation for or against PCC administration for patients on warfarin
  - Give PCC administration rather than FFP for patients on warfarin (conditional recommendation, very low certainty of evidence).
  - Do **not** use vitamin K for patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower) (conditional recommendation, very low certainty of evidence).
- Direct thrombin inhibitor reversal (dabigatran)
  - Do **not** use idarucizumab for patients on dabigatran (conditional recommendation, very low certainty of evidence).
  - Reversal of rivaroxaban/apixaban with andexanet alfa
  - Do **not** use andexanet alfa for patients on rivaroxaban or apixaban (conditional recommendation, very low certainty of evidence).
- Reversal of direct oral anticoagulant with PCC
  - Do **not** use PCC for patients on DOACs (conditional recommendation, very low certainty of evidence).
- Reversal of antiplatelet with platelet transfusion
  - Do **not** use platelet transfusions for patients on antiplatelet agents (conditional recommendation, very low certainty of evidence).

- Holding ASA vs continuing ASA
    - Do **not** hold the ASA for patients with GI bleeding on cardiac ASA for secondary prevention (conditional recommendation, very low certainty of evidence).

- Resumption of ASA after endoscopic hemostasis
    - For patients with GI bleeding on ASA for secondary cardiovascular prevention whose ASA was held, resume to ASA on the day hemostasis is endoscopically confirmed (conditional recommendation, very low certainty of evidence).

Abbreviations: ASA, acetylsalicylic acid; FFP, fresh frozen plasma; DOAC, direct oral anticoagulant; GI, gastrointestinal; GIB, GI bleeding; PCC, prothrombin complex concentrate

Adapted from: Abraham NS, et al. Am J Gastroenterol 2022;117(4):542-558 (Table 1)

Guideline statements, the strength of recommendation, and certainty of the evidence for the management of antithrombotic agents in the elective endoscopy setting

❖ Management of antithrombotic agents in the elective endoscopy setting

- Anticoagulant interruption vs continuation
    - Continued warfarin for patients on warfarin (conditional recommendation, very low certainty of evidence).
    - Do **not** use bridging anticoagulation for patients on warfarin, who hold warfarin in the periprocedural period for elective/planned endoscopic GI procedures (conditional recommendation, low certainty of evidence).
    - Temporarily interrupting DOACs rather than continuing DOAC for patients on DOACs (conditional recommendation, very low certainty of evidence).

- Antiplatelet interruption vs. continuation
    - Temporary interruption of the P2Y12 receptor inhibitor while continuing ASA for patients on dual antiplatelet therapy (conditional recommendation, very low certainty of evidence).
    - No recommendation for or against temporary interruption of the P2Y12 receptor inhibitor for patients on single antiplatelet therapy with a P2Y12 receptor inhibitor
    - Interrupt ASA for patients on ASA 81–325 mg/d (i.e., cardiac ASA monotherapy) (conditional recommendation, very low certainty of evidence).

- Timing of anticoagulant resumption after endoscopy
    - No recommendation for or against resuming warfarin the same day vs 1–7 d after the procedure
    - No recommendation for or against resuming the DOAC on the same day of the procedure vs 1–7 d after the procedure in patients who are undergoing elective endoscopic GI procedures whose DOAC was interrupted.
- Timing of P2Y12 inhibitor resumption after endoscopy
    - No recommendation for or against resuming P2Y12 inhibitor on the same day of the procedure vs 1–7 d after the procedure.

Abbreviations: ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant; GI, gastrointestinal

Adapted from: Abraham NS, et al. Am J Gastroenterol 2022;117(4):542-558 (Table 2)

❖ Empiric endoscopic procedural bleeding risk stratification

- High bleeding risk procedures (30-d risk of major bleed >2%)
    - Esophagus
        - Endoscopic mucosal resection (EMR)/ Endoscopic submucosal dissection (ESD)
        - Radiofrequency ablation
        - Peroral endoscopic myotomy (POEM)
        - Treatment of varices (including variceal band ligation)
        - Pneumatic or bougie dilation
    - Stomach
        - Percutaneous endoscopic gastrotomy (PEG) / percutaneous endoscopic jejunostomy (PEJ) placement
        - Endoscopic hemostasis (excluding argon plasma coagulation [APC])
        - Cystogastrostomy
        - Laser ablation and coagulation
    - Small bowel
        - Therapeutic balloon-assisted enteroscopy
    - Colon
        - Polypectomy (≥1 cm)
    - Pancreas
        - ERCP with biliary or pancreatic sphincterotomy
        - Endoscopic ultrasound fine needle aspiration (EUS-FNA)
        - Tumour ablation
        - Ampullary resection

Abbreviations: APC, argon plasma coagulation; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; FNA, fine-needle aspirate; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; POEM, peroral endoscopic myotomy

Adapted from: Abraham NS, et al. Am J Gastroenterol 2022;117(4):542-558 (Table 3)

GASTRIC EMPTYING AND GASTROPARESIS

❖ Gastric Emptying of Food and Fluid

- The steps and mechanisms of gastric emptying.
    - Food Intake
        - Begins the process of fundic receptive relaxation
        - Body grinding and mixing (“trituration”)
        - Antral peristalsis
        - Antropyloroduodenal coordination
        - Emptying through pylorus of 2 to 4 mL of chyme, containing particles < 4 mm, by varying coordinated resistance of pylorus and antrum
    - Food composition
    - Receptive relaxation
    - Smooth muscle cells
        - Food composition
        - Hormone/peptides
        - Receptors on smooth muscle
        - Pharmaceuticals
    - Nervous system
        - Autonomic [parasympathetic/sympathetic nervous system] (ANS [PNS/SNS])
        - Enteric nervous system (ENS) and interstitial Cells of Cajal (ICC) network
        - Migrating myoelectrical complex (MMC)
    - Modulation of gastric emptying
        - Food
        - GI peptides / pharmaceuticals

Abbreviations: ANS, autonomic nervous system; ENS, enteric nervous system; GI, gastrointestinal; ICCs, interstitial cells of Cajal; MMC, migrating myoelectrical complex; PNS, parasympathetic nervous system; SNS, sympathetic nervous system

- Receptive Relaxation
    - The IM-ICCs in the fundus
        - Sensory cells for mechanoreception
        - Innervated by inhibitory vagal neurons which regulate tone and receptive relaxation in the fundus
    - Ingested food and fluid stretch the fundus and stimulate mechano-/chemo-receptors.
    - The IM-ICCs (Intramuscular interstitial myoelectric contractions) activate vagal efferent and vagovagal reflexes → the nucleus of the tractus solitarius (NTS), periventricular nucleus (PVN) and dorsal motor nucleus (DMN) of the vagus are stimulated → inhibition of the vagal excitatory neurons.
    - Secretin is released from enterochromaffin cells.
    - IPANs (intrinsic primary afferent neurons) in the submucosa or myenteric plexus of the stomach

- Activated mechano- / chemo-receptors stimulate IM-ICCs.
- NO and VIP (vasoactive intestinal peptide) are released → ↓ normal tone of smooth muscle of the fundus.
- The end result is for filling of the fundus to result in receptive relaxation to allow for ↑ amounts of food to enter stomach without ↑ intragastric pressure.
- This process begins before mixing and grinding in the gastric body.

- Enteric Nervous System (ENS)
  - Main networks
    - Submucosal (SM)
    - Myenteric
    - Deep muscular
      - Interstitial cells of Cajal (ICC)
      - Plexi involved in pacemaking
    - Migrating myoelectric contractions (MMC)
  - "Stimulation of excitatory enteric neurons leads to depolarization of IM-ICCs".
  - "The depolarization [of IM-ICCs] …causes positive chronotropic effects on the frequency of gastric slow waves", and also...increases the contractile response of smooth muscle to slow wave depolarizations..."
  - Thus, "the ICC networks provide the control of frequency and propagation velocity for the circular muscle contractions that comprise gastric peristalsis waves"

- Autonomic Nervous System (ANS)
  - Parasympathetic nervous system (PNS) pathways from
    - Dorsal motor nucleus (DMN)
    - Nucleus ambiguous (NA)
    - Tractus solitarius (TS)

  - PNS
    - Stimulatory vagal nerves
      - ↑ gastric contraction
      - ↑ gastric secretion

  - Vagus efferents pass to MP (myenteric plexus) in wall of stomach

- Sympathetic nervous system (SNS) pathways
  - From IML (intermediolateral) columns in T5 to T10 levels of spinal cord from
    - Celiac ganglia to splanchnic efferents
      - Myenteric ganglia → norepinephrine
    - Splanchnic efferents to
      - Submucosa ganglia
        - Norepinephrine and neuropeptide
        - Circular muscle
        - Blood vessels
        - Pyloric sphincter
        - Non-sphincteric muscle

- Smooth Muscle Cells
  - The functions of the stomach include digestion, food/fluid storage, or accommodation, grinding and mixing as well as emptying.
  - Receptors in the excitable membrane of the smooth muscle cells
    - These bind to amines and GI peptides which reach the smooth muscle cells from neurocrine, paracrine and endocrine pathways → action potentials.
  - Ach (muscarinic)
    - Central and peripheral dopamine (D2)
    - 5 HT3 / 5 HT4 agonist, antagonist
    - Motilin
    - α-adrenergic agents
    - Somatostatin (SST)
    - Phosphodiesterase

➢ Electrophysiology of Smooth Muscle
  - The muscle cells are joined as a syncytium, which provides electrical syncytial coupling of neighboring muscle cell.
  - The spontaneous depolarization, action potential and syncytial coupling cause contraction in the circumferential and longitudinal axes of the stomach.
  - Pylorus
    - Electrical barrier between slow wave of distal antrum (3 cpm) and duodenum (12 cpm), i.e., the duodenal slow wave is 12 cpm (contractions per min).
  - Duodenal mucosal receptors for fatty acids (FA), amino acids (AA) and carbohydrates limit the rate of gastric emptying to ~150 kcal/h
  - Fat in the ileum slows small bowel emptying through the release of GLP-1 and -2 as well as peptide YY [PYY])
  - Modulation
    - ENS and ICC/MMC network
    - ANS (PNS/SNS)
    - Motilin

Abbreviations: ANS, autonomic nervous system; cpm, contractions per min; ENS, enteric nervous system; ICC, interstitial of Cajal; MMC, migrating motor complex; PNS, parasympathetic nervous system; SNS, sympathetic nervous system

- Interstitial Cells of Cajal (ICC)
  - ICCs arise from c-kit-positive mesenchymal cell precursors
  - ↑ activity of the plateau or action potentials causes gastric peristaltic contractions.
  - The fundus does not have MY-ICCs or a slow wave, so the fundus does not participate in the linking of slow waves to the plateau or action potentials, and therefore has no role in producing peristaltic contractions (e.g., as in antrum)

- Migrating Myoelectrical (Motor) Complex (MMC)
  - ICCs at the junction of the gastric fundus and body at the proximal part of the greater curve of the stomach have innate activity and spontaneously produce a slow wave (aka pacesetter potential, gastric myoelectrical activity)

- MMCs originate in the stomach / duodenum and travel to the ileum.
  - Begin and continue through non-vagal mechanisms.
- MMCs occur in other parts of GI tract besides stomach and duodenum: LES, sphincter of Oddi, gallbladder.
- MMC I to III recur every 90 to 120 min
- ICCs present in multiple layers of stomach wall
  - Myenteric (MY-ICCs)
  - Intramuscular (IM-ICCs)
  - Submuscular
  - Subserosal
- Slow waves occur at 3 cpm (cycles per minute) move circumferentially and distally at 14 mm/sec towards the antrum
- MY-ICCs: when the uptake of the slow wave depolarize → ↓ threshold for circular muscle contraction
- When the uptake of the slow wave depolarizes, there ↓ threshold for the circular smooth muscle to contract.
- When the membrane potential reaches the threshold potential, the force of contraction quickly increases (steep slope of the voltage-contraction curve)
- The slow wave becomes linked with the plateau or action potentials (APs).
- "APs are superimposed on the plateau potentials in the terminal antrum and pylorus.
- The action potentials are associated with ↑ amplitude of the contraction of the smooth muscle.
- Cyclical contractile activity
- Phase 1:
  - Quiet; little contractile activity
- Phase 2
  - Random, irregular contractions
- Phase 3:
  - Bursts of "regular, high – amplitude phasic contractions ["activity front"] that last from 5 to 10 min….and migrate from the antrum to the ileum in 90 to 120 min.
  - Motilin is of importance to Phase 3 contractions
  - Cyclical contractile activity beginning in phase 3 of MMC seen in
    - Stomach / small bowel and,
    - Lower esophageal sphincter (LES)
    - Sphincter of Oddi (SO)
    - Gallbladder

➢ Key factors involved in the modulation of rate of gastric emptying

- Sensation
  - Low threshold mechano-/chemo-receptors stimulate visceral sensations such as stomach emptiness or fullness, and symptoms such as nausea and discomfort.
  - 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.
  - Somatic nerves such as from the skin carry sensory information via A-delta and C fibers through the dorsal root ganglia

- Into the dorsal horn and then
  - Through dorsal columns and spinothalamic tracts to cortical areas of somatic representation for somatic pain.

- Conscious perceptions
  - 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).

- Afferent Neural Activity
  - 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.

- Interneurons and dorsal horn of the spinal cord
  - 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.

- Muscle activity (motility)
  - Vagal and splanchnic nerve activities modulate the neuromuscular activities of the stomach.
    - The balance between excitatory and inhibitory nerves to the stomach leads to slower or faster gastric emptying.
  - Fast
    - Slow wave gastric myoelectrical activity during fasting.
  - Postprandial period there is summation of the slow wave activity linked to plateau and action potential activity.
  - Only a large meal, hypoglycemia and ↓ fundic accommodation (relaxation) physiological ↑rate of gastric emptying of the stomach (↓ $T_{1/2}$ of emptying).
  - All other gastroduodenal, ileal and colonic neuromuscular factors, as well as meal-related factors, ↓rate of gastric emptying (↑ $T_{1/2}$).

- Gastric emptying may be slowed by either
  - Bradygastria (1 cpm [cycle per minute]) of low- or high- amplitude, or
  - Tachygastria (≥6 cpm), where the antral contractions are not coordinated with opening (relaxation) of the pylorus.
  - GI peptides and pharmacological agents also modify emptying

- GI peptides involved in gastric emptying
  - CCK (cholecystokinin)
    - Released from enteroendocrine cells in duodenal mucosa in response to fatty acids (from digested triglycerides) in the duodenum.
    - Activation of CCK receptors → ↑sensation of fullness → ↓ food intake

○ PYY (polypeptide-YY)	− Released from enteroendocrine cells in ileocolonic mucosa − ↓ gastric emptying and ↓ small bowel rate of transit ("ileal brake") − ↓ appetite, ↓ food intake
○ Corticotropin-releasing factor (CRF)	− Responds to emotional stress − Acts through central pathways in periventricular nucleus ▪ Central dopamine 1 and 2 ▪ Vasopressin (AVP) pathways
○ Stem cell factor (SCF)	− ↑ BS (increased blood sugar), i.e., hyperglycemia) → ↓ SCF − ↓ SCF → ↓ ICCs and ↓ contraction of smooth muscle

➢ Gastric Emptying

- Testing
  - A gastric emptying test performed with a solid and a liquid test meal will correctly establish whether the rates of gastric emptying was slow at the time of testing.
    - However, there is usually a poor correlation between the patient's symptoms, the T1/2 of emptying provided by the emptying study, and their response to prokinetic medication.
  - The assessment of gastric neuromuscular function is divided into tests of
    - Gastric emptying rates (scintigraphy, breath test, ultrasound, CT/MRI imaging, and capsule technology)
    - Gastric contractions (antroduodenal manometry or capsule technology), and gastric myoelectrical activity
  - Electrodes placed on the anterior wall may be used to detect the myoelectrical activity of the slow waves arising from the pacemaker region.
  - This recording of the gastric myoelectrical activity is employed clinically as the electrogastrogram (EGG).
  - Electrogastrography (EGG) shows the amplitude and frequency of the gastric electrical rhythm (bradygastria or tachygastria, or a mix dysrhythmia)

- Gastric Electrical Therapy
  - Acupuncture with electrical stimulation (acustimulation)

➢ Treatment

❖ Non-pharmacological

- Meal Factors
  - Avoid offending foods and beverages
  - Small, frequent, fluid, neutral pH and temperature, isotonic, low energy density, low fat meals
  - Certain amino acids (e.g., L-tryptophan – [cheese])
  - Vitamin B6 (thiamine)
  - Ginger
  - Soda crackers (unproven benefit!)

- Unproven
  - Botulinum toxin-injection into pylorus
- Treat complications
  - Dehydration, electrolyte disturbances
  - GERD, esophagitis
  - Hyperglycemia (in a diabetic)
  - Hypokalemia
  - Malnutrition
  - Metabolic alkalosis
- Gastric pacing
  - GES (gastric electrical stimulation)
    - High frequency (12 cpm)
    - Short duration (300 microsec)
  - Gastric pacing (to "entrain" the normal gastric slow wave rhythm)
    - Low frequency (3 cpm)
    - Long duration (300 millisec)
  - Sequential
    - Sequential pacing using a microprocessor
    - Activation of electrodes in a series around the distal 2/3 of the stomach
  - Acupuncture
    - Stimulation of P6 acupuncture point
      - Acupuncture with electrical stimulation (acustimulation) represents one of the alternate forms of electrical therapy for gastroparesis.
- Treat associated disorders
  - Underlying disease/condition causing/ aggravating gastroparesis
  - Rectal/colonic distention
  - Pregnancy
  - Ascites
  - Hyperglycemia
  - Avoid circular vectoral motion
  - Avoid medications which may relax smooth muscle and thereby aggravate gastroparesis

❖ Pharmacological

➢ The mechanism (s) of action of prokinetic drugs used for treatment of GERD, gastroparesis and nausea/vomiting.

Drug	Receptor
Anticholinergic (buscopan, for tachygastria)	Acetylcholine receptor
Bethanechol	Muscarinic receptor agonist
Botulism toxin injection	Acetylcholine esterase inhibitor
Cisapride	Muscarinic (acetylcholine) receptor agonist 5-HT3 receptor antagonist 5-HT4 receptor agonist
Clonidine	α-adrenergic antagonist

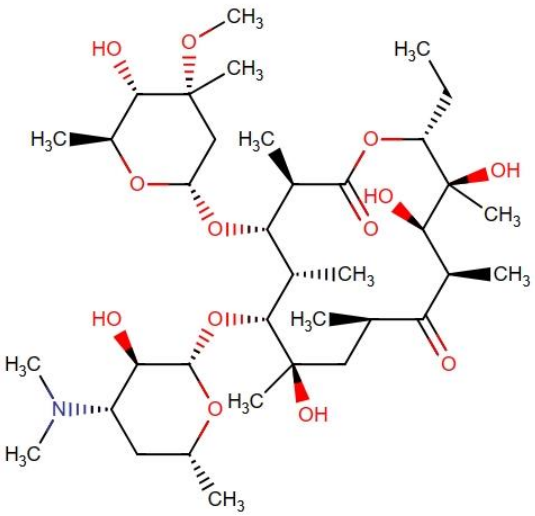
Drug	Receptor
○ Domperidone	– Peripheral D_2 antagonist
○ Erythromycin	– Motilin receptor agonist
○ Metoclopramide	– Central/peripheral dopamine receptor antagonist (D_2) – 5-HT3 receptor antagonist – 5-HT4 receptor agonist
○ Octreotide injection	– Somatostatin receptor agonist
○ Ondansetron	– 5-HT3 receptor antagonist
○ Tegaserod	– 5-HT4 partial agonist
○ Viagra®	– Phosphodiesterase inhibitor (NO, nitric oxide)

Adapted from: Koch KL. Chapter 49. *Sleisenger & Fordtran's gastrointestinal and liver disease: Pathophysiology/ Diagnosis/Management* 2016. 10th Edition. pg. 836-837.

❖ Surgery/Endoscopy

- Decompression
  - Nasogastric tube
  - Venting gastrostomy
  - Jejunostomy
- Conversion
  - Previous partial gastrectomy → subtotal gastrectomy or near-total gastrectomy and Roux-en-Y gastrojejunostomy
- Endoscopic therapy
  - Decompression with enterostomy tube

- **Erythromycin**



- Indication
  - Preparation for EGD in patient with upper GI bleeding (to ↑ emptying of blood from the stomach)
  - Gastroparesis
    - 3 mg/kg IV q8h, or
    - 40-80 mg po t.i.d. AC
  - Infection
    - Campylobacter
    - Vibrio cholerae
      - Erythromycin
        - 250 po q.i.d. for 3 days
        - 500 mg b.i.d. for 5 days

Abbreviations: AC, before meals/food; EGD, esophago-gastroduodenoscopy

- Mechanism of action
  - Release of motilin → stimulation of intestinal smooth muscle
- Pharmacokinetics
  - Absorption
    - Readily absorbed when given po
    - Food intake does not exert effects on serum concentrations of erythromycin.
    - Cmax, 1.8 mcg/L
    - Tmax, 1.2 h
    - Bioavailability is variable (18-45%) after oral administration and its susceptibility to broken down under acidic conditions
  - Volume of distribution
    - Found in most body fluids and accumulates in leucocytes and inflammatory liquid.
    - Concentration is low in spinal fluid, but diffusion through the blood-brain barrier increases in meningitis, due to the presence of inflamed tissues.
    - Can cross the placenta
  - Metabolism
    - Hepatic first-pass metabolism contributes significantly after an oral dose
    - Partially metabolized by CYP3A4 enzyme to N-desmethylerythromycin
    - Also, hydrolyzed to anhydroerythromycin (AHE) and other metabolites, which is promoted by acidic conditions.
    - AHE is inactive against microbes but inhibits hepatic drug oxidation, which is an important contributor to erythromycin drug-drug interactions.
  - Route of elimination
    - In patients with normal liver function, erythromycin concentrates in the liver and is then excreted in the bile.
    - Under 5% of the orally administered dose is excreted in the urine.
    - A high percentage of absorbed erythromycin is not accounted for, but is likely metabolized.

- Half-life
  - The elimination T1/2 of oral erythromycin, 2.5 - 3.5 h
  - Repetitive dosing of erythromycin leads to ↑ elimination T1/2
- Clearance
  - In healthy subjects, 113.2 ± 44.2 L/h
  - In cirrhotic patients, 42.2 ± 10.1 L/h (significantly reduced)

➢ Contraindication/precautions

- Known hypersensitivity to erythromycin or its components

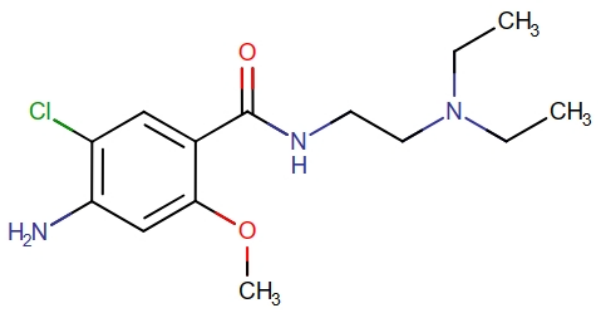
➢ Adverse effects (AEs)

- General
  - Anaphylaxis
- CNS
  - Convulsions
  - ↑ (worsening) myasthenia gravis
- Ear
  - ↓ hearing (ototoxicity)
- CVS
  - Arrythmias
  - ↑ QT (prolongation)
    - Torsades de pointes
- Skin
  - Erythema multiforme
  - Necrolysis, epidermal toxic
  - Stevens-Johnson syndrome (SJS)

➢ Peripartum

- Pregnancy
  - Safe
- Lactation
  - Safe

- **Metoclopramide**



- Indication
  - Gastroparesis
    - 5-20 mg po q.i.d.
  - Dyspepsia, undiagnosed
- Mechanism of action
  - Antagonist activity at D2 receptors
    - In the chemoreceptor trigger zone (CTZ) in the central nervous system → ↓ nausea and vomiting triggered by most stimuli
    - On smooth muscle to stimulate gastric emptying
- Pharmacokinetics
  - Absorption
    - Rapidly absorbed in the GI tract, absorption rate of ~84%
    - Bioavailability range of oral preparation 30-100%
  - Volume of distribution
    - ~ 3.5 L/kg (implies a ↑ level of tissue distribution)
    - Crosses the placental barrier and can cause extrapyramidal symptoms in fetus
  - Metabolism
    - Undergoes first-pass metabolism varying upon the individual
    - Metabolized by cytochrome P450 enzymes in the liver.
      - CYP2D6, CYP3A4, and CYP1A2 contribute to its metabolism
      - CYP2D6 more heavily involved. is also a minor contributing enzyme.
    - N-4 sulphate conjugation is a primary metabolic pathway
  - Route of elimination
    - About 85% of an oral dose measured in the urine within 72 h during a pharmacokinetic study
    - An average of 18-22% of 10-20 mg dose was recovered as free drug within 3 d of administration
  - Half-life
    - Mean elimination T1/2 in healthy renal function subjects, 5-6 h
    - Prolonged in patients with renal impairment (↓ dose adjustment should be considered).
  - Clearance
    - Renal clearance of metoclopramide 0.16 L/h/kg
    - Total clearance of 0.7 L/h/kg
    - Clearance reduced by up to 50% in patients with renal impairment

- Contraindication/precautions
  - Known hypersensitivity to metoclopramide or its products
  - Note: Adverse effects / drug-drug interactions
    - CNS
      - Seizures
      - Extrapyramidal AEs
      - ▪ Metoclopramide crosses blood brain barrier
    - GI
      - Hemorrhage, obstruction, perforation
    - Endocrine
      - Pheochromocytoma

- Adverse effects (AEs)
  - CNS
    - Dystonia/tremor
    - Neuroleptic malignant syndrome (NMS)
    - Restlessness
    - Sedative/somnolence
  - CVS
    - Arrythmia / QT prolongation
    - Edema

- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Safe

- Give the reason why misoprostol must be used with caution in all persons for the indication of gastroparesis.
  - In the doses necessary for gastroprotection, the higher doses may cause sufficiently frequent/severe symptoms that the patient may stop the medication.
  - If the patient is on misoprostol for gastroprotection and develops abdominal cramps, understandably they may stop the medication.
    - They are then at ↑ risk of severe consequences, without informing their prescribing physician and being placed on PPIs

NAUSEA AND VOMITING

➢ Treatment

❖ Non-pharmacological

- Non-prescription drugs, dietary and lifestyle modifications therapeutic options for the treatment of nausea and vomiting during **pregnancy**, including dietary and lifestyle modifications, and medical therapy.
  - Avoidance of precipitating factors
  - Frequent, small meals high in carbohydrate, and low in fat
  - Ginger
  - Vitamin B6
  - Stimulation of P6 acupuncture point

❖ Pharmacological

- CNS receptors responsible for the mechanism(s) of action for drugs used for the treatment of refractory nausea and vomiting
  - GI receptors
    - Please see previous page for treatment of gastroparesis and drugs acting on GI tract which are helpful to reduce patient's gastroparesis, and nausea/vomiting.
      - Erythromycin
        - Gastroparesis
          - Erythromycin 3 mg/kg IV q8h, or
          - 40-80 mg po t.i.d. AC
        - Pre-operation for EGD in patient with upper GI bleed
          - Erythromycin 500 mg po 30 min before EGD
        - Infectious diarrhea (= Vibrio cholera)
          - Erythromycin 250 po q.i.d. for 3 days
        - Campylobacter 500 mg b.i.d. for 5 days
      - Metoclopramide
        - Gastroparesis
          - Metoclopramide 5-20 mg po q.i.d.
      - Domperidone
        - Gastroparesis
          - Domperidone 10 mg po t.i.d.-q.i.d.

- Central
  - Benzodiazepines
  - Cannabinoids – dronabinol, nabilone
  - Corticosteroids (e.g., dexamethasone and Mannitol) (nausea and vomiting due to ↑ intracranial pressure)
  - H-1 receptor antagonists (inner ear) – diphenhydramine, promethazine
  - Neurokinin (NK)-1-antagonist – aprepitant, talnetant, osanetant
  - Neuroleptic – chlorpromazine, haloperidol
  - Tricyclic antidepressants (TCA)

❖ **Meclizine**

- Nausea/Vomiting –Vertigo
  - Meclizine 25-100 mg po qd in divided doses
- Motion sickness
  - Meclizine
    - 25-50 mg po 1 h before travel, then
    - 25-50 po qd prn

❖ **Dimenhydrinate**

- Nausea/Vomiting, vertigo, motion sickness
  - Dimenhydrinate
    - po 50-100 mg po q4-6 h, maximum 400 mg/d
    - IM 50 mg q4h
    - pr 50-100 mg, maximum q6-8 h

❖ **Ondansetron**

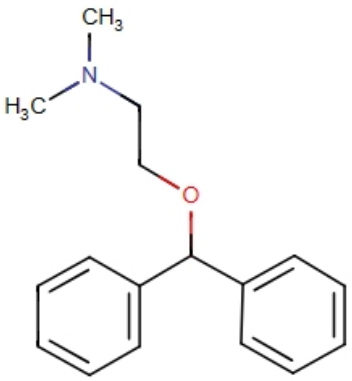
- Nausea/vomiting
  - Ondansetron
    - 4 mg q6-8 h, or
    - 8 mg q8-12 h

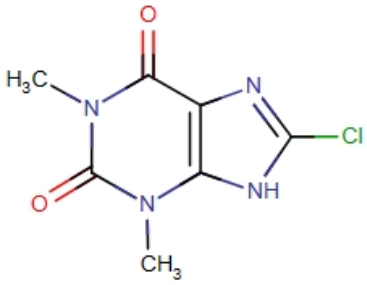
    } prn
- Prophylaxis of post-operative nausea/vomiting (N/V)
  - Ondansetron, 16 mg po 30 min before end of surgery, or for post-operative N/V

❖ **Scopolamine** patch

- Nausea/vomiting, chemotherapy-associated
  - Scopolamine patch q72h
- Motion sickness (MS)
  - Scopolamine patch 4 h before anticipated cause of MS, then q3d prn

❖ **Dimenhydrinate** (Dramamine®)





➢ Mechanisms of action

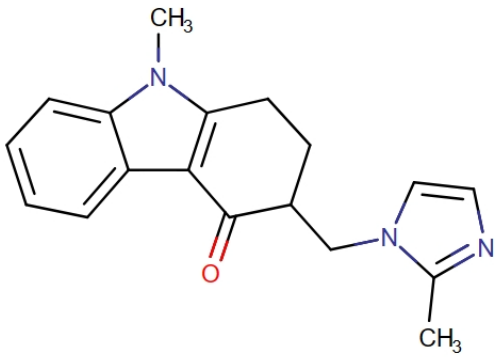
- Histamine-1 (H1) receptor antagonist
- ↓ central anticholinergic activity
  - Chemoreceptor
  - Vestibular apparatus
  - Labyrinth

➢ Pharmacokinetics

- Absorption
  - 50 mg film coated tablet po reaches Cmax of 72.6 ng/mL with Tmax 2.7 h
  - 100 mg suppository reaches Cmax 112.2 ng/mL with Tmax of 5.3 h
- Volume of distribution
  - 3-4 L/kg
- Metabolism
  - Theoclate salt that undergoes
    - N-glucuronidated by UDP-glucuronosyltransferases
    - N-demethylated by CYP2D6, CYP1A2, CYP2C9, and CYP2C19
    - Oxidative deamination
- Route of elimination
  - Predominantly eliminated in the urine
    - 1-3% dissociated diphenhydramine eliminated unchanged
    - 64% eliminated as metabolites
- Half-life
  - Plasma elimination T1/2 5-8 h
- Clearance
  - NA

- Contraindications/precautions
  - Known hypersensitivity
  - Older patients
  - CNS – Coma (↓ level of consciousness [LOC])
  - Eyes – Glaucoma
  - Ears – ↑ ototoxicity with some antibiotics
  - Heart – Tachycardia
  - Lungs – Asthma
  - GI tract – Obstruction
  - GU (prostate) – Benign hypertrophy
- Adverse effects (AEs)
  - CNS
    - Drowsy/excited
    - Headache/dizziness
    - Insomnia/fatigue
  - Eyes – Blurred vision
  - CVS – ↑ HR (tachycardia)
  - Respiratory
    - Thick secretions
    - Reactive airway symptoms
  - GI
    - Anorexia/nausea/vomiting
    - Dyspepsia
    - Dry mouth
  - GU – Dysuria
  - Skin – Rash
- Drug-drug Interactions
  - ↑ effect of
    - CNS depressants
    - Anticholinergics
- Pregnancy/lactation
  - Safe

- **Ondansetron (Zofran®)**



➢ Mechanism of action

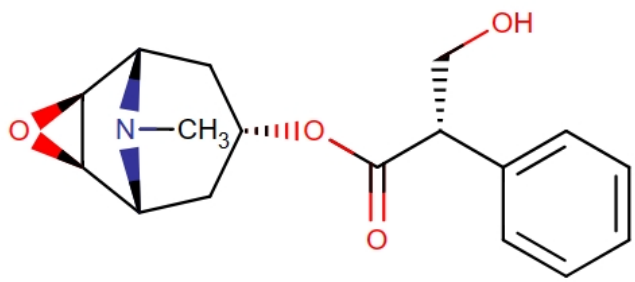
- 5-HT3 receptor antagonist
  - Vagus nerves
  - Chemoreceptor trigger zone (CTZ)

➢ Pharmacokinetics

- Absorption
  - Absorbed from GI tract and undergoes some limited first-pass metabolism
  - Mean bioavailability ~56-60% in healthy subjects, following 8-mg tablet po
  - Bioavailability slightly enhanced by the presence of food
- Volume of distribution
  - ~160 L
- Metabolism
  - substrate for human hepatic cytochrome P450 enzymes, including CYP1A2, CYP2D6 and CYP3A4
  - < 10% excreted unchanged in the urine
  - Major urinary metabolites are glucuronide conjugates (45%), sulphate conjugates (20%) and hydroxylation products (10%)
- Route of elimination
  - Oral or IV administration extensively metabolised and excreted in the urine and feces
- Half-life
  - T1/2 of 8 mg po or IV dose was, ~3-4 h and could be extended to 6-8 h in the elderly
- Clearance
  - Various patient age groups were recorded
    - 0.38 L/h/kg in normal adult volunteers aged 19-40 yr
    - 0.32 L/h/kg in normal adult volunteers aged 61-74 yr
    - 0.26 L/h/kg in normal adult volunteers aged ≥ 75 yr

- Contraindications/precautions
  - Known hypersensitivity
  - Advanced liver disease (Child-Pugh Class C)
- Adverse effects (AEs)
  - CNS
    - Drowsy/excited
    - Fatigue/coldness
    - Headache
  - CVS
    - QTc prolongation
  - Respiratory
    - Hypoxia
  - GI
    - Diarrhea
  - GU
    - Retention
  - Skin
    - Fever
    - Itching
- Drug-drug interaction
  - QTc-prolonging drugs
  - ↑ QTc
  - CYP 3A4 metabolized drugs ↓ metabolism → ↑ blood concentration
- Pregnancy-safe
  - Lactation-not known

- **Scopolamine**



- Mechanisms of action
  - Anticholinergic
    - ↓ salivary secretion → secretory glands dry mouth (xerostomia)
    - Smooth muscle
    - Cardiac muscle
    - ↑ HR (parasympatholytic)
  - Antagonizes
    - Histamine
    - Serotonin

- Pharmacokinetics
  - Absorption
    - Differ substantially between different dosage routes
      - 0.5 mg po in healthy subjects, Cmax of 0.54 ± 0.1 ng/mL, Tmax of 23.5 ± 8.2 min, with ↓ absolute bioavailability due to first-pass metabolism
      - 0.5 mg IV infusion over 15 min: Cmax of 5.00 ± 0.43 ng/mL, Tmax 5.0 min
      - 0.4 mg SC: Cmax 3.27 ng/mL, Tax of 14.6 min
      - 0.5 mg IM: Cmax 0.96 ± 0.17 ng/mL, Tmax of 18.5 ± 4.7 min
      - 0.4 mg intranasal: Cmax of 1.68 ± 0.23 ng/mL, Tmax 2.2 ± 3 min (higher bioavailability than po at 83 ± 10%)
    - Due to dose-dependent adverse effects, the transdermal patch was developed to obtain therapeutic plasma concentrations over a longer period of time.
      - Following patch application, scopolamine becomes detectable within 4 h and obtained Tmax within 24 h.
      - The average plasma concentration is 87 pg/mL
      - Total levels of free and conjugated scopolamine reach 354 pg/mL
  - Volume of distribution
    - IV infusion of 0.5 mg scopolamine over 15 min resulted in a volume of distribution of 141.3 ± 1.6 L.
  - Metabolism
    - Primarily metabolized in the liver, and the primary metabolites are various glucuronide and sulphide conjugates.
    - Oxidative demethylation linked to CYP3A subfamily activity, including CYP3A4
    - Pharmacokinetics significantly altered by coadministration with grapefruit juice, suggesting that CYP3A4 is responsible for at least some of the oxidative demethylation.
  - Route of elimination
    - Following oral administration
      - ~2.6% unchanged scopolamine recovered in urine
    - Transdermal patch system
      - < 10% unchanged scopolamine and metabolite recovered in urine over 108 h
      - < 5% recovered unchanged
  - Half-life
    - T1/2 differs on the route of administration.
      - IV, po, and IM administration have similar T1/2 of 68.7 ± 1.0, 63.7 ± 1.3, and 69.1 ±8/0 min, respectively.
      - T1/2 greater with SC administration at 213 min
      - Following removal of the transdermal patch system, scopolamine plasma concentrations decrease in a log-linear fashion with T1/2 of 9.5 h
  - Clearance
    - IV infusion of 0.5 mg scopolamine resulted in a clearance of 81.2 ± 1.55 L/h
    - SC administration resulted in a lower clearance of 0.14-0.17 L/h
- Contraindications
  - Known sensitivity
  - Caution in older persons

- CNS
  - Seizures
  - Psychosis
- Eye
  - Glaucoma (narrow single)
- CVS
  - Bradycardia
  - Hypotension
- GI/GU
  - Obstruction
  - ↓ liver function
- Endocrine
  - Hyperthyroidism

➢ Adverse effects

- Eyes
  - Agitation/ataxia
  - Drowsiness/confusion
  - Headache/dizziness
  - Psychosis/hallucinations/delusions/paranoid
- CNS
  - Vision
    - Blurred
    - ↓ accommodation
  - Conjunction
    - Drug/infection
  - Pupil
    - Dilation
    - Photophobia
  - Retina
    - Pigmentation
- CVS
  - Mouth dry
  - Esophagus
    - Dysphagia
  - Stomach
    - ↓/↑ BM (diarrhea/constipation)
  - Small/large bowel
    - Nausea/vomiting
- GU
  - Dysuria
  - Retention
- MSK
  - Weakness
  - Tremor
- Endocrine
  - Dry mouth / thirst
- Skin
  - Dry
  - Itchy (pruritis) / urticaria
  - Angioedema
  - Heat intolerance

➢ Drug-drug interaction

- ↑ effect of CNS depressants / ↑ effect of other anticholinergic drugs

➢ Pregnancy-safe

- Lactation
  - Use with caution

ENDOCANNABINOID SYSTEM AND CANNABINOIDS

➢ Pharmacology

- Endocannabinoid system
  - CB1 + CB2 receptors – classical receptors for cannabinoid (CB) agonists
    - CB1 highest density in myenteric + submucosal plexus of ENS
    - CB2 less frequent but overexpressed in inflammatory disorders
  - Endogenous CB ligands (Anandamide “AEA”, 2-AG) – lipid mediators synthesized from arachidonic acid, active on CB receptors
    - Synthesized on demand from membrane lipids
  - Degradative pathways for above
    - Fatty acid amide hydrolase (FAAH) in myenteric plexus
      - Inactivates 2-AG
    - Monoacylglycerol lipase (MAG lipase)
  - Membrane transporter and other receptors – e.g. TRPV1

Abbreviations: CB, cannabinoid; AEA, anandamide; ECS, endocannabinoid system; ENS, enteric nervous system; FAAH, fatty acid amide hydrolase; MAG, monoacylglycerol lipase; TRPV1, transient receptor potential cation channel subfamily V member 1

- Cannabinoid types
  - Broadly categorized as
    - Endocannabinoids
    - Phytocannabinoids
    - Synthetic cannabinoids
  - Compounds with affinity for cannabinoid receptors
    - THC (△9Tetrahydrocannabidiol)
      - Major psycho-active compound
    - Cannabidiol (CBD)
      - Acts on 5HT-1A receptors
      - Few psychotropic actions
    - Others:
      - Acidic CBs (Tetrahydrocannabinoic acid, cannabidiolic acid)
      - Cannabichromene
      - Cannabidivarin
      - Cannabigerol
      - Tetrahydrocannabivarin

➢ FDA Approved CB-based medications

- Sativex
  - THC + CBD (1:1 ratio)
    - Sublingual oromucosal spray for pain / spasticity (e.g. multiple stenosis)
- Marinol (dronabinol)
  - Oral capsule THC for
    - Appetite stimulant and
    - Anti-emesis (e.g. HIV/AIDS)
- Syndros
  - Oral liquid THC for
    - Chemotherapy associated nausea/vomiting
    - AIDS-associated anorexia
- Cesamet (nabilone)
  - Oral THC for nausea/vomiting, including N/V chemotherapy
- Epidiolex
  - Oral CBD solution approved for
    - Treatment of seizures from
      - Lennox-Gastaut syndrome
      - Dravet syndrome
      - Tuberous sclerosis
- Rimonabant (no longer available)
  - CB1 receptor antagonist used for loss of body weight, but, withdrawn because of ↑ risk of depression and vomiting

- ECS / Cannabinoid Effects on Gut
  - Gut motility is normally under tonic control by release of endocannabinoids
  - Myenteric CB1 receptors act as a physiological brake
  - CB analogues have dose-dependent effect in ↓ motility of small bowel and colon (especially with chronic CB exposure, when sensitive to CB1 blockade)
    - In contrast, the stomach may need second receptor, does not develop tolerance to CB effects

CB1 Antagonist

- ↑ CB Tone
  - Stomach
    - ↑ conditioned taste avoidance in rats
    - ↑ vomiting in humans
  - Small bowel
    - CB1 antagonist and cannabidiol
      - ↑ GI transit in experimental models of paralytic ileus
    - ↑ diarrhea in some obese patients
  - Colon
    - ↑ GI transit in patients with constipation

CB1 agonists

- ↑ CB Tone
  - Mouth
    - ↓ salivation
    - ↑ response to sweet taste via sweet receptors on the gustatory buds, and
    - ↑ periodontal healing
  - Esophagus
    - ↓ lower esophagus sphincter (LES) relaxation (i.e., ↑ LES contraction)
  - Stomach
    - ↓ gastric acid
    - ↓ gastric emptying
    - CB agonists +/- inhibitors of endocannabinoid degradation / reuptake
      - ↓ cisplatin, morphine, nicotine, apomorphine- and/or radiation-induced vomiting
  - Small bowel / Colon
    - CB1/CB2 agonist, inhibitors of endocannabinoid degradation/reuptake, and cannabidiol ↓ cisplatin hypermotility associated with gut inflammation and/or immune activation
      - ↓ diarrhea
      - ↓ signs of inflammatory bowel disease

- Diagnostic / Irritable Bowel Disease (IBS): Speculations
  - CB1 antagonist rimonabant (anorexiant) caused diarrhea in obese patients
  - CB1/CB2 agonist
    - Useful in IBS-D
    - CB1 antagonist
      - Useful in IBS-C
  - CB1/2 receptor activation
    - ↓ hypermotility associated with inflammation (via THC, CB1/2 agonist, inhibitors of anandamide or 2-AG breakdown)
  - FAAH blockers could raise anandamide and antagonize TRPV1, potential treatment
    - Useful for visceral hypersensitivity

- Nausea and Vomiting
  - Nausea (delayed and anticipatory)
    - Not well controlled with conventional anti-emetics

- CBs and THC analogues (nabilone) are effective anti-emetics, e.g.
  - Blockers of degradation of THC, anandamide, 2AGs
  - CBs have antinauseant effects
    - CB1 presynaptic receptors ↓ release of 5-HT
- THC analogues superior to dopamine receptor antagonist in preventing chemo-therapy associated N/V
  - Marinol was just as effective as Ondansetron

- Cannabinoid hyperemesis syndrome (CHS)
  - By the Rome IV
    - CHS is a distinct entity from cyclic vomiting syndrome (CVS) with different
      - Epidemiology
        - Young women (72%)
      - Bathing behaviour
        - Enjoy hot showers
      - Specific treatment

- Gastroesophageal Reflux Disease (GERD)
  - Transient lower esophageal sphincter (LES) relaxation → gastroesophageal reflux
    - Mediated by vasovagal reflex, which can be blocked by CB1 receptors
      - THC / synthetic cannabinoid WIN 55, 212-2 ↓ TLESR / ↑ LES pressure → ↑ GERD
  - THC → ↓ gastric acid (HCl) secretion

- Functional dyspepsia
  - No significant benefit of CBD 20mg/kg/d vs. placebo in
    - Relief of postprandial nausea, fullness, bloating or pain in patients with FD and no delay in gastric emptying
    - Effect in gastric emptying of solids, gastric volumes

- Microbiota
  - VSL3 (lactobacilli, bifidobacteria, strep thermophilus) →
    - IL-10 / dendritic cells
    - ↓ generation of pro-inflammatory Th helper cells
    - ↑ CB1/CB2 receptor in small intestinal ganglia of muscularis
    - ↑ gene expression coding AEA synthesis
    - ↓ breakdown of receptors by ↓ gene expression for FAAH, MGLL

- Inflammatory Bowel Disease (IBD)
  - Small ↓ symptom reduction
  - ↓ Harvey Bradshaw index

- ↓ Crohn disease activity index (CDAI) but no change in concentration of C-reactive protein (CRP) in medically refractory disease
- IBD, CRC, celiac disease, IBS
  - ↓ EOS
  - ↑/↓ endocannabinoid tone
- Giving CBD / stimulating CB2R
  - Does not make IBD better or worse
  - Studies do show ↓ inflammation / muscle contraction in mouse ileitis

➢ Adverse Effects on GI Tract / Liver

- Hepatotoxicity
  - Mild ↑ ALT/AST/ALP + hepatosplenomegaly in CBD use
  - Mild evidence for
    - ↑ fibrosis (↑ severity, ↑ rate of progression) / ↑ steatosis in persons with HCV infection
    - Variable in-vitro effect
    - European data → CBD in hep C associated with more/severe fibrosis, more rapid progression of fibrosis, higher rates of steatosis
    - Canadian study (Liu et al. 2018)→ no effect on fibrosis/steatosis
    - From data ↓ steatosis rate in HIV plus HCV co-infected patients (n=838)
  - 4 cases of liver failure (LF) with use of cannabis / analogues, but
    - 2 of these users had other more likely etiologies of the LF
  - Impact unclear
    - Not contraindicated

- Non-alcoholic Fatty Liver
  - Endocannabinoids affects causes
    - ↑ lipogenesis
    - ↓ lipolysis
    - ↑ appetite stimulation

    → ▪ Fat accumulation
  - CB1 receptors
    - Profibrotic
  - CB2 receptors (upregulated in chronic liver disease)
    - Protective against fibrosis but
    - ↑ steatosis
  - However, in US data
    - ↓ prevalence of NAFLD/NASH, independent of known metabolic risk factors
  - Other associated with CB use
    - ↓ insulin / ↓ insulin resistance
    - ↓ obesity / ↓ metabolic syndrome
    - ↓ diabetes

- Obesity
  - ECS has multiple effects on GI tract skeletal muscle and adipose tissue which could potentially ↑ risk of becoming obese.
    - Food intake
      - Brain
        - ↑ FI (depending in neuronal type)
        - ↑ motivation for palatable food
        - ↑ hedonic properties of palatable food
        - Modulation of gustatory and olfactory neurotransmission
        - ↓ EE and AT thermogenesis via SNS
        - ↓ WAT lipolysis via SNS
        - ↓ gastrointestinal motility via the vagus
      - Nose
        - ↑ odor sensitivity
        - ↑ food-seeking behavior
      - Mouth/oral cavity
        - ↑ neural responses to sweet taste
        - Regulation of taste sensitivity
        - Regulation of orosensory processes?
    - GI
      - Gastro-intestinal tract
        - ↑ fat preference and intake
        - ↑ secretion of ghrelin
        - ↑ nutrient absorption?
      - Pancreas
        - ↑ insulin secretion
        - ↑ Apoptotic activity and β cell death
      - Liver
        - ↑ lipogenesis
        - ↓ insulin clearance
        - ↓ insulin-induced signaling
    - Skeletal muscle
      - ↓ insulin-dependent glucose uptake
      - ↓ insulin-induced signaling
      - ↓ oxidative metabolism?
    - Adipose tissue
      - ↑ storage capacity
        - ↑ adipogenesis
        - ↓ fatty acid oxidation
        - ↑ glucose uptake
      - ↓ mitochondrial biogenesis

Key: ↑, increased ↓, decreased ?, further studies are required

Allan M, et al. Simplified guidelines for prescribing medical cannabinoids in primary care. Can Fam Physician 2018;64(2):111-120.

Andrews CN, et al. Canadian Association of Gastroenterology Position Statement: use of Cannabis in Gastroenterological and Hepatic Disorder. J Can Assoc Gastroenterol 2019; 2(1):37-43.

INFECTION

❖ Helicobacter pylori Infection

➢ Indications

- Uncomplicated peptic ulcer
  - PPI of your choice po b.i.d. for 2 wk plus 2 antibiotics, followed by PPI od for 2 wk
  - If patient experiences frequent recurrences
    - Perform urea breath test (UBT) with patient off PPI and antibiotics for 1-2 wk
    - If UBT positive, retreat H. pylori infection
    - If UBT negative, consider PPI po od continuously as maintenance therapy to ↓ HCl secretion / ↓ symptoms
- Complicated peptic ulcer
  - Complications of hemorrhage, obstruction, perforation
  - Treat PUD plus H. pylori infection as above for uncomplicated ulcer
  - Either repeat UBT off PPI and antibiotics, and retreat and prove eradication of H. pylori, with no PPI maintenance therapy (PPI po od), or
  - PPI maintenance therapy (PPI od), because of
    - Risk (low) of reinfection with H. pylori
    - Risk (low) of reulceration even without reinfection with H. pylori (but on PPIs)
    - Possibility that the original ulcer may have been caused by ASA/NSAIDs plus H. pylori infection
- Non-ulcer dyspepsia
  - In persons with H. pylori (Hp) associated non-ulcer dyspepsia, eradication of Hp results in long-term symptomatic relief in only about 8% of patients
    - This low rate of benefit should be communicated to patients when obtaining their consent to treat H. [pylori infection.
- Pre-/post- upper GI bleeding
- Post-banding of esophageal varices
- Post-operative diarrhea in patient with partial small intestinal resection
- Reducing risk of bleeding from upper GI tract in patient taking NSAIDs/ASA/COXIB (+/- associated H. pylori infection)

Reminder

- The indications for treatment of H. pylori are a positive non-serological test (e.g., urea breath test; stool test for H. pylori antigens; endoscopic biopsy histopathology, culture)
  - So, the important decision is, which patient should have a test for H. pylori?
  - It is now recommended that if it was indicated to test for an H. pylori infection, it is necessary to treat a positive non-serological test to prove eradication of the infection.

- Caution alert
  - Every patient being considered for long-term use of ASA/NSAIDs/ COXIBs should be tested (by UBT, stool antigen testing, or EGD plus biopsy) and treated for H.pylori
    - In every patient with a positive non-serological test for H. pylori(stool antigen, urea breath test, gastric mucosal biopsies), after a course of triple or quadruple therapy, a repeat test for H. pylori must be performed in order to prove eradication of the infection.

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

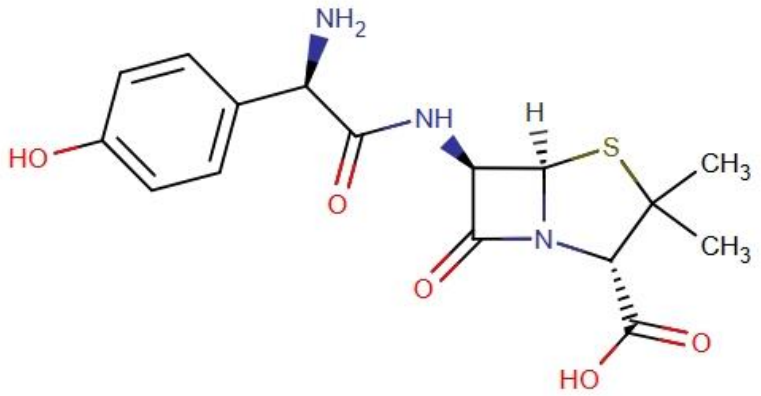
- All persons found to have an H. pylori infection should be treated.
- ↓ risk of PUD formation
- ↓ recurrent PUD → ↓ PUD bleeding, rebleeding, hospitalization, death
  - Endoscopic hemostatic therapy (EHT) does not prevent recurrent PUD bleeding in high risk ASA/NSAID users on PPI unless there is also an H. pylori infection
- Combine anti-H. pylori therapy with PPI to
  - ↑ anti-H. pylori effect of antibiotics
  - Accelerate improvement of ulcer healing and symptom relief

Treatment Pearl

- The indication to treat an H. pylori is a positive non-serological test
  - Do **not** treat a positive serological test → perform a stool, breath, or biopsy-based test for active infection
    - Thus, do **not** perform a test for H. pylori infection unless you and the patient are prepared to treat the infection, and to repeat a non-serological test for infection to prove H. pylori infection.
- If a non-serological test for H. pylori infection is positive, and the patient is appropriately treated with a guideline-based protocol for triple-/quadruple therapy, then a second non-serological test must be performed to prove eradication of the infection, even if the patent is asymptomatic.
- The reason to prove eradication
  - Relatively low (~70%) eradication rate of first-line complication therapies.
  - Failure to eradicate H. pylori is associated with ↑ risk of
    - Progression to gastric metaplasia, dysplasia, adenocarcinoma/MALT lymphoma
    - Peptic ulcer recurrence and GI bleeding.
  - ↑ complications when on ASA/NSAIDs (non-steroidal anti-inflammatory drugs)

➢ Treatment Options

- Antibiotics (plus PPI or Bismuth) used to eradicate H. pylori infection
- **Amoxicillin** (Amoxil®)



➢ Indication (in the GI context)

- Eradication of H. pylori infection

➢ Mechanism of action

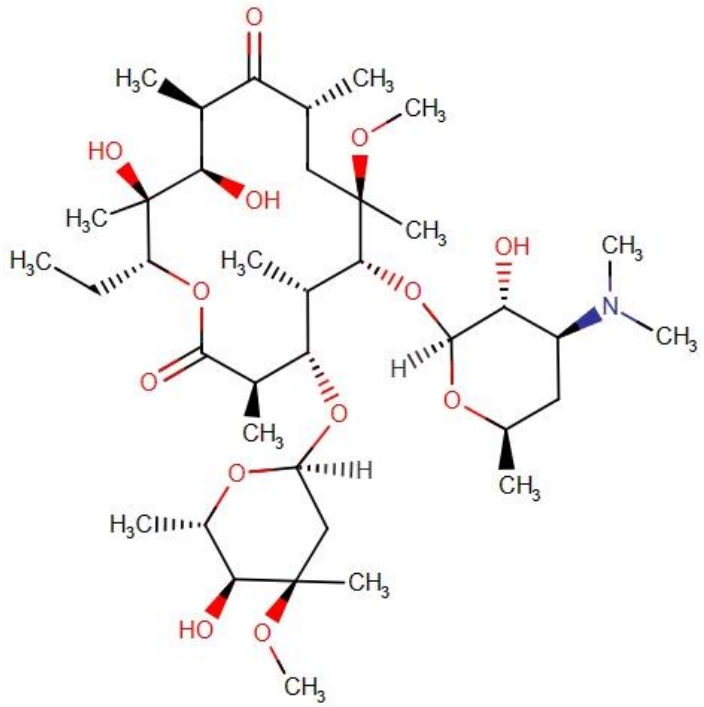
- Inhibition of bacterial cell wall synthesis, leading to cell death

➢ Pharmacokinetics

- Absorption
  - Amoxicillin po is approximately 60% bioavailable
  - 250 mg po reaches a Cmax 3.93±1.13 mg/L with a Tmax 1.31±0.33 h
  - 875 mg po reaches a Cmax 11.21±3.42 mg/L with a Tmax 1.52±0.40 h
- Volume of distribution
  - Central volume of distribution is 27.7 L
- Metabolism
  - Incubation with human liver microsomes lead to the detection of 7 metabolites
    - M1, hydroxylation
    - M2, oxidative deamination
    - M3 to M5, oxidation of the aliphatic chain
    - M6, decarboxylation
    - M7, glucuronidation
- Route of elimination
  - 125 mg to 1 g doses of amoxicillin are 70-78% eliminated in the urine after 6 h
- Half-life
  - The half life of amoxicillin is 61.3 min
- Clearance
  - Mean clearance of amoxicillin is 21.3 L/h

- Contraindication/precautions
  - Known sensitivity to amoxicillin, penicillin, cyclosporin (cross-reactivity)
  - Adverse effects / drug-drug interactions
  - Concurrent mononucleosis infection → skin rash
  - Phenylketonuria (PKU)
- Adverse effects
  - Immune
    - Hypersensitivity
    - Rash
  - GI
    - Nausea/vomiting
    - Diarrhea/ C. difficile infection
- Drug-drug interaction
  - Amoxicillin/antibiotics → ↓ effectiveness of oral typhoid vaccine
- Peripartum
  - Pregnancy – Safe
  - Lactation – Safe

- **Clarithromycin** (Biaxin®)



- Indication
  - H. pylori infection (in this context)
- Mechanism of action
  - Inhibits bacterial protein synthesis by binding to the bacterial 50 S ribosomal subunit → ↓ peptidyl transferase activity → interferes with amino acid translocation during the translation and protein assembly process.
- Pharmacokinetics
  - Absorption
    - Well-absorbed, acid stable and may be taken with food.
  - Volume of distribution
    - NA
  - Metabolism
    - Hepatic - predominantly metabolized by CYP3A4 resulting in numerous drug interactions.
  - Route of elimination
    - After 250 mg tablet every 12 h, ~ 20% is excreted in the urine unchanged
    - After 500 mg tablet every 12 h, the urinary excretion of clarithromycin is somewhat greater, approximately 30%.
  - Half-life
    - 3-4 h
  - Clearance
    - NA
- Contraindication/precautions
  - Known sensitivity to clarithromycin, erythromycin, and other macrolide antibiotics, or any component in their formulation
  - Adverse effects / drug-drug interactions e.g., arrythmias, QT prolongation, SJS / toxic epidermal necrolysis
  - Renal failure (use renal dosing)
  - Hypersensitivity reaction / anaphylaxis
- Adverse effects
  - CNS
    - Headache
  - GI
    - Abdominal pain
    - Abnormal taste
    - Nausea
    - Diarrhea
    - Hepatotoxicity / hepatic failure
  - Skin
    - Stevens-Johnson syndrome (SJS)
    - Toxic epidermal necrolysis

- Drug-drug interaction
  - Astemizole
  - Dihydroergotamine / ergotamine / ergot alkaloids
  - Pimozide
  - Eplerenone
  - Ranolazine
  - Phenothiazines
  - Dofetilide
  - Ergots

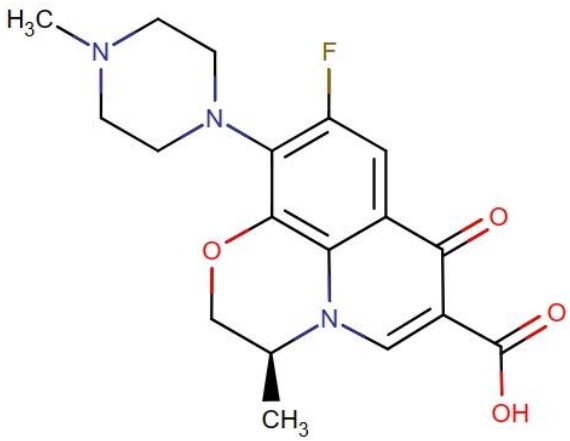
  Astemizole, Dihydroergotamine / ergotamine / ergot alkaloids, Pimozide:
  - Cardiac arrythmias
  - ↑ QTc prolongation

  Eplerenone: ↑ risk of ↑ K^+_s (hyperkalemia)

  Ranolazine, Phenothiazines, Dofetilide, Ergots:
  - risk of vasospasm
  - Ischemia

- Peripartum
  - Pregnancy – Safe
  - Lactation – Safe

- **Levofloxacin** (Levaquin®)



- Indication
  - Eradication of H. pylori infection (in the context)
- Mechanism of action
  - ↓ DNA gyrase → breaks DNA strands
- Pharmacokinetics
  - Absorption
    - Rapid and essentially complete, with an oral bioavailability ~99%
    - Due to its nearly complete absorption, the IV and po formulations of levofloxacin may be interchangeable
    - Tmax is attained 1-2 h following administration

- Cmax is proportional to the given dose
  - IV dose
    - 500 mg infused over 60 min resulted in a Cmax of 6.2 ± 1.0 µg/mL
    - 750 mg dose infused over 90 min resulted in a Cmax of 11.5 ± 4.0 µg/mL
- Oral administration with food prolongs the Tmax by approximately 1 h and slightly decreases the Cmax, but these changes are not likely to be clinically significant
- Systemic absorption following oral inhalation is approximately 50% lower than that observed following oral administration

- Volume of distribution
  - Widely distributed in the body, with an average volume of distribution following oral administration 1.09-1.26 L/kg (~89-112 L)
  - Concentrations in many tissues and fluids may exceed those observed in plasma.
  - Levofloxacin is known to penetrate well into skin tissue, fluids (e.g. blisters), lung tissue, and prostatic tissue, amongst others.

- Metabolism
  - Only 2 metabolites, desmethyl-levofloxacin and levofloxacin-N-oxide, have been identified in humans, neither of which appears to carry any relevant pharmacological activity
  - Following oral administration, < 5% of the administered dose was recovered in the urine as these metabolites, indicating very little metabolism of levofloxacin in humans

- Route of elimination
  - Majority administered levofloxacin excreted unchanged in the urine
  - Following the administration of a single oral dose of levofloxacin, ~87% eliminated unchanged in the urine within 48 h and < 4% was eliminated in the feces within 72 h

- Half-life
  - Average terminal elimination half-life, 6-8 h

- Clearance
  - Average apparent total body clearance ranges from 8.64-13.56 L/h
  - Renal clearance ranges from 5.76-8.52 L/h
  - Relative similarity of these ranges indicates a small degree of non-renal clearance

➢ Contraindication/precautions

- Known sensitivity to levofloxacin and other fluoroquinolones, or any component in their formulation

- Adverse effects / drug-drug interactions

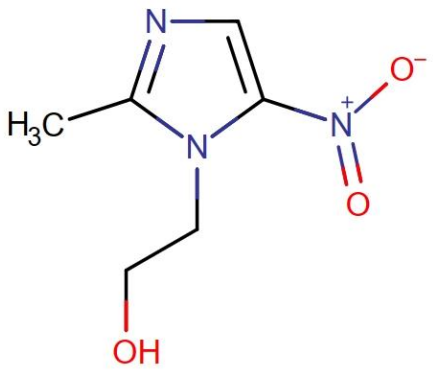
- CNS – Toxic psychosis

- CVS – Cardiac disease / QTc prolongation
  Myasthenia gravis-associated weakness

- Blood – G6PD deficiency / hemolytic anemia

- Adverse effects
  - CNS
    - Headache / dizziness
    - Insomnia
  - CVS
    - Chest pain
    - Peripheral edema
    - QT prolongation
  - GI
    - Abdominal pain
    - Nausea / vomiting
    - Diarrhea / constipation
  - GU
    - Vaginitis
  - MSK
    - Tendon rupture
  - Skin
    - Rash
    - Pruritis
- Drug-drug interaction
  - Antacids → ↓absorption / ↓ blood levels of levofloxacin
  - ↑ QTc prolongation caused by other drugs which also have potential to ↑ QTc
- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - **Stop** drug / **stop** breastfeeding

- **Metronidazole** (Flagyl®)



- Indication
  - H. pylori infection
  - Clostridium difficile infection (CDI)
  - Amebiasis
    - Intestinal tract
    - Hepatic abscess
  - Giardiasis (Giardia lamblia infection)
  - Crohn disease
    - Perianal disease
    - Post resection prophylaxis against recurrence
    - Associated small intestinal bacterial overgrowth (SIBO), secondary to strictures/fistula)

Clinical Emerald

- It used to be thought that CDI occurred only in very sick patients in hospital (especially "dirty" hospitals) who had been given antibiotics, such as clindamycin
  - It is now known that CDI may be acquired in the community in otherwise well, non-immunosuppressed persons who have not been on antibiotics.
- What is the point
  - Include CDI in cause of outpatient/inpatient

- Mechanism of action
  - Diffuses into the organism → interacts with DNA → ↓ helical DNA structure/strand breakage → cell death in susceptible organisms.

- Pharmacokinetics
  - Absorption
    - After 1.5 g IV infusion dose, Tmax 1 h, Cmax 30-40 mg/L
    - 500 mg 3x IV, Cmax 26 mg/L
    - Orally tablet form, entirely absorbed, showing a bioavailability > 90%
    - Insignificant percutaneous absorption occurs after the application of 1% metronidazole cream topically.
  - Volume of distribution
    - Widely distributed throughout the body and various body fluids, including the bile, saliva, breastmilk, cerebrospinal fluid, and the placenta.
    - Steady-state volume distribution of metronidazole in adults ranges from 0.51 to 1.1 L/kg.
    - Attains 60 to 100% of plasma concentrations in various tissues, such as the central nervous system
    - Not measured in high concentrations in the placental tissue

- Metabolism
  - Undergoes hepatic metabolism via hydroxylation, oxidation, and glucuronidation, yielding 5 metabolites
  - Hydroxy metabolite, 1-(2-hydroxy-ethyl)-2-hydroxy methyl-5-nitroimidazole, is considered the major active metabolite
    - Unchanged metronidazole is found in the plasma with small amounts of its 2-hydroxymethyl metabolite.
    - Several metabolites of metronidazole are found in the urine.
    - 20% unchanged drug found in the urine
- Route of elimination
  - 60 to 80% eliminated in the urine
  - 6-15% excreted in the feces
- Half-life
  - The elimination T1/2 is 7.3 ± 1.0 after a single 500 mg IV dose in healthy subjects.
- Clearance
  - Dose adjustments may be required in patients with hepatic impairment, as clearance is impaired in these patients.
  - Clearance in the kidneys is estimated at 10 mL/min/1.73 m^2.
  - Total clearance from serum ~ 2.1 to 6.4 L/h/kg

➢ Contraindication/precautions
- Known hypersensitivity to metronidazole, nitroimidazole, or components
- Adverse effects / drug-drug interaction
- Pregnancy (**T1**; first trimester)
- Associated
  - Blood dyscrasias
  - CNS disease
  - Liver dysfunction

➢ Adverse effects
- CNS
  - Headache / dizziness
  - Ataxia
  - Seizure
  - Peripheral neuropathy
  - Ototoxicity
- Lung
  - Upper respiratory infection
- GI
  - Abdominal pain
  - Anorexia / metabolic taste in mouth
  - Nausea/vomiting

- GU
  - Candida infection of the genital area
  - Cervicitis
  - Pelvic pain
  - Vaginitis / vaginal discharge
- Blood
  - Leukopenia
  - Thrombocytopenia
- Skin
  - Jarisch-Herxheimer reaction
- MSK
  - Weakness (Tinidazole)

➢ Drug-drug interaction

- Disulfiram-like reaction
  - Alcohol
- ↑ toxic effects of disulfiram
  - Diazoxide
  - Ritonavir
  - Tipranavir
- ↑ serum levels / ↑ toxicity of
  - Cyclosporine
  - Lithium
  - Phenytoin
  - Tacrolimus

➢ Peripartum

- Pregnancy
  - Do **not** use in T1
- Lactation
  - Do **not** use (until 3 days after cessation)

HELICOBACTOR PYLORI-NEGATIVE PEPTIC ULCER DISEASE

- The proportion of all peptic ulcers which are H. pylori-negative is increasing (~25%); especially in persons with a non-NSAID-associated non-variceal upper GI bleed.
- Ensure that if the diagnosis of H. pylori infection is based on the urea breath test UBT) or gastric mucosal biopsies, anti-secretory therapy and antibiotics must be stopped at least 1 wk before taking (mucosal gastric) biopsies, and these biopsies must be taken from antrum (2), body (2), and angularis (1).
- Before deeming that the patient has H. pylori-negative peptic ulcer disease, care must be taken to exclude
  - H. pylori infection, using 2 different types of standard tests
  - Use of ASA, NSAIDs, COXIBs, bisphosphonates (check platelet aggregation or thromboxane B2 levels)
  - Fasting hypergastrinemia (ensure patient not currently taking anti-secretory therapy and was in fact fasting, as instructed)

➢ Factors which suggest that. H. pylori-negative (Hp-) peptic ulcers are more serious/severe than are H. pylori-positive peptic ulcers (Hp+).

Clinical	Hp+	Hp-
○ ↑ bleeding ulcer	4%	50%
○ ↑ recurrent ulcer bleeding	11%	42%
○ ↑ ASA risk ≥ grade 3	18%	~50%

Abbreviations: ASA, American Society of Anesthesiologist

HYPERGASTRINEMIA

- **Zollinger-Ellison Syndrome** (ZES)

A Tricky Question

- In a patient with a known enterochromaffin-like cell (ECL) gastric "carcinoid" tumour,(term is now replaced by "ECL" tumour), what does the development of flushing andwheezing (carcinoid syndrome) tell the clinician?
    - Carcinoid syndrome does **not** occur unless there is hepatic involvement (metastases).

➢ Clinical

- Abdominal pain (75%-100%)
- Diarrhea (35%--73%) (isolated presentation in up to 35%)
- Pain and diarrhea (55%-60%)
- Heartburn (44%-64%)
- Ulcers
    - Duodenal and prepyloric ulcers (71%-91%)
    - Multiple ulcers in unusual places
    - Stromal ulcers
    - PUD refractory to treatment
    - Ulcer complications (bleeding, 1%-17%; perforation, 0%-5%, or obstruction, 0%-5%)
- Associations
    - MEN-1 associated tumours (22%-24%)
    - ZES may be associated with MEN-1 (multiple endocrine neoplasia type 1) in ~20% of the patients, in which the commonest associated adenoma is the parathyroid gland.
    - Hyperparathyroidism may be associated with hypercalcemia and its complications, such as nephrolithiasis.

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

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

Remember

- Commonest cause of diarrhea in patients with treated peptic ulcer disease (PUD)
    - Drugs used to treat PUD, such as Mg-containing antacid use of prostaglandin analogues (e.g., misoprostol), as well as PPIs and H2RAs.
    - Drugs used to treat H. pylori infection
        - Antibiotics

- Laboratory tests
  - Confirm fasting state for gastrin measurement, and patient not on PPIs for last 1-2 wks
  - Serum calcium, PTH, TSH as a cause of ↑ gastrin
  - Serum creatinine (exclude renal failure)
  - Chromogranin A
  - Urinary metanephrines
  - Vitamin B12 concentration
  - Schilling test (vitamin B12 absorption/secretion)
- Provocative stimulation tests
  - Secretin infusion → ↑ gastrin paradoxically in ZES (due to secretin receptors on tumour cells)
  - Ca^{+2} infusion (→ ↑↑ serum gastrin)
  - Basal (↑↑ BAO) and pentagastrin stimulated acid secretion (↑↑MAO), BAO/MAO>60% (ZES)
  - ↑ food-stimulated acid secretion (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]) and for H. pylori infection
    - Thick gastric folds
    - Fundic gland polyps
  - EUS for possible tumour localization in gastrin triangle (especially in wall of duodenum and head of the pancreas)
  - The "Gastrin Triangle"
    - Junction of cystic duct with common bile duct
    - Junction of head with body of pancreas
    - Second portion of duodenum (D2)
- Diagnostic imaging
  - Abdominal ultrasound
  - Endoscopic ultrasound (EUS)
  - CT/ MRI of head (pituitary fossa tumour in MEN I)
  - MRI of abdomen
  - Octreotide scan
  - MBIG scan
  - $Galium^{68}$ scan
  - CT scan of abdomen
  - Parathyroid scan

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

MULTIPLE ENDOCRINE NEOPLASIA TYPE I (MEN-1) **GASTRINOMAS**

➢ Clinical

- Parathyroid adenoma ~93% for
  - Symptomatic hypercalcemic patients
  - Parathyroid gland removal
  - Parathyroid autograft ± cervical thymectomy
- Pancreas
  - ~80% of MEN-1 patients

Tumours	Approximate Frequency (%)
Gastrinoma	54
Insulinoma	21
Glucagonoma	3
VIPoma	1

  - 40% have asymptomatic ↑ gastrin (serum), or Zollinger-Ellison syndrome (ZES)
- Pituitary adenomas, ~40%

Tumours	Approximate Frequency (%)
Cushing syndrome	16
Prolactin-secreting	30
Growth-hormone secreting	16
Adrenal cortical adenoma	30%
Thyroid adenoma	20%

➢ Types

- Differences between sporadic versus MEN-1-associated gastrinomas.

	Sporadic	MEN-1 Associated
➢ Pathology		
Neuroendocrine tumours	~1%	30%
Number of tumours	Often single	Often multiple, and in different sites
Site, gastrinoma triangle	80%	Pancreas, duodenal wall
Growth rate of metastases	Rapid	Slow
Liver metastases at diagnosis	25%	5%
➢ Laboratory		
Identification of source of excess gastrin	Yes	No – imaged tumours may not necessarily be source of ↑ gastrin

	Sporadic	MEN-1 Associated
➢ Clinical		
○ Family history	No	Yes
➢ Treatment		
○ Consider exploratory laparotomy with curative intent when no evidence of metastatic disease	Yes	No
○ Surgical cure (duodenotomy and subtotal pancreatectomy)	50%	No definitive evidence of benefit of surgery

- PPI
  - Optimal outcome is to ↓acid secretion to < 10 mEq/h, measured just before the next planned dose of PPI
    - Control symptoms
    - ↓ complications of peptic ulcers
    - Control gastrin-producing tumour (gastrinoma)
- Patients with metastatic gastrinoma with somatostatin receptor-positive tumours, may benefit from
  - External beam radiotherapy, and
  - Octreotide or lanreotide-SR for control of symptoms.
- Octreotide binds to the somatostatin receptor which is on some NETs.
  - This reduces the release of peptides, such as gastrin, which contribute to the causation of the tumour-syndrome
    - Drugs may be bound to octreotide to ↑ binding to NET with octreotide receptors
- Therapeutic options directed at the metastatic liver disease include
  - Resection of tumour
  - Embolization of the hepatic artery ± chemotherapy
  - Radiofrequency ablation (RFA) or cryoablation ± surgical debulking
  - Systemic chemotherapy
    - Doxorubicin
    - mToR (mammalian target of rapamycin)
    - Peptide receptor radioligand therapy
    - Streptozotocin
    - Temozolomide
    - TK (tyrosine kinase) inhibitors

MCQ Trick

- The NET may stain positive by immunohistochemistry for one peptide, such as insulin, but a different peptide may be elevated in the blood, and is the cause of the patient's symptoms (such as gastrin in ZES)

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

- Useful background
  - Dyspepsia occurs in about 25% of persons taking NSAIDs, COXIBs, ASA (NSAIDs >COXIBs)
  - Ulcers (GU, DU) occur in ~25% of persons on NSAIDs
  - NSAID-associated ulcers are often
    - Asymptomatic
    - GU > DU (DU > GU with H. pylori infection)
  - The absolute risk of a bleeding GU/DU associated with the use of NSAIDs is ~2.5%
  - This ↑ risk of bleeding with NSAIDs and COXIBs is further increased with the use of
    - ASA
    - Clopidogrel
    - H. pylori infection
    - History of previous NSAID-associated upper GI bleed
  - NSAIDs (excluding naproxen) and COXIBs ↑ risk of
    - Hypertension
    - Renal dysfunction
    - Fluid retention
    - Coronary artery disease events
  - PPIs (but not H_2RAs) reduce by ~50% the risk of ulcer, ulcer symptoms and ulcer bleeding.
    - Be certain to caution patient on NSAIDS/ASA plus PPI that the PPI decreases but does **not** completely prevent ulcer bleeding.
  - Eradication of an H. pylori infection → ↓risk of ulcer bleeding in persons starting on NSAIDs/ASA
    - Eradicate H. pylori before starting NSAID therapy
      - Mandatory in persons with a history of peptic ulcer disease
      - Always necessary to prove eradication of H. pylori infection after guideline-based combination of antibiotics plus PPI or bismuth compound
    - In the patient with non-variceal upper gastrointestinal bleeding (NVUGIB) associated with H. pylori (Hp) infection, start the Hp. treatment as soon as oral feeding is started.
  - Maintenance therapy with PPIs is "…superior to H. pylori eradication alone in primary or secondary prevention of endoscopic ulcers among NSAID users" (Rostom et al., Aliment Pharmacol Ther 2009; 29: 481-496.

Abbreviations: ASA, aspirin; COXIB, COX-2 inhibitor; NSAID, non-steroidal anti-inflammatory drug; NVUGIB, non-variceal upper gastrointestinal bleeding

Adapted from Rostom, A. et al., Aliment. Pharmacol. Ther. 2009; 29: 481-496.

➢ Pharmacological considerations

- COXIBs
  - COX-2 inhibitors are "…probably as effective as a combination of non-selective NSAIDs combined with PPI in patients at risk for [NSAID-associated] ulcers".
  - Consider using celecoxib versus diclofenac plus PPI, "…. neither treatment could eliminate the risk of recurrent bleeding in very-high-risk patients" (recent history of bleeding peptic ulcer, 6 mon risk of ulcer ~20%, risk of recurrent bleeding,5%).
  - "….COX-2 inhibitors but also non-selective NSAIDs, with the exception of full-dose naproxen (1000 mg a day), increase cardiovascular risk" (risk ratio for most myocardial infarction, 1.42), and ".....there was no significant difference in cardiovascular risk between COX-2 inhibitors and non-selective NSAIDs. Naproxen(500 mg twice daily) was the only exception"
- H. pylori
  - H. pylori increases risk of ulcer bleeding ~2 fold, NSAIDs ~5-fold, and H. pylori plus NSAIDs ~ 6 fold.
  - "Among patients who are about to start NSAID therapy, eradication of H. pylori reduces [by about 50%, but does not prevent] the subsequent risk of ulcer development."
  - Thus, "….eradication of H. pylori infection alone is not sufficient for the prevention of ulcer bleeding in NSAID users with high ulcer risk.
  - Although H. pylori increases the ulcer risk in patients receiving low-dose aspirin, "co-therapy with PPI after eradication of H. pylori is still required…."

Adapted from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. *Saunders/Elsevier*, Philadelphia, 2022.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- In persons who require an NSAID, it is recommended to "use the least ulcerogenic NSAIDs at the lowest effective dose"; such as naproxen 500 mg b.i.d. is effective.
- Ibuprofen is available OTC (over-the-counter), and is often advertised as being relatively safe.
  - In persons with **high GI risk plus high cardiovascular risk**
    - Ibuprofen is **not recommended**, even if PPI co-therapy is used
    - A COXIB is **not recommended** because of its risk of cardiovascular complications

- In this clinical scenario, give the reasons why ibuprofen is **not** recommended include
  - Aspirin reduces cardiovascular (CV) risk.
  - In high risk CV patients, ASA must be taken.
  - Ibuprofen reduces the serum concentration of ASA.
  - The lower serum concentration of ASA given with ibuprofen reduces the CV protection of the ASA.
  - So, do **not** combine ibuprofen with ASA in high CV risk patient.

Therapeutic Warning

- Ibuprofen negates the prophylactic benefit of ASA (↓ absorption).
  - Implication
    - In patients who require ASA for example, to ↓ risk of thromboembolic complications in patients with atrial fibrillation, warn patient not to take over-the-counter ibuprofen, because the prophylactic benefit of ASA would be lost
- ASA negates the benefit of COXIBs on gastric mucosa (COXIBs → ↓ damage, but ASA
  - ↑ damage

- Anti-platelet drugs
  - Low-dose aspirin alone slightly ↓ all-cause mortality (relative risk, 0.93; 95% confidence interval, 0.87-0.99), but ↑ the risk for major GI bleeding (adds ratio,1.55; 95% CI, 1.27-1.90).
  - PPI use with aspirin ↓ likelihood of bleeding (OR, 0.34; 95% CI, 0.21-0.57).
  - Low-dose aspirin negates the GI mucosa-sparing effect of COX-2 inhibitor.
  - In combination of ASA with clopidogrel or anticoagulants, the risk for major bleeding is higher than with aspirin alone (OR, 1.86; 95% CI, 1.49-2.31 and OR, 1.93; 95% CI, 1.42-2.61, respectively).
  - PPIs ↓ risk of adverse upper gastrointestinal events in patients receiving clopidogrel alone.
  - In patients with acute coronary syndrome or ST elevation myocardial infarction, esomeprazole is superior to famotidine in preventing upper gastrointestinal complications related to aspirin, clopidogrel, and enoxaparin or thrombolytics.

Questions

- Use of famotidine, an H2 receptor antagonist, to ↓ risk of NSAID-associated peptic ulcer disease: is it useful?
  - Answer: Yes and no; “it depends”
    - Requires high dose
    - Protective effect is against duodenal ulcer (DU) but not gastric ulcer (GU) in patients on NSAIDs, the ratio of GU to DU is 2:1.
    - So, a high dose of famotidine → ↓ risk of DU, but not GU, which is the more common peptic ulcer of patients on ASA / NSAIDs

INFLAMMATORY BOWEL DISEASE (IBD)

❖ Pharmacology of IBD-treating Drugs

- General Treatment Principles in IBD
  - Treat early
    - Better response
  - Treat first (naïve)
    - The more drugs the patient fails, the more resistant/refractory, severe the disease
  - End points (targets) for therapeutic response
    - Symptoms (including patient related outcomes [PROs],
    - Laboratory (calprotectin, fecal calprotectin)
    - Endoscopy (ideally, no ulceration)
    - Diagnostic imaging
    - Histopathology
    - Inhibition of pathogenic factors

Peyrin-Biroulet L, et al. Am J Gastroenterol 2015; 110; 1324-38.

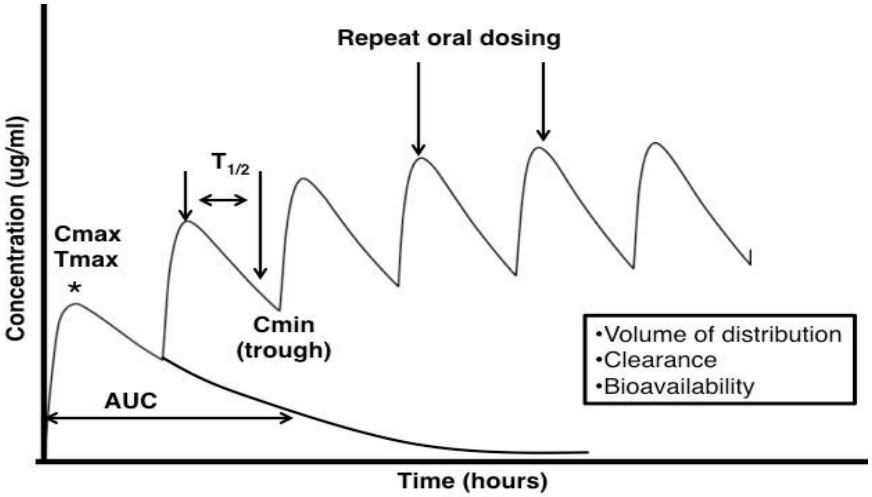
➢ Definition

- The study of drugs in humans
  - Includes the basic science of pharmacology with the application of pharmacological principles and methods in the real world
    - Discovery of new target molecules
    - Evaluation of a drug's effect in a given population

➢ Terminology

- Pharmacokinetics (PK)
  - What happens to a drug while it is in the body
  - The study of how an organism affects a drug
  - Components
    - Absorption
    - Distribution
      - Metabolism (biotransformation or inactivation)
      - Excretion

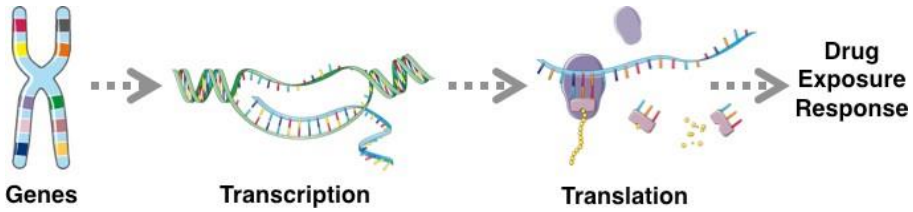
- The metrics of pharmacokinetics



  - therapeutic drug monitoring (TDM)

- Pharmacodynamics (PD)
  - Clinical endpoints
  - Drug-drug interactions
    - What drugs do to each other in the body

- Pharmacogenomics
  - The effect of gene patterns on drugs
  - *"The study of how our genetic makeup affects drug response"*
    - Variation in key genes (metabolism, transport, regulation) may affect gene expression and the end effect of the drug.



    - Most drugs mimic or inhibit physiological or pathological processes in the patient, or
    - Inhibit vital processes of microbial organisms which in turn alter these processes in the host.

➢ Treatment challenges

- Multiple disease phenotypes
- Pathogenesis may remain mystery
- Drug exposure does **not** necessarily equal drug response
- Significant inter- and intra-patient variability
- Risk of significant/severe adverse drug effects (AEs)
- Biomarkers predicting efficacy or failure of biologics and small molecule drugs in the hope of personalized therapy."

➢ Pharmacokinetics

- **5-aminosalicylates (5-ASAs) Mesalamine, and Bal-/Olsalazine/Sulfasalazine**
  - 5-ASA is converted to active agent, N-acetyl-5-ASA, by N-acetyltransferase (NAT-1) in enterocytes and colonocytes.
  - Plasma concentrations are variable in both IBD patients and in healthy persons.
  - Because this class of drug acts locally on the bowel mucosa, its efficacy depends upon
    - The amount of the drug delivered to the intestinal site of inflammation (e.g., small bowel or colon)
    - Not on the blood concentration (systemic bioavailability)
  - Systemic bioavailability of 5-ASA is low (20%), vs 80% topical availability at terminal ileum (TI) and colon
    - ↑ bioavailability with multiple daily dosing
    - Steady state at 5 days
    - Since the action of n-acetyl-5-ASA is topical in the enterocytes and colonocytes, a lower concentration in the blood (bioavailability) reflects
      - More active drug in the mucosa, or
      - Unabsorbed non-active drug (5-ASA) in the gut lumen
  - Postulated mechanisms of action
    - Interaction with pathways of inflammation and apoptosis
    - “Interferes” with TNF-α, TGF-β, NFκB
    - Scavenger for reactive oxygen species (ROS)
    - Alters fecal bacteria profiles
    - ↓ leukocyte motility
  - Effective for inducing remission and preventing relapse in patients with ulcerative colitis (UC), but **not** in Crohn disease (CD) (some controversy re CD of colon)
  - Combined oral (po) and topical (pr) therapy is superior to oral therapy alone for induction of remission in mild to moderate UC (5-ASA po plus pr > po alone)
  - 5-ASA enemas are more effective than corticosteroid enema in distal UC.

- The treatment goals of IBD patients (Crohn disease, ulcerative colitis)
  - Induce and maintain clinical remission (symptoms), correct laboratory abnormalities, correct endoscopic abnormalities,and histological changes ("deep healing" of mucosa), restores patient's quality of life, prevent need for IBD-related surgery, reduce risk of IBD-related complications.
  - Optimizing quality of life (QoL) of patient
  - Avoid hospitalization
    - Prednisone use
    - Surgery

➢ Contraindication/precautions

- Known hypersensitivity to mesalamine
  - Sulfasalazine
  - Mesalamine
  - Olsalazine
  - Balsalazide

➢ Adverse effects

- CNS
  - Asthma
  - Blurred vision
  - Headache
- CVS
  - Hyper-/hypotension
  - Pericarditis
- Lung
  - Pneumonitis
  - Pulmonary infiltration
  - Upper respiratory infection (URI)
- GI
  - Dyspepsia / abdominal pain
  - Nausea/vomiting
  - BM (constipation, diarrhea)
  - ↑/↓ BM (alternating constipation, diarrhea)
  - Exacerbation of IBD
  - Hepatitis
  - Pancreatitis
- GU
  - Nephritis
  - Oligozoospermia/infertility
  - Urinary crystals
- Skin
  - Pruritis
  - Rash
  - Urticaria

- Blood
  - Agranulocytosis
  - Folate deficiency
  - Hemolysis
  - Neutropenia
  - Porphyria relapse
- MSK
  - Arthralgia
  - ↑ risk of myelosuppression

➢ Drug-drug interactions
- Sulfasalazine, balsalazide, olsalazine →
  - ↑ blood levels of 6-thioguanine (6-TG) from ↑ 6-MP

➢ Peripartum
- Pregnancy
  - Safe
- Lactation
  - Safety unknown

❖ Mild UC
- Confirm diagnosis
- Provide patient education
- Exclude precipitants
  - Non-compliance with maintenance therapy
  - Drugs (e.g., 5-ASA, NSAIDs)
  - Infection (e.g., C. difficile)
  - Stop smoking (tobacco use ↑ clinical activity of UC/CD)
- 5-ASA or sulfasalazine
  - po or pr (enema or suppository) or both, depending on extent of disease
- Prepare for possible future use of immune suppression, or biological therapy (combination of 5-ASA po plus pr superior to just po)
  - TB
    - Tuberculosis skin test
    - Quantitative interferon test
  - Hepatitis B infection
    - Even for healthy carrier, concern for reactivation of HBV
- Sample meta-analyses of efficacy of 5-ASA in UC (vs placebo)

	OR
5-ASA suppositories/enemas	
Achieving remission of distal colitis	7.4
Maintaining remission	16.2

	RR
– po-5-ASA less likely to fail in	
▪ Achieving remission	0.79
▪ Maintaining remission	0.65

	RR
– ↓ risk of colorectal cancer (CRC)	0.51
– ↑ risk of renal toxicity	2.48

Abbreviations: 5-ASA, 5-amino salicylic acid; CRC, colorectal cancer; HBV, hepatitis B virus; OR, odds ratio; TBST, tuberculosis saliva test

- Rectal (topical) therapy
  - 5-ASA suppositories (coats 10 cm of distal bowel)
    - 1 gm pr at bedtime each day for 4 wks, then taper (q2d for 2 wks then q3d for 3 wks)
    - Remission ~90%
  - 5-ASA enemas (coat up to splenic flexure of colon)
    - 4 gm at bedtime
    - Consider combining with 5-ASA po for greater effect

Weeks to Remission	5-ASA Enemas	5-ASA Enema plus 5-ASA po
▪ 4 wks	34%	44%
▪ 8 wks	43%	64%

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Unless you frequently check the US Food and Drug Administration (FDA) website, you may not have noticed that Asacol and Asacol HD have had their pregnancy category changed from B to C.

- Give the reason for this change the FDA pregnancy category of Asacol.
  - No, there are no new studies suggesting the mesalamine has previously unrecognized adverse effects in pregnancy.
  - It's all about the coating: the enteric coating in generic Asacol has been found to contained DBP (dibutyl phthalate), which when given in high doses to animal may cause abnormalities in skeletal formation and male reproductive system.
  - The coating has been modified and is now safe to use in pregnancy in many countries.

- Is there a “better” 5-ASA product?

Product	Comparator	Outcome	Stats
– Mesalamine	Sulfasalazine	Induction of remission	Trend
– Balsalazide	Mesalamine (5-ASA)	Induction ofremission	RR 1.30

  - It is likely that most mesalamine preparations are similarly effective, but there have been few head-to-head trials.

- Ulcerative proctitis (UP)
  - Inflammation of distal 15 cm of colon
  - Present in 30% of UC patients at time of diagnosis
  - Proximal spread of proctosigmoiditis, 50% in10 yr.
  - Healing is from right to left colon
  - Rectal sparing: think of
    - Use of local ASA therapy (5-ASA enemas)
    - UC-associated with primary sclerosing cholangitis (PSC)
    - Crohn disease of colon, not involving (“skipping”) the rectum

- Proctocolitis, left-sided colitis or pancolitis
  - Mild-to-moderate activity:
    - Achieve remission with 5-ASA-containing drugs
    - Sulfasalazine 500 mg, tab II-III q.i.d. for 3 mon
    - Asacol 400 mg po, tabs II-III q.i.d. for 3 mon
      - Mesalamine vs placebo 0.79
    - Other 5-ASA 500 mg po tab II-III q.i.d. for 3 mon (Salofalk, Mesasal, Pentasa,Lialda, Dipentum, Colazal, Apriso)
      - Annual relapse on 5-ASA, 20%; not on 5-ASA, 80% relapse of UC in 1 yr
    - Mucosal healing rates at 6 wk, 4.8 g/day, 80% 2.4 g/day, 68%
    - To maintain remission 500 mg po tab II b.i.d.
    - Recent evidence suggests that 5-ASA products may be taken od, but this increases risk of adverse effects suggestion: start with lower doses, ↑ dose slowly to achieve high dose

- Corticosteroids
  - Prednisone 5 mg po tab 8/day in am for 4 wks; then begin slow taper by eliminating one 5 mg tab each week (e.g., 40 mg for 4 wks – 35 mg for 1 wk, 30 mg or 1 wk, 25 mg for 1 wk ……. STOP)
    - Once taper of prednisone is nearing completion and patient is in remission,restart 5-ASA po.
  - If rectal complaints are prominent, may use co-therapy with corticosteroid or 5-ASA enemas (5-ASA enemas are superior to corticosteroid enemas)
    - If symptoms do **not** improve, stop improving or worsen after ~2 wks of prednisone 40 mg po per day, then increase dose to maximum of 12 tabs (60 mg)per day.

- If no response,
  - Do **not** continue increasing oral dose of prednisone
    - Begin IV steroids, Solumedrol 40 to 60 mg per day (may use twice daily split dosing)
    - After 3-5 days, if not a marked (50%) reduction of UC clinical activity and ↓ C-reactive protein (CRP), then consider starting biologic (e.g., anti-TNF) or cyclosporine IV, or alternate biological chosen on a per patient basis.
  - If patient was on 5-ASA when prednisone started, 5-ASA may be stopped.
  - To emphasize the learning point-do **not** use steroids in any form for maintenancetherapy.

➢ Causes of "steroid resistance" in patients with "colitis" (factors causing persistence of symptoms).

- Infection – C. difficile, CMV
- NSAIDs
- Discontinuation of smoking tobacco (in UC)
- Drug interactions
- Crohn disease -like features
  - Discontinuous disease
  - Superficial fissuring/serpiginous ulcers
  - Aphthous ulcers
  - Ileal involvement
  - Involvement of the upper GI tract, granulomas
- CD with UC-like features – pancolitis, superficial colitis
- Other forms of "colitis" that may mimic UC (diverticular colitis, radiation-associated colitis, infectious colitis)
- Development of colorectal cancer (CRC)

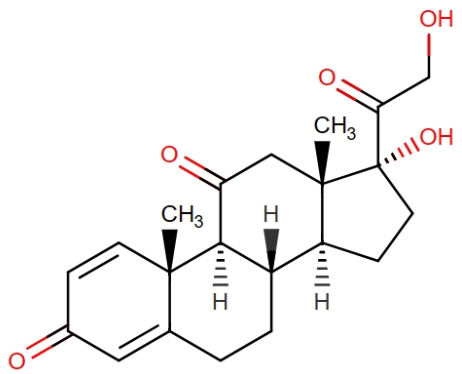
❖ **Corticosteroids**

➢ Mechanism of action

- Absorption in small intestine
- Binding to CS receptors in membrane (isoforms α, β, γ)
- CS receptor ligands bind to nuclear DNA → ↑ expression of
  - Transcription factors
    - AP-1
    - NFκβ
  - Cytokine
    - IL-2/-4
    - P38-activated MAP kinase
- Generic factors affecting CS resistance
  - Multidrug resistance-1 (MDR-1, P-glycoprotein 170)
  - HLA class II allele DRB1*c103
- Defects in these steps may cause CS resistance.

- Indications
  - Colon
    - IBD: CD, UC
    - Microscopic colitis (collagenous, lymphocytic)
  - Esophagus
    - Eosinophilic esophagitis which is refractory to PPIs
  - Liver
    - Autoimmune hepatitis (AIH)
    - Liver transplantation
    - Severe alcoholic hepatitis
  - Pancreas
    - IgG4 pancreatitis
  - Bile duct
    - Cholangiopathy
  - "Stress dosing" when on long-term corticosteroids

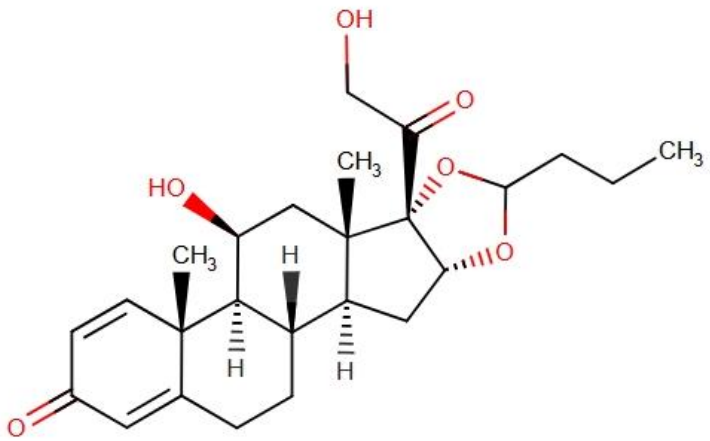
- **Prednisone**



- Pharmacokinetics
  - Absorption
    - Proximal jejunum
    - Tmax
      - Oral prednisone, 2 h
      - Delayed-release, 6-6.5 h
    - ~75% systemic bioavailability
    - Significant inter-patient variability

- Volume of distribution
  - 0.15mg/kg dose has a volume of distribution of 29.3 L
  - 0.30mg/kg dose has a volume of distribution of 44.2 L
- Metabolism
  - Reversibly metabolized to prednisolone
  - Its metabolites and their glucuronide conjugates are excreted predominantly in the urine
- Route of elimination
  - Prednisone is excreted mainly in the urine as sulphate and glucuronide conjugates
- Half-life
  - Prednisone and its active metabolite (prednisolone) have T1/2 of 2-3 h from both immediate and delayed release preparations
- Clearance
  - A 5.5µg/h/kg infusion has an average clearance of 0.066±0.12L/h/kg
  - A 0.15±0.03L/h/kg infusion has an average clearance of 0.15L/h/kg

- **Budesonide**



- Topical potency is 5x > Prednisone
- Release pattern
  - Jejunum
    - Entocort®, pH > 5.5
  - Colon
    - Cortiment®, pH > 7

- Pharmacokinetics
  - Absorption
    - Large interpatient variability in budesonide plasma concentrations
    - Inversely reflects variable delivery of drug to target tissue (GI tract, liver)
    - Extended release po capsules 9-21% bioavailable
    - A 9 mg dose reaches a Cmax of 1.50±0.79 ng/mL with a Tmax of 2-8h and an AUC of 7.33ng*hr/mL
    - A high fat meal ↑ Tmax by 2.3 h but otherwise does not affect the pharmacokinetics of budesonide.
  - Volume of distribution
    - 2.2-3.9 L/kg
  - Metabolism
    - 1st pass metabolism by CYP3A4 and P-glycoprotein in liver and intestine (90%)
    - Systemic exposure (10-15%)
  - Route of elimination
    - Approximately 60% of a budesonide dose is recovered in the urine as the major metabolites
    - No unchanged budesonide is recovered in urine.
  - Half-life
    - Plasma elimination T1/2 of 2-3.6 h
  - Clearance
    - Plasma clearance of 0.9-1.8 L/min
    - The 22R form has a clearance of 1.4 L/min while the 22S form has a clearance of 1.0 L/min

- Response

  - Cochrane Review:
    - Budesonide more effective than placebo in CD for inducing remission
  - Core II study:
    - MMX budesonide in UC for 8 wk → remission 18% in UC vs. 5% in placebo
    - Low to minimal risk of adrenal suppression and infection

Rezaie A, et al. Cochrane Database Syst Rev 2015; 6 :CD000296.Travis SP, et al. Gut 2014; 63(3): 433-41.

❖ Other treatments of IBD

- **Probiotics**
  - The data on clinical efficacy of probiotics is difficult to interpret because of
    - Wide variability in products used
    - Selection of patients, and
    - Evaluation of outcomes etc.
  - Prevention (variable strength of data)
    - Antibiotic-associated diarrhea (AAD)
    - Candidiasis, oral
    - Chemoradiation-induced diarrhea, prevention
    - Clostridium difficile-associated diarrhea
    - H. pylori eradication therapy, prevention
    - Necrotizing enterocolitis
    - Post-operative sepsis
    - Pouchitis
    - Traveler's diarrhea
  - Treatment
    - Irritable bowel syndrome
    - Ulcerative colitis
    - Hepatic encephalopathy
  - Maintenance
    - Ulcerative Colitis
    - Pouchitis

Quigtej EMM. Sleisenger and Fordtran's Gastrointestinal and Liver Disease- Pathophysiology, Diagnosis, Management. 11th Edition, 2020, Chapter 130, pages 2187-2191.

- **Fecal Transplantation**
  - Mixed results in UC, depending upper route of delivery (nasoduodenal vs. enema), donor
    - Nasoduodenal — Clinical remission — wk 12 — NS
    - Enema — Remission — wk 6 — 24% vs. 5%
    - Colonoscopy then enema — Steroid-free remission — wk 8 — 24% vs. 8%
  - Negative results in Crohn disease
  - C-difficile overall efficacy to prevent recurrent CDI, stool administered into
    - Stomach, small intestine, 81%
    - Colon, rectum, 93%

	Prevention of Recurrent CDI
○ Nasoduodenal infusion	
− Vancomycin	31%
− Vancomycin plus bowel lavage	23%

○ Single IMT vs. multiple IMTs
− Cure rate 75% vs. 100%

➢ Contraindication/precautions

- Rectal therapy
  - ○ Steroid enemas/foams
    - − Inferior to 5-ASA enemas
  - ○ Budesonide enemas (please also see next section)
    - − Use for failure of 5-ASA enemas or in patient with CS adverse effects while on non-topical steroid enemas

- Oral therapy (for distal UC)
  - ○ Use if patient cannot tolerate 5-ASA po
  - ○ Response PO < PR
  - ○ Response usually seen within 4 wk, then taper
  - ○ PO steroids (including budesonide) not used for maintenance

➢ Adverse effects

○ CNS/psyche	– Anxiety/depression – Euphoria/psychosis – Headaches/dizziness – Mood swings
○ Eyes	– Cataracts – Glaucoma
○ CVS	– Hypertension – Precipitation of heart failure (fluid retention)
○ Lung	– Respiratory tract infections

- Endocrine
  - Hypernatremia
  - Hypoglycemia
  - Primary aldosterone deficiency
  - Primary adrenocortical therapy
  - Fluid retention
  - ↓ growth
- GI-peptic ulcer disease
  - Nausea/vomiting
  - ↑ appetite /↑ body weight
- Skin
  - Easy bruising
  - Atrophy
  - Acne
- MSK
  - Osteoporosis
    - Steroids cause osteoporosis by changing the optimal ratio of Rank-L relative to OPG/ OCIF;this effect of steroids is greatest in the first 6 mon of their use
  - ↓ wound healing
- ↑ risk of infection/ immunosuppression
  - TB / histoplasmosis
  - Respiratory infection
  - Fungal infections
  - CMV/HSV infection
  - Disseminated infection
  - ↓ response to immunization/vaccines

➢ Peripartum

- Pregnancy – Safe
- Lactation – Safe

IMMUNE MODULATORS

Immunosuppression Drugs (IBD, CD, UC, AIH)

- Mechanisms of action
  - Cytochrome inhibitors
    - Prednisone
      - ↓ IL-1, -2, -6, TNF, IFN-ɣ
    - Basiliximab
      - ↓ IL-2R (interleukin 2 receptor)
  - T-/B-cell inhibitors
    - Azathioprine } → ↓ purine synthesis → → Non-selective
    - Mycophenolate mofetil } ↓ T-/B-cell proliferation → Selective
    - Everolimus → ↓ mTOR (mammalian [mechanistic] target of rapamycin) → ↓ T/ ↓ B cell proliferation
  - T cells
    - Calcineurin inhibitor
    - Cyclosporin/tacrolimus → ↓ IL-2 dependent T cell proliferation
    - Sirolimus → ↓ T cell functions (late)
  - T cell CD3 receptor inhibitor
    - OKT3 (muromonab – CD3) – blocks T cell CD3 receptor → ↓ T cell stimulation by antigen
  - Activated lymphokines
    - Basiliximab
      - Inhibits IL-2 receptors on activated lymphocytes

- Monitoring of immunosuppressants
  - Drug concentration
    - Cyclosporine, tacrolimus, sirolimus, everolimus
  - WBC count: Azathioprine, mycophenolate mofetil
  - CD3 counts: OKT3 (Muromonab-CD3)
  - Thiopurine methyltransferase (TPMT): Azathioprine
  - Perform in every patient considered for use of AZA
    - Dosing

TPMT	AZA starting dose
Normal	Usual weight-based
Low	1/2 usual weight-based dose
Absent (1/300)	Do **not** use AZA

*Note that even in patient with normal TPMT activity, frequent and careful laboratory monitoring of WBC is necessary to detect signs of leucopenia due to lesser pathways of metabolism, such as NUDT 15

Common Adverse Effects of Commonly Used Immunosuppression Drugs in Gastroenterology/Hepatology

				Azathioprine	Basiliximab	Cyclosporin	Everolimus	MPM	OKT3	Prednisone	Sirolimus	Tacrolimus
○	CNS	−	Depression/ psychosis							+		
		−	Damage			+				+		+
○	Skin/hair	−	Edema				+			+		
		−	↓ healing				+			+	+	
○	CVS	−	Pericardial effusions				+				+	
		−	Hypertension			+				+		
○	Lung	−	Pneumonitis				+					
		−	Pulmonary edema						+			
		−	Pleural effusion				+					
		−	Pneumonia									
○	GI	−	Hepatotoxicity	+								
		−	Diarrhea					+				
○	GU					+						+
○	Endocrine	−	Hyperlipidemia				+			+	+	
		−	Diabetes mellitus							+		
		−	Obesity							+		
○	Immune	−	Hypersensitivity reactions		+							
		−	Cytokine release syndrome									
○	Infection	−	↑ risk							+	+	
○	Hematology	−	↓ WBC	+							+	
		−	↓ platelets								+	
		−	Bone marrow suppression	+				+				
○	MSK	−	Osteopenia						+			
○	Drug	−	Drug interactions	+		+		+				

Abbreviations: MPM, mycophenolate mofetil; WBC, white blood cells

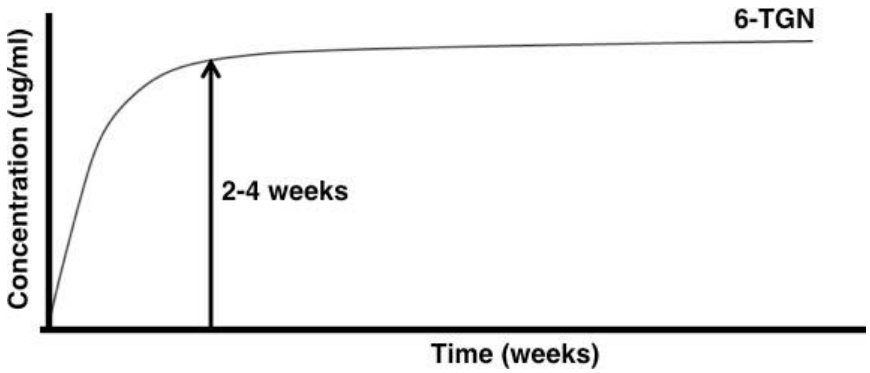
❖ **Azathioprine** (Imuran®) **/ 6-mercaptopurine** (6-MP)

➢ Mechanism of action

- Azathioprine
  - ↓ purine nucleotide synthesis/metabolism → ↓ phosphoribosyl pyrophosphate amidotransferase (PRPP amidotransferase) → ↓ synthesis/function of RNA and DNA.
  - 6-thioguanine (6-TG) triphosphate, a metabolite of azathioprine
    - ↑ T-cell apoptosis Modulates activation of rac1 → ↑ mitogen-activated protein kinase, NF-kappa B
    - Rac1 → ↑ CD28 → ↑ T cell apoptosis
- 6-mercaptopurine (6-MP)
  - Competes with hypoxanthine and guanine for the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT), and
  - Convert to thioinosinic acid (TIMP)

➢ Pharmacokinetics (PK) and Pharmacodynamics (PD)

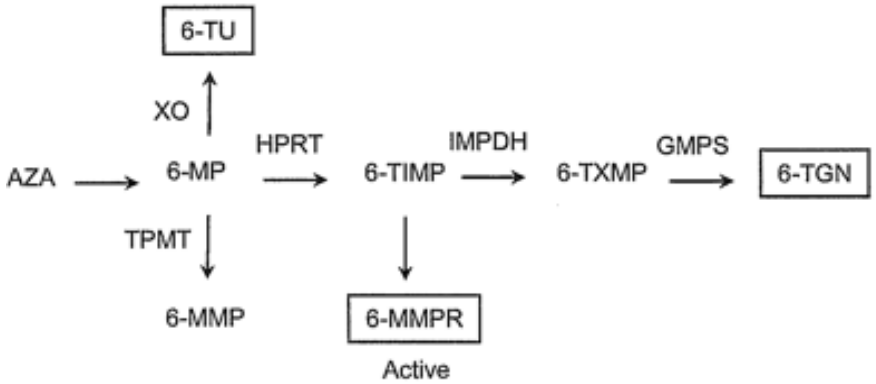
- Bioavailability ranges widely (27-83%)
- Biologically active component is 6-TGN
- Erythrocyte 6-TGN concentrations rise to a plateau after 2-4 wks of oral dosing



- Biological benefit may take as long as 2-3 mon to achieve optimal therapeutic benefit
  - High rate of adverse events (AEs, ~30%)
  - Up to 30% of patients discontinue treatment due to AEs or lack of benefit

Chande N, et al. Cochrane Database Syst Rev 2015; 10:CD000067.Timmer A, et al. Cochrane Database Syst Rev. 2016; 5:CD000478.

- Metabolism
  - 50% of IBD patients are exposed to AZA (azathioprine) within the first 3 yr after diagnosis.

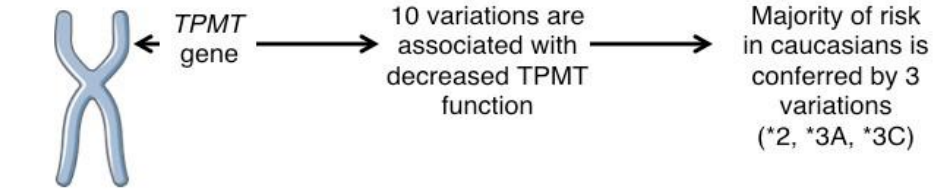


  - If ↓ TPMT, then ↑↑ 6-TGN → ↑↑ immunosuppression, risk of clinically significant adverse effects
    - TPMT low in 11%, negligible in 0.3%

Abbreviations: IMPDH, inosine-5′-monophosphate dehydrogenase; LE, liver enzyme; 6-MMP, 6-methylmercaptopurine; 6-MMPR, 6-methylmercaptopurine ribonucleotide; 6-MP, 6-mercaptopurine; 6-TIMP, 6-thioinosine 5'-monophosphate; 6-TU, 6- thiouric acid; AZA, azathioprine; HPRT, hypoxanthine phosphoribosyl transferase; TPMT, thiopurine methyltransferase; XO, xanthine oxidase

➢ Pharmacogenetics

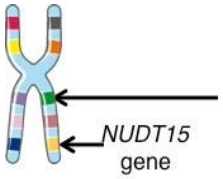
  - Thiopurine methyl transferase (TPMT)



  - Pattern of inheritance:
    - ~90% wild type
    - 11% heterozygous variant carrier
    - 0.3% homozygous variant carrier
  - Risk of severe myelosuppression: Wild-type, ~3%
    - Carriers 1 variant allele, 30-60%
    - Carriers 2 variant allele, 100%
  - Benefit to test for TPMT
    - 10-fold reduction in myelotoxicity in individuals who undergo TPMT testing

Relling et.al. CPIC guidelines 2005; Dean Med Gen Summ 2016; Coenen et.al. Gastro2015

- Implication of ↓ TPMT
  - If TPMT is low (↑ risk of excess immunosuppression), either do **not** use azathioprine, or start with very low dose, and gradually ↑ dose while actively monitoring patient's WBC count.
- Other emerging genetic determinants of azathioprine toxicity



HLADQA1-DRB1 gene
- HLA-DQ1 – HLADRB1 polymorphism is a major predictor of azathioprine-induced pancreatitis in patients with inflammatory bowel disease
- Association of genetic variations in NUDTIS with thiopurine-induced myelosuppression in patients with inflammatory bowel disease

➢ Indication

- IBD (CD/UC) / microscopic colitis
- Autoimmune hepatitis (AIH)
- IgG4 disease, poor response to corticosteroids
- Non-responsive celiac disease
- Induction/maintenance of relapse in UC/CD

- The immunosuppressants (azathioprine, 6-MP) and biologics (e.g., anti-TNF-α drugs) are generally considered in UC patients if they are steroid refractory or steroid-dependent
  - Corticosteroids-responsive disease: "meaningful clinical response to high dose glucocorticoids (prednisone 40 to 60 mg/day or equivalent) within 30 days for oral therapy or 7 to 100 days for IV therapy".
  - Corticosteroids-refractory disease: "lack of meaningful clinical response to glucocorticoids up to doses of prednisone 40 to 60 mg/day (or equivalent within 30days for oral therapy or 7 to 10 days [*] for IV therapy".

Note that in patients with severe acute UC, failure of CS is assessed after 3-5 day use)

  - Corticosteroids-dependent disease – "patients [initially] respond to glucocorticoids, but experience a clinical recurrence when glucocorticoids are tapered to less than 10 to 30 mg/day, or rapidly relapse once glucocorticosteroids are stopped".
    - Patients must **not** be maintained on as long term

➢ Contraindication/precautions

- Known hypersensitivity to azathioprine / 6-MP and its components
- Adverse effects / drug-drug interactions
- Cautious use in patients with pre-existing / ↑ risk of immunosuppression
- Persons with low/absent TPMT

- Adverse effects
  - GI
    - Nausea/vomiting
    - Ulceration/bleeding
    - Hepatotoxicity (abnormal liver enzymes [LEs])
    - Hepatic veno-occlusive disease / sinusoidal obstruction syndrome [SOS]
  - GU
    - Cervical dysplasia
    - Nephrolithiasis
    - Nephropathy, urate
    - Renal dosing to be considered
  - Blood
    - Immunosuppression
    - Leukopenia
    - Megaloblastic anemia
    - Thrombocytopenia
  - Cancer
    - Lymphoma
      - Special consideration for rare hepatosplenic lymphoma in young male patients on AZA

- Drug-drug interaction
  - ↓ immune response to vaccines / ↑ risk of dissemination
  - ↑ immunosuppression / ↑ risk of disseminated infection when used with
    - Other IBD drugs
      - Anti-TNF blockers
      - Balsalazide
      - Mycophenolate Mofetil (MMF)
      - Sulfasalazine
    - HBV infection
      - Alpha interferon
    - CNS
      - ACE inhibitors
      - Clozapine
      - Leflunomide

- Perinatal
  - Pregnancy
    - Use
  - Lactation
    - Safety uncertain

- Monitoring
  - Complete blood count (CBC), liver enzymes (Les) q1yr (more frequent monitoring when starting immunosuppressant, e.g., q3d x 4, q2d x 2, q1mon x 3, then annually)

- In discussing with a patient the risk of starting azathioprine, give potential risks and their likelihood of occurrence of these adverse effects
  - 20-25 % risk of leucopenia
  - 3% risk of allergic reaction including pancreatitis and hepatitis, usually within the first mon of therapy
  - Intolerance to medication (i.e., headache, nausea, malaise) that requires drug withdrawal in 10% of patients
  - Drug interaction: e.g., allopurinol, 5-ASA
  - ↑ levels of 6-TG → ↑ immunosuppression
    - Acute
      - ↓ leucopenia (↑ risk of infection)
    - Chronic
      - ↑ risk of malignancy

- Different ways of monitoring during azathioprine therapy to ↓ risks of adverseeffects.
  - Gene assay that measures the thiopurine methyl transferase (TPMT) genotype (mutation)
  - 6-TGN (metabolic products) (6-thioguanine nucleotides, active metabolite)
  - Monitor CBC and LEs

- The clinical interpretations of the following blood concentrations of azathioprine metabolites.

6-TGN		6-MMP	Clinical Interpretations
↓	–	↓	▪ Non-adherent, or ▪ Under-dosed (sub-therapeutic)
N	–	↑	▪ ↑ risk for ↑ liver enzymes
↑	–	↓	▪ ↓ TPMT ▪ ↑ risk of leucopenia
↑	–	↑	▪ Over-dosed

Abbreviations: 6-TGN, 6-Thioguanine nucleotides; 6-MMP, 6-methyl mercaptopurine; MP, Mercaptopurine

➢ Benefits
  - Indications
    - Corticosteroid-sparing
    - Maintenance therapy
      - Crohn disease
      - Ulcerative colitis
    - ↓ production of antibodies in patients on biologics

Azathioprine (AZA) Tips

- In patients with reduced TPMT activity, the risk of myelotoxicity when using the standard rather than a reduced dose of AZA/6-MP is increased 4-fold.
- 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 A, et al. Inflamm Bowel Dis 2007;13:380-5).
- Persons with normal TPMT activity may still develop myelotoxicity when given AZA.
- Patient starting on low doses of AZA may still develop myelotoxicity.
- This is why all patients on AZA must have regular monitoring of their WBC count

- Approximate percentage of patients reported from meta-analysis of trials of AZA/6-MP to achieve and to maintain remission in patient with CD

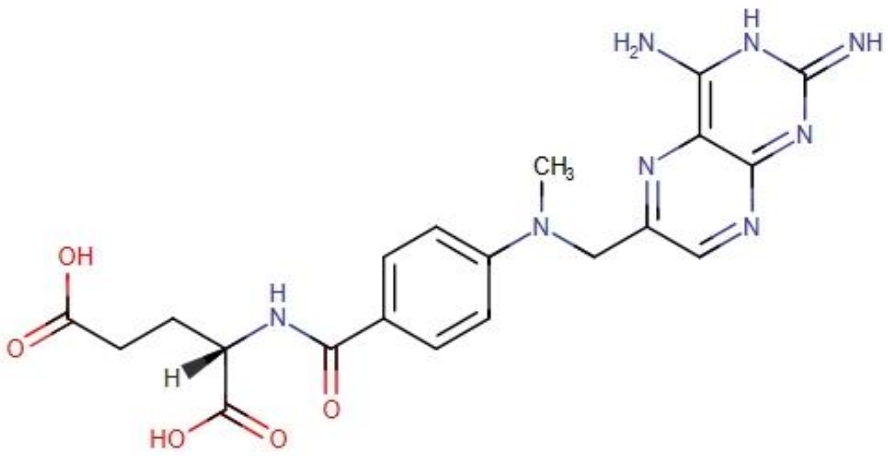
	AZA/ 6-MP	Placebo	TG	OR	NNT
○ Achieve remission*	54	33	21	2.36	5
○ Maintain remission	67	52	15	2.16 4.13*	7

* 17 wks necessary, optimal dose, 2.5 mg/kg

- Threshold level of 6-TG of 230 to 260 pmol / 8 x 10^8 RBC to achieve remission with TG of 26% (62% vs 36% placebo); aim for a ratio of 6-MMP: 6-TG of < 10

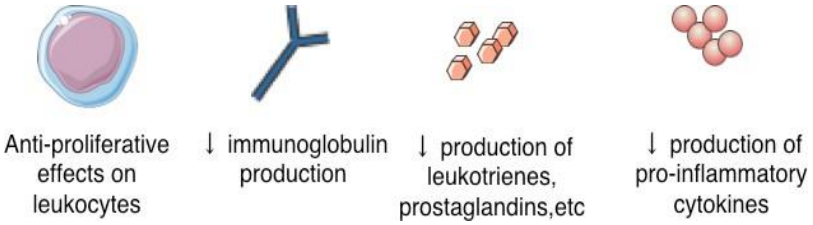
Abbreviations: OR, odds ratio; NNT, number needed to treat; TG, therapeutic gain

❖ **Methotrexate** (MTX)



- Indication
  - Not effective in patients with ulcerative colitis (UC)
  - Moderate quality evidence suggests SC MTX (15-25 mg weekly) is superior to placebo for maintenance of remission in Crohn disease
  - Add to anti-TNF therapy to ↓ risk of ↓ response because of development of antibodies to anti-TNF drugs.

- Mechanism of Action
  - Folic acid analogue with inhibitory activity against enzymes in the folic acid metabolism pathway (folate antimetabolite).



  - MTX and its polyglutamated metabolites inhibit dihydrofolate reductase (DHFR); essential for purine synthesis.
  - Inhibit dihydrofolate reductase → ↓ reduction of dihydrobiopterin (BH2) to tetrahydrobiopterin (BH4) → uncoupling of nitric oxide synthase (NOS) → ↑ sensitivity of T cells to apoptosis → ↓ immune responses.
  - Bioavailability ranges from 50-90%
  - IM/SC absorption is rapid
    - peak concentrations seen at 1 h
  - T1/2 = 44-55 h

- Pharmacokinetics
  - Absorption
    - Absorbed in the proximal jejunum
    - Bioavailability 64-90%, but ↓ when oral doses > 25 mg due to saturation of the carrier mediated transport of methotrexate
    - Tmax, 1 to 2 h
  - Volume of distribution
    -
  - Metabolism
    - Oxidation in the liver
    - 7-OH MTX metabolite is excreted renally
  - Route of elimination
    - Volume of distribution at steady state ~ 1 L/kg

- Half-life
  - T1/2 of ↓dose, 3-10 h in adults
  - T1/2 for ↑dose, 8-15 h in adults
- Clearance
  - Varies widely between patients and ↓ with ↑ing doses
  - Currently, predicting clearance of methotrexate is difficult and exceedingly ↑ serum levels can still occur when all precautions are taken

➢ Contraindication/precautions

- Known sensitivity to MTX and its metabolites
- Chronic liver disease (↑ risk of hepatic fibrosis)
- Pulmonary fibrosis
- Active infection
- Pregnancy (teratogenic)
  - **Stop** in men/women **6 mon** before planned conception

➢ Monitoring

- Complete blood count (CBC), liver enzymes (LEs) q1yr (more frequent monitoring when starting MTX)

➢ Adverse effects

- GEN
  - Hypersensitivity reaction
- CNS
  - Blurred vision
  - Drowsiness/malaise
  - Headache/dizziness
- CVS
  - Pericardial effusion
  - Pericarditis
  - Pulmonary embolism / thromboembolic events
- Lung
  - Alveolitis
  - Interstitial pneumonia
  - Pulmonary fibrosis
- Blood
  - Pancytopenia / myelosuppression (↑ risk of infection)
    - Anemia
    - Leucopenia
    - Thrombocytopenia
  - Lymphoproliferative disorders / lymphoma

- GI
  - Abdominal pain
  - Acute hepatitis
  - Diarrhea
  - Gingivitis
  - Hepatic fibrosis
    - ↑ by mean cumulative dose of MTX > 2.5 g
    - ↑ risk of hepatic fibrosis: by alcohol, obesity, diabetes
  - Hepatic fibrosis / cirrhosis Stomatitis
  - Hepatotoxicity
  - Nausea/vomiting
  - Pancreatitis
  - Pharyngitis
- GU
  - Hematuria / proteinuria
  - Nephropathy
  - Renal failure
- Reproduction
  - Women: Abortifacient, teratogenic
  - Men: Toxic to sperm
- Skin
  - Pruritis/urticaria
  - Rash

➢ Drug-drug interaction

- ↓ immunological response to vaccination
- ↑ risk of disseminated infection

➢ Peripartum

- Pregnancy – Do **not** use
- Lactation – Do **not** use

➢ Treatment

❖ General

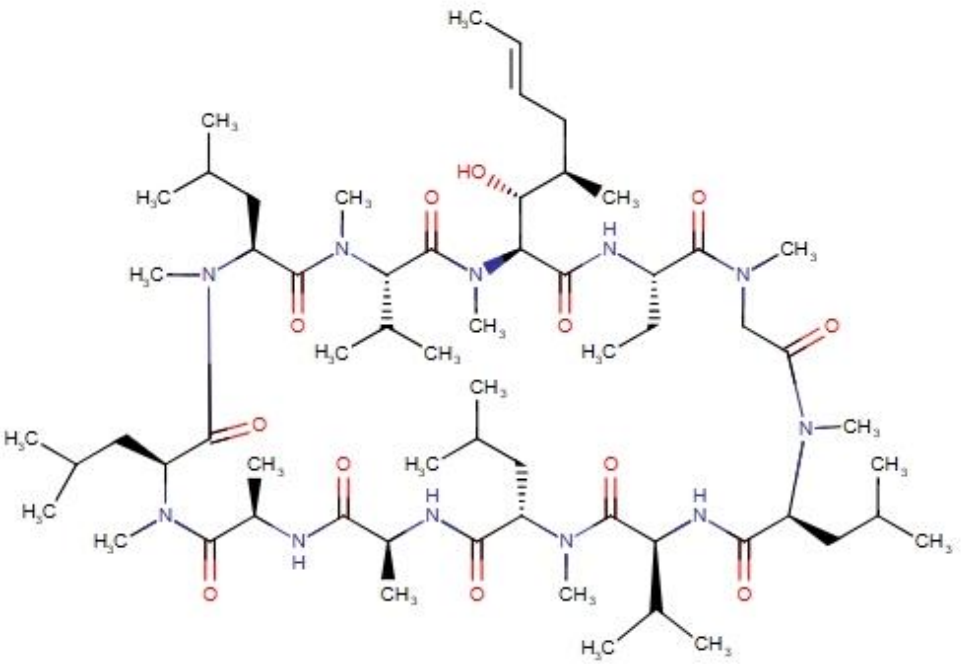
- Preventative measures to advise patients treated with prednisone +/- azathioprine
  - Monitor for weight gain
  - Supplement with calcium, vitamin D, +/- bisphosphonates
  - Monitor blood sugar, lipids, fat soluble vitamins
  - Monitor CBC, ALT (if on Azathioprine)
  - Annual checks for BP, cataract, glaucoma, BMD, Pap' smear, esophageal varices
  - Check stools for ova/parasites after foreign travel
  - "Stop" order on all medication prescriptions

- Screening mammography, colonoscopy (guidelines based, age-appropriate)
- Access for depression
- Stress high doses of steroids, if necessary
- Wear medical alert bracelet.
- Avoid stopping corticosteroids suddenly (Addisonian crisis, recurrence of AIH)
- Avoid unplanned pregnancy; consider avoiding pregnancy if portal hypertension is marked contraception
- Drug interactions
- Immunizations (see below)

❖ Specific complications

- If cirrhotic: avoid sedation, NSAIDs, anesthesia, interferon
- If cirrhotic, screen for HCC
- Avoid vaccination with varicella, MMR, yellow fever
- Vaccination for H. influenza, HAV, HBV, pneumococcus
- Assess for esophageal varices for primary prevention with banding or non-specific beta blockers (avoid use in pregnancy – fetal hypoglycemia)
- Assess for presence of ascites and spontaneous bacterial peritonitis (SBP)

- **Cyclosporine A**



- Indication
  - Severe acute UC which fails to respond to corticosteroids (no benefit in CD)
  - Liver transplantation to ↓ risk of rejection
- Mechanism of action
  - Calcineurin inhibitor → ↓ IL-2 dependent T cell proliferation
- Pharmacokinetics
  - Absorption
    - Occurs mainly in the intestine
    - Highly variable with a peak bioavailability of 30% sometimes occurring 1-8 h after administration with a second peak observed in certain patients
    - Absorption from the GI tract incomplete, due to first pass effects
    - Cmax in both the blood and plasma occurs at approximately 3.5 h post-dose
  - Volume of distribution
    - Distribution of cyclosporine in the blood consists of
      - 33-47% in plasma
      - 4-9% in the lymphocytes
      - 5-12% in the granulocytes, and
      - 41-58% in the erythrocytes
    - Volume of distribution ranges from 4-8 L/kg.
    - Concentrates mainly in leucocyte-rich tissues as well as tissues that contain high amounts of fat because it is highly lipophilic.
  - Metabolism
    - Metabolized in the intestine and the liver by CYP450 enzymes, predominantly CYP3A4 with contributions from CYP3A5.
  - Route of elimination
    - After sulphate conjugation, cyclosporine remains in the bile where it is broken down to the original compound and then re-absorbed into the circulation.
    - Excretion is primarily biliary with
      - Only 3-6% of the dose (including the parent drug and metabolites) excreted in the urine
      - 90% of the administered dose is eliminated in the bile.
      - < 1% of the dose is excreted as unchanged
  - Half-life
    - T1/2 is biphasic and very variable on different conditions but it is reported in general to last 19 h
  - Clearance
    - Linear clearance profile that ranges from 0.38 to 3 Lxh/kg[5], however, there is
    - Substantial inter- patient variability
    - A 250 mg dose of cyclosporine in the oral soft gelatin capsule of a lipid micro-emulsion formulation shows an approximate clearance of 22.5 L/h

- Contraindication/precautions
  - Known hypersensitivity to cyclosporine or its components
  - Adverse effects / drug-drug interactions
  - Use kidney/liver dosing
  - Seizures / ↓ seizure threshold (e.g., ↑ risk of seizure with ↓ serum magnesium concentration)

- Adverse effects
  - GEN
    - Anaphylaxis
  - CNS
    - Encephalopathy
    - Eyes: Optic disc edema
    - Headache
    - ↑ intracranial pressure (ICP)
    - Tremor / seizures
  - CVS
    - Hypertension
    - Myocardial infarction
  - GI
    - Diarrhea
    - GI bleeding
    - Gingival hyperplasia
    - ↑ LEs / hepatotoxicity
    - Nausea/vomiting
    - Pancreatitis
  - GU
    - Hyperkalemia
    - Renal failure
  - Skin
    - Pruritis
  - Blood
    - Anemia, hemolytic
    - Leukopenia
    - Thrombocytopenia
    - Immunosuppression
      - ↑ risk of infection / poor immunological response to vaccinations
  - Endocrine
    - Diabetes mellitus
    - Dyslipidemia
    - Hirsutism
    - Hyperuricemia
  - ↑ risk of cancer

- Drug-drug interaction
  - Taking cyclosporine plus bosentan →
    - ↑ bosentan → ↑ toxicity
    - ↓ cyclosporine → bosentan (↓ efficiency)

- Peripartum
  - Pregnancy – Safe
  - Lactation – Safety **not** established

- Immunosuppressive agents commonly used in gastroenterology or hepatology (for example for Crohn disease, ulcerative colitis, autoimmune hepatitis), and their mode of action, common toxic effects, and recommended monitoring

Agent	Mode of Action	Monitoring	Toxic Effects
Azathioprine	– Inhibition of T and B cell proliferation by interferingwith purine synthesis (↓DNA/RNA)	– White blood cell count – Liver enzymes	▪ Bone marrow suppression ▪ Hepatotoxicity
Cyclosporine (CyA), tacrolimus	– Calcineurin inhibitor: which suppresses IL-2-dependent T cell proliferation	– Blood level (CyA, cholesterol, magnesium, creatinine) – Blood pressure (BP) – Blood sugar (BS)	▪ Renal ▪ Neurologic ▪ Hyperlipidemic ▪ Hypertension ▪ Hirsutism
IL-2 receptor blocker	– Competitive inhibition of IL-2 receptor on activated lymphocytes	– None	▪ Hypersensitivity reactions with basiliximab
Methotrexate	– Folate antimetabolite (↓DNA)	– Liver biopsy after 1,500 mg (only 2 yr maintenance therapy) – Alcohol intake	▪ Bone marrow suppression ▪ Hepatic fibrosis
Myco-phenolate mofetil (Cellsept)	– Inhibition of T and B cell proliferation by interferingwith purine synthesis	– White blood cell count	▪ Bone marrow suppression ▪ Diarrhea
OKT3	– Blocking of T cell CD3 receptor, depletion of effectorT cells and Tregs, preventingstimulation by antigen	– $CD3^+$ count	▪ Cytokine release syndrome ▪ Increased risk of infections

	Agent	Mode of Action	Monitoring	Toxic Effects
○	Prednisone	– Alter gene transcription of steroid response elements (SRE); cytokine inhibitor (IL-1, IL-2, IL-6, TNF, and IFN gamma)	– BP – BS – Annual eye exam – DEXA scan	(see previous questions)
○	Sirolimus (Rapamycin)	– Inhibition of mTOR, whichdisrupts IL-2 induced intracellular signaling in lymphocytes	– Blood level	▪ Hyperlipidemia ▪ Thrombocytopenic

Abbreviations: BP, blood pressure; BS, blood sugar; DEXA, DEXA scan for bone mineraldensity; IFN, interferon; IL, interleukin; LEs, liver enzymes; MTOR, mammalian target of rapamycin; TNF, tumour necrosis factor

Adapted from: *Sleisenger & Fordtran's gastrointestinal and liverdisease: Pathophysiology/Diagnosis/Management* 2020, chapter 116.

Biological Therapies

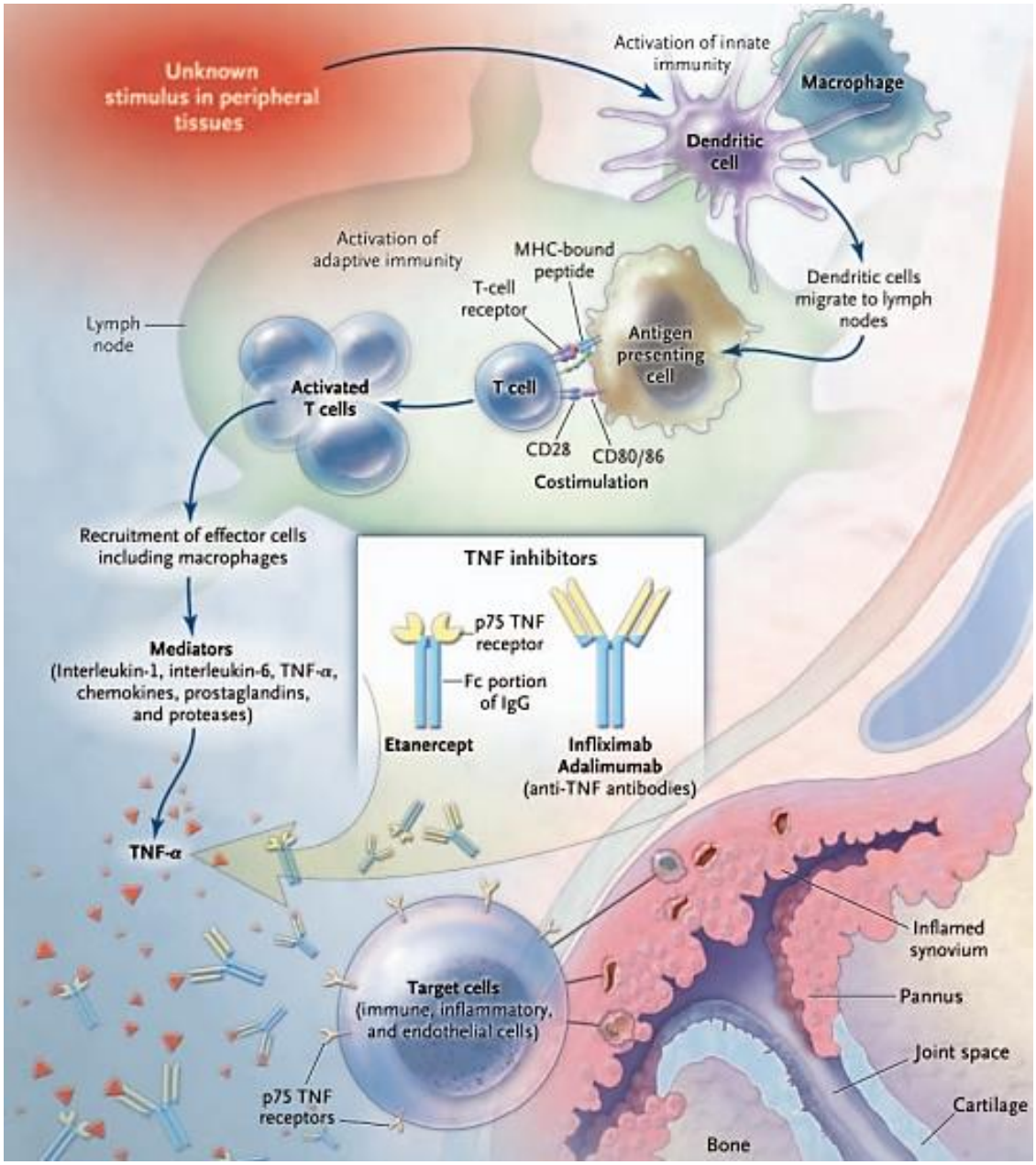
❖ **Anti-TNF Agents**

- "Large molecule" drugs (~150 kDa; rather than vs. small molecule drugs: <900 Da)
- IgG class
- T1/2
  - Chimeric 10-14 d
  - Humanized 10-20 d
- Cleared from the circulation by catabolism dependent on
  - Proteolysis – internalization in phagocytic cells of the reticuloendothelial system (mediated via FCγR)
  - "Antibody salvage" via Fc neonatal receptor (FcRn aka "Brambell receptor")
- Catabolized in the hostile proteolytic environment GI tract
- Target soluble or membrane-bound antigen (or both)
- No renal clearance (due to large size of molecule)

➢ Mechanisms of action

- Can be specific (membrane-bound antigen) or non-specific (soluble antigen)
- Antibodies made by identical immune cells that are clones of a unique parent cell.
- Bind to the same or to a single epitope
- Block the function of the target molecule
  - Induces apoptosis of the target-expressing cell
  - Modulates the signaling pathway

Pathophysiological Role of Cytokines and Other Mediators and Their Inhibitors in RA



- An infective agent or other stimulus binds to receptors on dendritic cells, activating the innate immune system.
  - Dendritic cells migrate into lymph nodes → present antigen to T cells, which are activated by the dual signal of
    - Antigen presentation
    - Costimulation through CD28

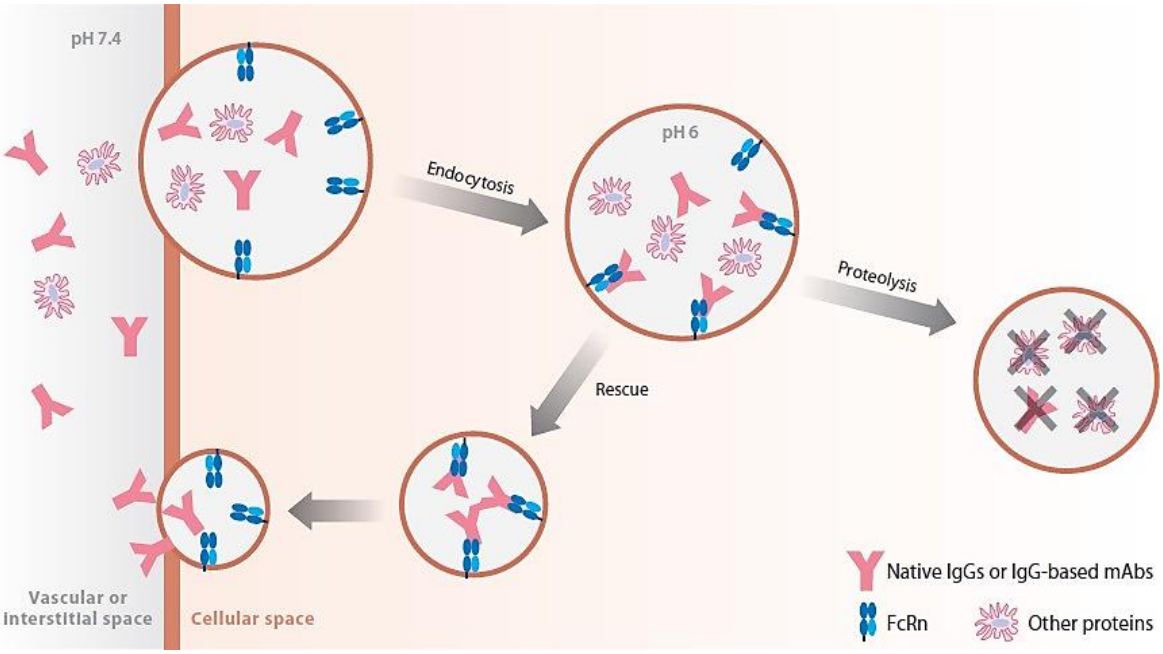
- Activated T cells
  - Proliferate
  - Migrate
  - Produce interferon-ɣ and other proinflammatory cytokines
  - Stimulate macrophage and B cells
- Activated macrophages and fibroblasrs release cytokines, including TNF-α.
- TNF-α is a central component in the cascade of cytokines → stimulates the production of additional inflammatory mediators and
  - ↑ recruitment of immune and inflammatory cells
- Infliximab and adalimumab are monoclonal anti-TNF-α antibodies that bind to TNF-α with high affinity → prevent it from binding to its receptors.

Printed with permission: Scott DL and Kingsley GH. N Engl J Med 2006; 355:704-712 (Figure 1).

- Bioavailability (exposure) is dependent on
  - Antigen distribution
  - Antibody structure (chimeric vs human)
  - Concentration
  - Concurrent medications
  - Host factors (weight, inflammatory state)
  - Immunogenicity

- Antibodies targeting soluble and membrane-bound antigen
  - Anti-TNF agents:
    - Adalimumab
    - Certolizumab
    - Golimumab
    - Infliximab

- Antibodies targeting membrane-bound antigens
  - Vedolizumab (α4β7 integrin)
  - Natalizumab (α4β1/β7 integrin)



Printed with permission: Zhou H and Mascelli MA. Annu Rev Pharmacol Toxicol 2011; 51: 359-72. (Figure 4).

➢ Miscellaneous

- Proposed standard of care for anti-TNF therapy
  (Papamichael K and Cheifety AS. Am J Gastroenterol 2017; 112: 673-676)
  - Anti-TNF drugs are widely used in the treatment of patients with CD/UC
    - Up to 30% of patients show no initial benefit
    - ~40% lose their benefit over time
  - This may require ↑ dose of that anti-TNF, or
    - ↓ interval between doses, or
    - Switching to another anti-TNF, or
    - Adding an immunosuppressant
    - Switching to another class of biological, or even possibly surgery
  - The mechanisms of non-response / loss of response include
    - TNF driven process
      - Inadequate concentration (dose) of anti-TNF
      - Development of anti-drug antibodies (ADAs)
      - ↑clearance of anti-TNF (non-immune, such as ↑ loss into lumen of GI tract)
    - Non-TNF driven process

- Head-to-head Clinical Trials to Compare Anti-TNF, Anti-p40 IL-12/-23 and Anti-integrin α4β7 (Neeraj N, et al. Am J Gastroenterol 2022; 117: 106-17)
  - Post-hoc analysis of 4 clinical trials of patients with moderate-severe Crohn disease assessed for endoscopic healing after 1 yr maintenance therapy with anti-TNF (infliximab [IFX], adalimumab [ADA], anti-p40 IL-12/-23 ustekinumab [UST], or alpha-integrin-α4β7 vedolizumab [VEDO]
    - Extent of healing depends upon drug, as well as site and type of IBD
  - Ileum plus colon
    - IFN (25%) = ADA (23%) > UST = VEDO (7%)
  - Ileum
    - For Simple Endoscopic Score [SES] ≥ 3, IFX = ADA = UST = VEDO
    - For ileal ulcers > 0.5 cm IFX (42%) > VEDO (91%)
  - Colon
    - IFX (52%) = ADA (63%) > UST (29%)
  - This data suggests that the 1 yr endoscopic healing of the ileum +/- colon is superior (2 to 4 times greater) with infliximab or adalimumab, as compared with anti-p40 IL-12/-23 ustekinumab or anti-integrin-α4β7

- **Second-line Biologicals**
  (Onali S, et al. Am J Gastroenterol 2022; 117: 1279-87)
  - When anti-TNF therapy fails in patients with Crohn disease (CD), new biologicals may be used as second-line therapy.
    - Those include ustekinumab (UST)
  - A large multicentre retrospective cohort of patients with CD failing anti-TNF therapy have been assessed at 6 and 12 mon, using UST vs. VEDO
    - Clinical response
      - 6 mon, UST = VEDO; clinical response at 26 wk predicted steroid-free remission at wk 52
      - 12 mon, UST < VEDO* (56%) (P = 0.01)
    - Steroid-free remission, 12 mon UST (41%) < VEDO* (51%) (P = 0.03)
    - Safety profiles, at 12 mon, UST = VEDO

* small differences, plus no difference in laboratory biomarkers, diagnostic imaging – CTE/MRE, small bowel ultrasound; or endoscopic assessment

❖ Non-anti-TNF biologics

- If patient with active CD fails to respond to “conventional therapy”
  - Thiopurines/methotrexate
  - Anti-TNF

  } ▪ Use vedolizumab or ustekinumab to induce complete remission

- Vedolizumab (VEDO)
  - Anti-TNF naïve
    - Symptomatic remission (OR, 1.76; 95% CI, 1.11 to 2.78
    - Failure to achieve remission (OR, 0.86; 95% CI, 0.79 to 0.94; P= 0.001)
    - At 1 yr
      - Mucosal healing, 63% (deep remission)
      - Symptomatic remission plus mucosal healing, 26% (complete remission)
      - ↑ rate if corticosteroids
    - No recommendation (no evidence) for or against adding immunosuppressant to vedolizumab
  - Non-anti-TNF naïve
    - If patient on anti-TNF and requiring corticosteroids because they
      - Fail to achieve/maintain corticoid-free symptomatic remission → vedolizumab
    - Patients who have been on anti-TNF therapy have ↓ likelihood of achieving mucosal healing
  - Evaluate for symptomatic response to vedolizumab at 10 to 14 wk to determine if there is a need to modify therapy.
  - Once symptomatic response achieved with vedolizumab
    - Continue therapy to achieve and to maintain complete remission
    - For maintenance of remission with vedolizumab
      - Naïve to anti-TNF (RR, 1.49; 95% CI, 1.19 to 1.86)
      - Not naïve to anti-TNF "there was a statistically significant risk difference of ~15 for vedolizumab once every 4 wk and once very 8 wk versus placebo
    - Benefit of maintenance of vedolizumab

Remission	52 wk	152 wk all patients	Anti-TNF	
			Naïve	Not naïve
▪ Symptomatic	35%	74%	82%	66%
▪ Mucosal healing	63%			

  - No recommendation was made for or against treating vedolizumab failure with Ustekinumab
  - Use with moderate severe CD/UC
    - Not responding to conventional therapy (including anti-TNF) (1.11 to 2.78) → VEDO to induce complete remission, and then reactivate symptomatic response in 10 to 14 wks
    - No recommendation for or against combination therapy with azathioprine or methotrexate
    - If successful symptomatic response with vedolizumab, continue vedolizumab to achieve and to maintain complete remission
      - 52 wk symptomatic remission, ~35% (RR, 2.20; 95% CI, 1.4 to 3.44); anti-TNF naïve, RR of maintaining remission, 1.49; 95% CI, 1.19 to 1.86
    - Anti-TNF naïve, VEDO superior to placebo for
      - Symptom remission (OR, 1.76; 95% CI
      - Failure to achieve symptomatic remission
    - No recommendation for or against combination therapy of VEDO plus azathioprine / methotrexate 3 yr (RR, 0.86; 95% CI, 0.79 to 0.94, P = 0.001)

- 1 yr maintenance
  - Symptomatic remission, 35% - 74% (82% anti-TNF naïve, 66% with prior anti-TNF failure)
  - Mucosal healing, 63%
  - Deep remission, 26% (mucosal healing plus symptomatic remission)
  - ↑ corticosteroid-free remission

Recommendations

- "…a monoclonal antibody to the α4β7 integrin and blocks trafficking to the gut by blocking of α4β7 to the mucosal addressin cell adhesion molecule 1 (MAdCAM-1).
- Use vedolizumab in both anti-TNF naïve patients with CD, as well as in those who had failed previous anti-TNF therapy, both for induction (GRADE: strong recommendation, moderate-quality evidence), as well as for maintenance therapy (GRADE: strong recommendation, high-quality evidence. Agreement: 96%).
- Rates of induction and maintenance of remission are modestly better in persons who are naïve to treatment with anti-TNF therapy, than in those who have been treated with anti-TNF and have failed (GEMINI-1/-2 studies).

Treatment History	Response	Remission
− Anti-TNF naïve	48% / 30%	27% / 15%
− Previously failed anti-TNF	40% / 23%	22% / 11%

  - Persons who responded to vedolizumab continued to be in remission over time
    - 2 yr 83%
    - 3 yr 89%
  - Comparing

	Vedolizumab	anti-TNF	HR, 95% CI
▪ Remission at 1 yr	38%	34%	1.27 (0.91 to 1.27)
▪ Steroid-free remission	26%	18%	1.75 (0.90 to 3.43)
▪ Endoscopic healing	50%	41%	1.67 (2.23 to 2.47)

- Moderate/severe CD, failure to achieve complete remission on any of corticosteroids, thiopurines, methotrexate, a anti-TNF therapy → use vedolizumab to induce complete remission (GRADE: Strong recommendation, moderate-quality evidence)
- Also use vedolizumab if anti-TNF therapy does not provide corticosteroid-free remission/maintenance (GRADE: Conditional recommendation, low-quality evidence)
- Evaluate for symptomatic response to vedolizumab at 10-14 wk (GRADE: Conditional recommendation, very low-quality evidence)
- If vedolizumab induction produces complete symptomatic response → vedolizumab maintenance (GRADE: Strong recommendation, moderate-quality evidence)

- Ustekinumab (UST)
  - Failure of conventional therapy, use ustekinumab, both in those patients who were anti-TNF naïve (~55%) and non-naïve (34%) (greater benefit in secondary non-responders to anti-TNF) to achieve
    - Symptomatic remission at 6 wk (RR, 0.8; 95% CI 0.85 to 0.92)
    - Mucosal healing
    - Corticosteroid-free remission at week 52
  - Evaluate for response of 6 to 10 wk to determine if therapy should be altered
    - There's an early response group, 6 wk, and a later subresponse group.
  - No recommendation for or against starting ustekinumab with or without thiopurine or methotrexate.
  - Patients who have not demonstrated a response before the second subcutaneous dose modification of therapy.
    - If a response occurs, subsequent assessment may include endoscopy to confirm complete remission.
      - The optimal timing for this colonoscopic evaluation for mucosal healing is "…currently uncertain"
  - If ustekinumab induction therapy results in symptomatic response, continue ustekinumab to achieve and to maintain complete remission.
    - Symptomatic remission at
      - 22 wk, versus placebo 42% vs. 27%
        - Absolute difference, 14%; 95% CI, 2 to 27.1; P = 0.03
      - 52 wk vs. placebo, 51% vs. 36%
        - Absolute difference, 15%; 95% CI, 4.86 to 25.3; P = 0.005
    - Symptomatic remission at wk 49
      - Anti-TNF naïve 57%
      - Not naïve ~40%
    - Corticosteroid-free remission, ustekinumab vs. placebo, 48% vs. 30%; P = 0.004
  - No recommendation made for or against treating ustekinumab failure with vedolizumab

Recommendations

- "…an anti-IL-12/23 p40 antibody
- Use ustekinumab in both anti-TNF naïve patients with CD, as well as in those who had failed anti-TNF therapy, both for induction and for maintenance therapy (GRADE: strong recommendation, high-quality evidence. Agreement: 98%).

	Clinical response at wk 8; 6 mg/kg, 130 mg/ (placebo)
− Mostly anti-TNF naïve	58%, 47% / 32% (P < 0.001, both doses)
− Previously failed anti-TNF	38%, 34% / 20% (P = 0.001, both doses)

  - Clinical maintenance anti-TNF refractory, wk 44, ustekinumab 41% vs. placebo 26% (P=0.01; IM-UNITI study)

- Refractory to anti-TNF
  - Treated with Ustekinumab
  - Clinical benefit with 3 mon, 68%
  - Benefit maintained, 68% (GETAID study)

- ↑ risk of infection (serious, opportunistic) from treatment with corticosteroids, immunosuppressants, and
  - This ↑ risk of infection is greatest with use of corticosteroids
- Use with moderate-severe CD not responding to conventional therapy (including anti-TNF) →ustekinumab (UST) to induce complete remission (GRADE: Strong recommendation, moderate-quality evidence), then reevaluate symptomatic response in 6 to 10 wk (GRADE: Conditional recommendation, very low-quality evidence).
  - If successful symptomatic response to UST, continue maintenance therapy with UST to achieve and to maintain complete remission (GRADE: Strong recommendation, moderate-quality evidence)
  - No recommendation for or against combination therapy of UST plus azathioprine or methotrexate

❖ Miscellaneous others

- Do **not** use probiotics, omega-3 fatty acids, enteral mutation, diet modification, marijuana or naltrexone to induce or to maintain symptomatic remission of CD.

Recommendations against

- Do **not** use for induction or maintenance of suboptimal remission
  - Diet
    - Probiotics (GRADE: Strong recommendation, very low-quality evidence)
    - Omega-3 fatty acids (GRADE: Strong recommendation, moderate-quality evidence)
    - Enteral nutrition (GRADE: Conditional recommendation, very low-quality evidence)
    - Dietary modification
  - Pharmacological agents
    - Naltrexone (GRADE: Conditional recommendation, low-quality evidence for induction of remission, very low-quality evidence for maintenance of remission)
    - Marijuana (GRADE: Conditional recommendation, very low-quality evidence)

THERAPEUTIC DRUG MONITORING (TDM) **OF ANTI-TNF THERAPY**

- Definition
  - "The evaluation of serum drug concentration and anti-drug antibodies to optimize the therapeutic benefit of the drug."
  - Benefits of TDM
    - ↑ induction of remission
    - ↑ maintenance of remission

    } ▪ Clinical, biochemical, endoscopic, histopathological targets

- Favorable therapeutic outcomes related to therapeutic drug monitoring of anti-TNF therapy in different clinical scenarios of inflammatory bowel disease (IBD)

- Secondary loss of response to anti-TNF therapy
  - Patients undergoing reactive therapeutic drug monitoring for loss of response with adequate adalimumab (> 4.5 µg/mL) concentration who change to a biological agent with a different mechanism of action have a better long-term outcome compared to those who undergo anti-TNF optimization by either a dosage increase or a switch within the anti-TNF class.
  - Patients undergoing reactive therapeutic drug monitoring for loss of response with high titres of anti-drug antibodies (> 4 µg/mL / equivalent for adalimumab, and > 9 µg/mL / equivalent for infliximab)
    - Longer duration of response when anti-TNF agents are switched than when dosage increased (although ↑ dosage more effective for patients with no or low titres of anti-drug antibodies).
  - Patients undergoing reactive therapeutic drug monitoring for loss of response to adalimumab with adequate drug concentration (> 4.9 µg/mL who subsequently change to infliximab have ↑ risk of failure
  - Patients achieving higher drug concentration after infliximab dose escalation for loss of response have
    - ↑ rate of recapturing clinical response and improved therapeutic outcomes compared to patients without

- Stable clinical response of remission on anti-TNF therapy
  - Patients who undergo proactive therapeutic drug monitoring have
    - ↑ infliximab retention compared to standard-of-care
  - Patients who undergo concentration-based dosing have
    - ↓ frequency of undetectable infliximab concentration
    - ↓ risk of relapse compared to those followed on clinical-based dosing

- Patients with supra-therapeutic drug concentration can safely de-escalate therapy to reach an ideal target based on proactive therapeutic drug monitoring
  - No detrimental effect on remission rates, thus ↓ treatment cost
- Patients with CD and a suboptimal infliximab concentration
  - ↑ clinical remission and a concomitant significant ↓ CRP levels following dose escalation based on proactive therapeutic drug monitoring
- Patients who receive dual therapy and have infliximab trough concentration > 5 µg/mL at the time of the immunomodulator discontinuation
  - ↓ risk IBD-related surgery and infliximab dose escalation or cessation for loss of response after withdrawal of the immunomodulator compared to those without
- Withdrawal of anti-TNF therapy due to clinical remission
- Patients who discontinue infliximab due to clinical remission with undetectable or low drug concentration
  - ↓ risk of relapse compared to those without

- Restarting anti-TNF therapy after a "drug holiday"
  - Patients who reinitiate infliximab therapy after a drug holiday with early undetectable antibodies to infliximab and higher concentration
    - ↑ short- and long-term response rate compared to those with detectable antibodies to infliximab and lower drug concentration, respectively

Abbreviations: CD, Crohn disease; CRP, C-reactive protein; IBD inflammatory bowel disease; TNF, tumor necrosis factor

Papamichael K and Chiefetz AS. Am J Gastroenterol 2017;112(5):673-676.

Please also see details for TDM for individual biologics on the following pages.

- **Infliximab** (IFX)
  - Murine variable region grafted into a human IgG1 scaffold
  - Small volume of distribution (3-6L) (confined to blood stream)
  - T1/2
    - 11-19 d
  - Exposure to infliximab correlates with clinical, biochemical and endoscopic outcomes
  - Clearance = 0.230L-0.407L/d
  - ↑ clearance → ↓ blood levels → ↓ clinical benefit
  - Patient factors associated with changes in clearance of infliximab and changes in biological activity
    - ↓ albumin and infliximab clearance
      - IgG and albumin share a common elimination pathway
      - High fecal load on day 1
        - Low blood concentration at week 2

- ↓ anti-infliximab antibodies
  - Formation of anti-drug antibodies (ADAs) is associated with
    - Drug clearance (2.5x)
    - ↓ response
    - ↑ infusion reaction
  - Incidences range from 6-73%
  - Transient ADAs are less likely to affect infliximab effect vs sustained ADAs (5x ↑ risk of stopping infliximab due to LOR or ADR)
  - There is no defined cutoff for low or high ADA titre, but
    - ADA 8 AU/mL is associated with ↓ duration of infliximab response
- ↓ body weight
- ↑ biological activity
  - GI inflammation → ↓ intestinal barrier function / ↑ "leakiness" and → ↑↑ loss of body albumin pool(up to 60%)
    - In acute colitis this affects other large proteins
- ↓ concomitant immunosuppression
  - A concurrent immunomodulator ↓ infliximab clearance (↑ biological activity)
  - In patients with combination therapy infliximab peak concentration is (↑ 1.44x compared to monotherapy
  - Withdrawal of an immunomodulator has been associated with loss of response
- ↑ inflammation (↑CRP)
- Therapeutic drug monitoring (TDM)
  - Reactive monitoring
    - ↓ exposure is associated with ↓ response
    - Maintain Infliximab trough concentration >5ug/mL
  - Crohn disease
    - ↑ exposure (> 10.1 ug/mL) is associated with ↑fistula closure
    - Based on combined analysis of patient-level data from four studies that evaluated 483 patients with Crohn disease using a fluid phase mobility shift assay, IFX trough concentrations > 2.79 ug/mL during maintenance therapy were associatedwith remission as measured by C-reactive protein concentration (Vande CasteeleNV, et al. Gut. 2015; 64(10): 1539-45)
    - AGA recommends reactive TDM to guide treatment changes in the patient with active IBD
  - Ulcerative colitis
    - Infliximab concentration ≥ 23.1 ug/mL at 2-wk interval predicts endoscopic healing at 8 wk
    - Infliximab concentrations >10.6 ug/mL in UC predicts endoscopic healing in the maintenance phase
  - Proactive TDM
    - ↑ clinical remission with ↑ drug concentration (3-7ug/mL) in optimization phase
    - Proactive infliximab TDM no better than reactive TDM/clinical symptoms, whenIFX concentration targeted at > 13 ug/mL (D'Haens G, et al. Gastroenterology 2018; 154: 1343-1351)
    - Overall correlation between tissue and serum drug concentration in quiescent disease (no "serum concentration-tissue concentration mis-match"
    - Subjects with active IBD more likely to have ↓ tissue infliximab (IFX) concentrations despite normal serum IFX concentrations (Yarur AJ, et al. Gut 2016; 65(2): 249-55)

➢ Terms

- Causes of Failure of Infliximab (IFX)
  - Primary
    - No response to induction therapy, possibly due to
      - High pre-treatment TNF-α levels
      - Inadequate dose of IFX (low trough IFX concentration), or
      - TNF-α independent inflammatory pathways
  - Secondary (loss of symptomatic response after initial successful induction therapy mechanisms
    - Antibody to IFX (especially with on-demand IFX infusions)
    - Antibodies to anti-TNF agents
      - Inadequate dose of IFX (low trough IFX concentration)
      - ANA (antinuclear antibodies) develop in 50% of anti-TNF blockers of these, 30%develop anti-dsDNA (a double-stranded)
      - ↑ clearance (rapid metabolism) of IFX in the inflamed bowel
      - Non-TNFα dependent inflammatory pathways
      - Development of IBD-related complications e.g., stricture, abscess
      - Non-IBD related symptoms e.g., IBS, SIBO, bile acid wastage, C. difficile infection

Abbreviations: IBS, irritable bowel syndrome; IFX, infliximab; SIBO, small bowel intestinal bacterial overgrowth

Adapted from: Ben-Horin S, et al. Autoimmun Rev 2014;13(1):24-30; Roda G, et.al. Clin Transl Gastroenterol 2016;7(1): e135.

➢ Indications

- Indication of remission in patients with inflammatory disease failing to respond to adequate doses and durations of steroids and immunosuppressants
  - Unclear whether patients at high risk of severe disease are candidates for early anti-TNF treating
- Maintenance of remission in
  - CD and UC, after failure of usual maintenance indications
  - In surgically patients with resected inflammatory CD
- Induction and maintenance of CD
- Severe acute UC/CD not responding to corticosteroids
- Possible patients with CD with ↑ risk of future severe disease
- "Start high" or "step-up" therapy in IBD – the hope is that if the patient is treated early with effective therapy (anti-TNF), there will be
  - ↓ rate of progression of IBD (e.g., fistulae, strictures)
  - ↓ use of corticosteroids, or need for hospitalization/surgery

- Three shortcomings of SONIC study
  - Open-label
  - No comparative group of early anti-TNF vs early immunomodulator treatment
  - Episodic rather than regularly scheduled anti-TNF
  - No stratification for whom was likely to develop disabling, complicated or severe disease
  - Used IBD symptoms, not mucosal changes
- Possible future outcome considerations
  - Treat to target (mucosal healing), rather than just symptoms
  - We may underestimate the need to treat when we don' treat the asymptomatic patients"

➢ Response and secondary failure after anti TNF-α therapy

- Approximately 1/3 of primary responders lose the initial response over a course of 6-12 mon due to
  - Inadequate drug concentration
  - Change in behavior of disease
  - Development of antibodies to therapy
- Use immunosuppressant once the anti-TNF therapy has been started, especially since withdrawal of azathioprine 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.
  - This issue remains controversial.
- For patients with secondary loss of response to IFX, switching to ADA gives "recapture" remission rates of 21% at 4 wk and 40% at 1 yr
  - Switching fromIFX to certolizumab pegol at 6 wk gives a "recapture" response of 60% and remission of 40%.
- Induction of remission (5-10 mg/kg T0, T2, T6 wk)
  - Symptoms ~70%
  - Mucosal healing ~55%
- Maintenance (1 yr) (q8wk), ~30%
  - Symptoms ~55%
  - Mucosal healing ~20%

Cautions: Clinical Trial Design

- Many of the ATNF trials had an initial 2 wk lead-in period, and only those persons who improved on therapy were continued for the randomized portions of the study to determine rates of remission and maintenance of remission
  - Since the response rate of patients in clinical practice is not known in advance, the rates of induction of remission may be lower because some will be initial non-responders

- Relative contraindications to anti-TNF therapy.
  - Pre-existing severe immunosuppression
  - Allergy to anti-TNF
  - Intestinal stenosis
  - Fistulizing disease with
    - Abscess
    - Fistulae to bladder
  - Untreated active infection (TB, HBV)
  - Multiple sclerosis (MS), optic neuritis
  - Cardiac failure (New York grade III, IV)
  - Lymphoma
  - Acute liver failure
  - Cancer **in the past** (other than non-melanoma skin cancer [NMSC])

Abbreviations: HBV, hepatitis B viral infection; HCV, hepatitis C viral infection; MS, multiple sclerosis; TB, tuberculosis

- Contraindication/precautions
  - Known sensitivity to infliximab
  - Adverse effects / drug-drug interactions
  - Infection
    - Active
    - Latent e.g., latent TB, HBV
    - Live vaccines
  - CNS
    - Demyelination disease (e.g., multiple sclerosis [MS])
    - Immunosuppression
    - Seizure disorder
    - Vasculitis

- Adverse effects
  - CNS
    - Please see contraindications/precautions
  - CVS
    - Heart failure NYHA class III or IV
    - Acute coronary syndrome

- Lung
  - Reactivation of latent TB
  - Upper respiratory tract infections
  - 6.4x ↑ mortality rate in persons with pre-existing pulmonary disease
- GI
  - Abdominal pain
  - Nausea/vomiting
  - Hepatotoxicity
  - Reactivation of HBV
- Blood
  - Pancytopenia
  - Neutropenia/leukopenia
  - Aplastic anemia (adalimumab)
  - Thrombocytopenia
  - Hepatosplenic T cell lymphoma, especially in young boys
  - ↑ risk of lymphoma when combined with immunosuppressants

Group	Incidence (per 10^5 patient-year)
− General population	1.9
− Crohn disease treatment with	
▪ Immunomodulators	1.7
▪ Anti-TNF blocker	6.1

- Musculoskeletal (MSK)
  - Drug-induced systemic lupus erythematosus (SLE)
  - Hypersensitivity reaction delayed
    - Flare of rheumatoid arthritis
    - Anaphylaxis
    - Angioneurotic edema (adalimumab)
- Infections
  - ↑ risk/severity of infections
- Skin
  - Rash
  - Eczematous lesions
  - Erythema multiforme (EM)
  - Infusion related reaction
  - Lupus-like lesions
  - Psoriatic lesions ± pus
- Immunologic
  - Development of antibodies which ↓ efficacy of anti-TNF inhibitor

- Drug-drug interaction
  - Vaccinations
    - ↓ immunological response
    - Do **not** give live vaccines
      - ↑ risk of disseminated infection (sepsis)
  - Infection
    - ↑ risk when given with
      - Abatacept
      - Anakinra
    - Immunosuppressants may
      - ↑ toxicity
      - ↑ risk of concurrent infection

- Peripartum
  - Pregnancy – Safe
  - Lactation – Safe

- Approximate frequency (per 10^5) of the serious side effects of anti-TNF agents in patients with Crohn disease (CD).

Event	Approximate Frequency per 10^5
Non-Hodgkin lymphoma (baseline)	20
– On immunosuppression	40
– Also on anti-TNF therapy	60
Tuberculosis infection	50
Death from sepsis	40

  - Surgery is commonly needed in persons with CD.
    - After diagnosis
      - 1 yr ~20%
      - 20 yr ~80%
    - The operative mortality is $80/10^5$, compared with a $40/10^5$ mortality rate for dying of sepsis from anti-TNF therapy.
  - Patients who develop extra nodal hepatosplenic T-cell lymphoma (HSTCL) have always been on anti-TNF and usually also on AZA therapy; there does not appear to be a risk with other biologics.
  - The number of persons needed to heal with azathioprine / G mercaptopurine per year to cause one case of lymphoma is 4,357, compared to 2,380 for an anti – TNF drug.
  - Do **not** use risk data from patients with rheumatoid arthritis (RA) to calculate/estimate risk in patients with CD/UC.

➢ Combination therapy (adding concomitant immunomodulators to anti-TNF therapy in Crohn disease).

Advantages	Disadvantages
○ ↓ Antibodies (at least to infliximab)	− ↓duration of response (with episodic therapy)
○ Benefit in steroid-dependent CD (SONIC)	− No difference in short- or long-term responses to induction + maintenance therapy in refractory CD (ACCENT, CHARM, PRECISE [clinical trials])
○ ↓ acute/delayed infusion reactions	− No benefit with steroid-induction (COMMIT)
○ ↓ immunogenicity	− ↑ long-term toxicity ▪ ↑ risk of infections, including serious infections − High cost

- **Adalimumab** (ADA)
  - ○ Fully human IgG1
  - ○ Cmax
    - − 4.7ug/mL
  - ○ Bioavailability
    - − 64%
  - ○ IBD current guidelines recommend an adalimumab target concentration of > 7.5 µg/mL for maintenance of remission
  - ○ If loss of response at this concentration, switch to a drug out of this class.
  - ○ Adverse effects (in addition to those for infliximab)
    - − CVS
      - ▪ Hypertension
    - − Blood
      - ▪ Aplastic anemia

❖ Other Biologics

- **Ustekinumab** (UST)
  - ○ Fully human mAb against IL12/23 p40 subunit
  - ○ Low rates of immunogenicity (0.2-2.3%)
  - ○ The adverse effects of use are similar to VEDO (please see below), as well as injection site reactions”

➢ Mechanism of action

- ○ Binds to IL-12 and IL-23 that are unbound to IL-12Rβ so it is unlikely to initiate Fc effector functions, such as ADCC or CDC.
- ○ Inhibition of the IL-12/23 signalling pathway leads to profound suppression of both the Th1 and Th17 cell lineage of cytokines and chemokines and their inflammatory pathways.

- Pharmacokinetics
  - Absorption
    - IV induction, SC maintenance
      - Peak concentration following IV administration 125 ug/mL
        - Trough concentration = 2.5 µg/mL
    - Trough concentrations > 0.8 µg/mL associated with clinical remission
    - Following IV induction dose administration, Cmax was 125.2 ± 33.6 µg/mL in patients with Crohn disease and 129.1 ± 27.6 µg/mL in patients with ulcerative colitis.
  - Volume of distribution
    - Small volume of distribution (4 L) (mAb is confined to blood stream)
    - The total volume of distribution at steady-state was 4.62 L in patients with Crohn disease and 4.4 L in patients with ulcerative colitis.
  - Metabolism
    - Metabolic pathway not been fully characterized
    - Expected to undergo non-specific protein degradation via catabolic pathways in the same manner as endogenous IgG
  - Route of elimination
    - Limited information on the main route of elimination
    - Expected to undergo renal excretion following degradation
  - Half-life
    - The estimated median terminal T1/2 ~19 d in patients with Crohn disease or ulcerative colitis
  - Clearance
    - In patients with Crohn disease, the clearance was 0.19 L/day in patients with Crohn disease or ulcerative colitis

- **Vedolizumab** (VEDO)

- Mechanism of action
  - Targets α4β7 integrin
  - Prevents interaction of α4β7 integrin with MAdCAM-1 and extravasation of T-cells into inflamed intestinal tissues

    T1/2 = 15-22 d

- Pharmacokinetics
  - Absorption
    - Route of administration is IV, therefore there is no absorption data and bioavailability is expected to be 100%.
    - Following administration of 300 mg of vedolizumab as a 30-minute IV infusion from week 0 to 2 and 300 mg every 8 wk starting from Week 6, the trough serum concentration of vedolizumab is 26.3 ± 12.9 and 27.4 ± 19.2 mcg/mL for Ulcerative Colitis and Crohn Disease patients respectively at week 6.

- At week 46, the trough serum concentration of vedolizumab is 11.2 ± 7.2 and 13.0 ± 9.1 mcg/mL for Ulcerative Colitis and Crohn Disease patients respectively.

- Volume of distribution
  - Serum apparent volume of distribution at steady-state moderately greater than the serum volume (approximately 5 L).
  - Expected to be confined to the systemic circulation, as expected for a high molecular weight protein
- Metabolism
  - Proteolytic degradation to small peptides and individual amino acids, and receptor-mediated clearance
- Route of elimination
  - Renal clearance is negligible as vedolizumab is a high molecular weight protein
- Half-life
  - Long terminal elimination T1/2 of 25 d
- Clearance
  - Depends on both linear and non-linear pathways
    - Non-linear clearance decreases with increasing concentrations
    - Linear clearance approximately 0.157 L/d or 0.180 to 0.266 mL/h/kg

➢ Adverse effects

- CNS
  - Fatigue/depression
  - Headache
  - Progressive multifocal leukoencephalopathy (PML)
- Lungs
  - Upper/lower respiratory tract infection (URI/LRI)
    - Nasopharyngitis (vedolizumab)
- GI
  - Abdominal pain
  - Hepatotoxicity
  - Nausea/diarrhea
- GU
  - Urinary tract infections (UTIs)
- MSK
  - Pain
    - Back
    - Limps
    - Arthralgias
- Infection
  - ↑ risk of serious/disseminated infection e.g., disseminated hepatic infection
  - Reactivation of latent infections
- Skin
  - Infusion-related infections
- Immunological
  - Development of antibodies to drugs

- Drug-drug interaction
  - Vaccines
    - ↓ immunological vaccine response
    - ↑ risk of disseminated infection
    - ↑ risk of reactivation of latent infections
  - Immunosuppression
    - ↑ risk of infection / ↑ toxicity
  - Echinacea
    - ↓ therapeutic effect of vedolizumab
- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Safe
  - Gemini I:
    - Evaluated exposure-efficacy relationship
    - Positive association for UC for response, remission and mucosal healing
    - Vedolizumab trough concentrations >30.0 µg/mL at week 2, >24.0 µg/mL at week 6, and >14.0 µg/mL during maintenance therapy associated with a higher probability of attaining the effectiveness endpoints for patients with UC or CD (Dreesen E, et al. Clin Gastroenterol Hepatol 2018;16(12):1937-1946.
    - More data needed to confirm role of TDM
  - Infusion-related reactions < 5%
  - No ↑ risk of infection with vedolizumab exposure
  - No cases of progressive multiple leukoencephalopathy (PML) detected
  - Malignancy risk $1/10^3$ person-years (similar to IBD patients in general)

- **Natalizumab**

- Mechanism of action
  - α-4 integrin inhibitor
- Pharmacokinetics
  - Absorption
    - In patients with Crohn Disease
      - Cmax 101 ± 34 mcg/mL
      - Steady-state trough concentration was 10 ± 9 mcg/mL
      - Time to steady-state ~16-24 wk after every 4 wk of dosing
  - Volume of distribution
    - Following repeated 300 mg natalizumab IV in patients with Crohn Disease, 5.2 ± 2.8 L
  - Metabolism
    - NA
  - Route of elimination
    - NA

- Half-life
  - Following repeated 300 mg natalizumab IV in patients with Crohn Disease, 10 ± 7 d
- Clearance
  - Following repeated 300 mg natalizumab IV in patients with Crohn Disease, 22 ± 22 mL/h
  - Natalizumab clearance increased with body weight in a less-than-proportional manner.
  - The presence of persistent anti-natalizumab antibodies increased natalizumab clearance ~3x.

➢ Indication

- Moderate to severe CD in adult patients who have had an inadequate response to other therapies

➢ Contraindication/precautions

- Known hypersensitivity to natalizumab
- Adverse effects / drug-drug interactions
- Do **not** use in conjunction with
  - Immunosuppressants
  - Anti-TNF agents
- Active infections

- **Tofacitinib**

➢ Mechanism of actions

- JAK inhibitors ↓ phosphorylation / ↓ activation of JaK-1/3 associated with the cytokine receptor → bind to STAT → ↓ transcription → regulate cytokine signaling and activation of proinflammatory genes.

➢ Pharmacokinetics

- Benefits over monoclonal antibodies
  - Short half-life (might be useful for on/off therapy, e.g., replacing corticosteroids)
  - Lack of immunogenicity
  - High bioavailability when delivered orally
  - Large volume of distribution ~ 115 L
  - High clearance (hepatic CYP3A4) ~ 25 L

➢ Disadvantages / adverse effects

- Immunosuppression
  - ↑ risk of infections e.g., HZV
- Metabolic
  - Hyperlipidemia
- Infection, Interactions and Immunization

- Risk of treatment-associated opportunistic infections in patients with IBD.

	Odds Ratio
5-ASA	0.98
Corticosteroids	3.4
AZA/6MP	3.1
MTX	4.0
Infliximab	4.4
− One medication	2.7
− Two medications	9.4

- **Sphingosine-1 Phosphate** (S1P) **Receptor Agonists**
  - Mechanism of action of ozanimod in UC
    - ↓ exit of lymphocytes from lymph nodes
  - Complications
    - Lymphopenia
    - Transaminitis (↑ ALT, ↑ AST)
    - May interfere with cardiac AV node (arrhythmias)

- **IL-23** (P19) **Inhibitors**
  - Mechanism of action of Risankizumab (RZB)
    - ↓ hyperexpression of IL-23 in IBD by SC injection q8-12 wk
    - Breaks the barrier
    - Good safety profile: no signs for immunogenicity
    - Long half-life, durable benefit

- **Head-to-head Clinical Trails** (to Compare Anti-TNF, Anti-p40, IL-12/-25 and anti-integrin α4β7; Neeraj N, et al. Am J Gastroenterol 2022; 117: 1106-17)
  - Post-hoc analysis of 4 clinical trials of patients with moderate-severe Crohn disease assessed for endoscopic healing after 1 yr maintenance therapy with anti-TNFs (infliximab [IFX], adalimumab [ADA], anti-p40, IL-12/-23 ustekinumab [UST], or alpha-integrin α4β7, vedolizumab [VEDO].
  - Ileum plus colon
    - IFX (28%) = ADA (28%) > UST = VEDO (7%)
  - Ileum
    - Simple Endoscopic Score (SES) for Crohn Disease ≥ 3, IFX = ADA = UST = VEDO
  - Colon
    - 1 yr endoscopic healing of the ileum +/- colon with infliximab or adalimumab is superior (2 to 4 times greater), as compared to anti-p40, IL-12/-23, ustekinumab or anti-integrin-α4β7 vedolizumab

➢ Vaccination

- Live vaccines which should **not** be given while the IBD patient is on anti-TNF therapy.

❖ Non-oral
- Bacilli Calmette-Guerin (BCG)
- Herpes Zoster Virus (HZV)
- Inhaled nasal influenza
- Japanese encephalitis
- Measles, mumps, rubella (MMR)
- Rotavirus
- Vaccinia (smallpox)
- Varicella
- Yellow fever

❖ Oral
- Polio
- Typhoid

Abbreviations: IBD, inflammatory bowel disease; TNF, tumour necrosis factor

➢ Drug Interactions

- Potentially serious interactions with other drugs

5-ASAs	− ↑ INR, 6-TG and methotrexate (MTX) − ↓ digitalis levels
Allopurinol	− ↑ 6-TG
ACE inhibitors	− ↑ 6-MP-associated risk of anemia, leucopenia
Methotrexate (MTX) levels are	− ↓ by tetracycline, and ↑ (greater toxicity) by penicillin, 5-ASAs and NSAIDs; folic acid deficiency
Metronidazole	− ↑ effect of statins, sildenafil, calcium channel blockers, and ↑ INR

Abbreviations: ASA, amino salicylic acid; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory; OCIF, osteoclastogenesis inhibitory factor; OPG, osteoprotegerin; TG, thioguanine

ENTEROHEPATIC CIRCULATION (EHC) **OF BILE ACIDS**

➢ Bile acid (BA) metabolism

- Functions of bile acids.
  - Liver
    - ↑ hepatic secretion of cholesterol and phospholipids (cholesterol homeostasis)
    - ↑ bile water flow (choleretic effect)
  - Intestine
    - ↑ solubilisation of cholesterol, triglycerides, phospholipids, fat-soluble vitamins
    - Interact with pancreatic colipase to modify activity of lipase
  - Mucosal defense
    - Jejunum
      - Bacteriostatic
    - Ileum
      - ↑ expression of antimicrobial genes
  - Stones
    - Gallbladder
      - ↓ formation of calcium stones
    - Kidney
      - ↓ formation of oxalate stones
  - Metabolic function
    - Regulate their own EHC
    - Signal nuclear and G-protein-coupled receptors → helps to maintain homeostasis of fat, glucose and energy

➢ BA metabolism

- Size of BA pool
  - 2 g to 4 g (50 to 60 mmol per kg body weight)
- Cycles of BA pool
  - Per meal 2 to 3
  - Per day 6 to 10
- Absorption of BA per day
  - 10 to 30 g (pool size x number of cycles)
- Colonic loss of BA per day
  - 200 to 600 mg
- Hepatic synthesis of BA per day to match daily fecal losses
  - >> 95%
- Efficiency of EHC
  - Recovery (efficiency) ~ 98%

➢ Physiology

- The rate-limiting stop for the classical pathway of bile acid synthesis and secretion is the enzyme CYP7A1.
- As the throughput of the bile acids (BA) increases in the cytosol of the ileocyte or hepatocyte, CYP7A, falls and bile acid synthesis and secretion fall.

- Hepatocyte synthesis
  - FGF-dependent, SHP-dependent and mitochondrial cholesterol-dependent negative feedback regulation of bile acid synthesis and secretion.
  - Classical ileocyte and hepatocyte CYP7A1 pathway
    - Overall
      - ↑ BA passing through ileocyte → ↓ BA synthesis in hepatocyte
    - FGF12: ↑ BA in cytosol of ileocyte → activate FXR → ↑ FGF_{12} → ↓ hepatic CYP7A1→ ↓ hepatic synthesis of BA
    - SHP →
      → ↑ HNF4α → hepatic CYP 7A1 → ↓ hepatic synthesis of BA
      → ↓ LRH-1
      → Activation of c-Jun (JNK) pathway
  - Alternate pathway
    - ↑ cholesterol in mitochondria

Abbreviations: HNF4α, hepatocyte nuclear factor 4α; JNK, c-Jun NH_2-terminal kinase; LRH, liver receptor homology; FGF19, fibroblast growth factor-19; FXR, farnesoid X receptor; SHP, small heterodimer partner, a nuclear receptor

- Canalicular membrane secretion
  - When bile acids (BA) are conjugated in the liver to the amino acids glycine and taurine, the conjugated BA become more hydrophilic and less hydrophobic, so then passive absorption in the proximal intestine is less.
  - Less passive absorption of conjugated BA in the proximal intestine maintains an adequate concentration of BA in the intestinal lumen to provide for continued solubilization, digestion and absorption of lipids.
  - As the BA pass along the length of the small intestine, there becomes less and less exogenous or endogenous lipids to be absorbed, and the BA needs to be reabsorbed.
  - The reabsorption of bile acids, their return to the liver, resecretion by the hepatocyte, and return to the lumen of the small intestine represents the EHC (enterohepatic absorption of bile acids).

- Microbiotica
  - The endogenous microbiotica in the lumen of the terminal ileum deconjugates the primary and secondary bile acids.
  - Enteric bacteria dehydroxylate Ba (primary (1^o) → secondary (2^o) BA), and deconjugate $1^o/2^o$ BA; enteric bacteria also epimerize the 7α-hydroxy group of CDCA (chenic acid), forming UDCA (ursodeoxycholic acid, 3α, 7β – dihydroxy BA).
  - About 95% of BA in the lumen of the intestine are reabsorbed and recycled to the liver, representing the high efficiency of the EHC.
  - The ~5% of the luminal bile acids that are not reabsorbed and recycled spill into the colon bacterial 7α-dehydroxylate in the colon produce 2^o from 1^o bile acids:

    CA → DCA (50% absorbed by colon)

    CDCA → LCA

Abbreviations: BA, bile acid; CA, cholic acid; CDCA, chenodeoxycholic acid (aka chenic acid); DCA, deoxycholic acid; LCA, lithocholic acid; UDCA, ursodeoxycholic acid

➢ Bile secretion

There is bile acid (BA)-dependent and BA-independent bile flow, as well as Na^+-dependent bile acid clearance.

- Bile acid (BA)-dependent flow
  - Transport of BA across hepatocyte canalicular membrane by
    - BSEP (bile salt export protein)
    - MRP_2 (multidrug resistance-associated protein-2)
    - See "cholestatic shunt, below
- BA-independent flow
  - MRP_2 (multidrug resistance-associated protein 2) transport of GSH (reduced glutathione)
  - GGTP (gamma glutamyl transpeptidase, which catabolizes GSH in lumen)
  - AE_2 (chloride [Cl^-] bicarbonate [HCO_3^-] anion exchanger isoform 2, which secretes HCO_3^- from cholangiocytes into the lumen of bile duct

- Give inborn errors of bile acid or phospholipid transport, and for each name the defective transporter.
  - PFIC type 1
    - Progressive familial intrahepatic cholestasis
  - PFIC type 2
    - BSEP (ABCB11) deficiency
  - PFIC type 3
    - MDR3 (ABCB4) deficiency
  - BRIC (benign recurrent intrahepatic cholestasis) syndrome
- Function of hepatocytes in zone I versus zone 3.

	BA Absorption	BA Secretion
Zone I, periportal	− During fasting	▪ Recycled BA
Zone III, pericentral (aka perivenous)	− During feeding	▪ Newly synthesized BA

- Give the physiological basis for the choleretic effect of ursodeoxycholic acid (UDCA).
    - Unconjugated dihydroxy bile acids such as UDCA are partially reabsorbed from the duct lumen across the luminal membrane of the cholangiocytes.
    - ASBT on the cholangiocytes luminal membrane also quickly shunts conjugated BA back to the hepatocyte for resynthesis.
    - The UDCA quickly returns to the hepatocytes through the periductular capillary plexus.
    - The uptake of the protonated (H^+) unconjugated UDCA generates HCO_3.
    - The UDCA is quickly resecreted into the bile by the hepatocyte canalicular membrane.
    - The HCO_3^- produced from the uptake of the protonated UDCA through the cholehepatic shunt causes a bicarbonate-rich
        - Reuptake of BA by active [ASBT] and by passive process of the luminal membrane of the cholangiocytes choleresis
    - Because this bicarbonate-rich choleresis depends on the uptake of the protonated unconjugated BA, this rapid reabsorption and resecretion of the BA because of uptake by the cholangiocytes is, of course, causing BA-dependent bile flow.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Bile acids in the ileocytes bind to and activate FXR (a member of the family of sterol nuclear receptors)

- Give the functions of FXR (farnesoid X receptor).
    - BBM
        - Sodium-dependent bile salt transporter
    - FXR alters the activity of
        - Enzymes in the ileocyte cytosol: 7α – hydroxylase
        - Transporters in hepatocyte
            - NTCP (sodium-dependent), sinusoidal membrane
            - BSEP (bile salt export protein), canalicular membrane

The liver synthesizes and secretes the primary bile acids (cholic and chenic acid).

- Give the reason why an estimate of the types of bile acids synthesized by the liver cannot be made from assessment of stool bile acids.
  - The conjugated primary bile acids are deconjugated and 7α-dehydroxylate by luminal bacteria to deoxycholic acid (from cholic acid) and lithocholic acid (from chenic acid).
  - And that's the answer! Fecal bile acid is mostly deoxycholic and lithocholic acid, reflecting the action of the colonic microbiotica, and not the secretory pattern of the liver.

➢ Transport proteins for bile acids in the EHC

Cell Type	BBM/SM	BLM/CM	Cytosol
○ Ileocyte	– ASBT (apical sodium bile acid transporter)	▪ OST αβ (organic solute transporter)	– FXR (farnesoid X receptor) – FXF19 (fibroblast growth factor 19)
○ Hepatocyte	– NTCP (Na^+-taurocholate cotransporting polypeptide)	▪ BSEP (bile salt export pump)	
○ Cholangiocytes	– ASBT	▪ OST α/β	
○ Renal proximal tubular cell	– ASBT	▪ OST α/β	

Abbreviations: BBM, brush border membrane of ileocyte; BLM, basolateral membrane of ileocyte; CM, canalicular membrane; SM, sinusoidal membrane

DIARRHEA

- **Absorption of Sodium and Water**

➢ Intestinal Fluid Balance: Overview

- Water absorption is linked to
  - The transport of sodium (Na^+) and nutrients, as well as to the permeability of the epithelial surface (as influenced by tight junctions [TJs], paracellular), and the contribution of aquaporins (water pores)
- The intestinal brush border membrane (BBM) of the villi of the enterocytes absorbs solutes such as glucose and water by
  - Transcellular transporters and aquaporins in the membrane, and
  - Paracellular movement across TJs between cells
    - For example, the Na^+ - dependent sugar transporter in the intestinal BBM by SGLT1 co-transports H_2O
- Up to ~8 L of fluid normally flows through the small intestine each day.
- Salivary, gastric, biliary, pancreatic, and intestinal secretions make up the bulk of this amount, with about 1.5 L arising from oral intake.
- Of this ~ 8.0 L/day, 1.5-2.0 L enters the colon, thanks to the small intestinal fluid reabsorption efficiency of about 80%.
  - Of this 1.5- 2.0 L/day entering the colon, only about 0.1-0.2 L/day escapes absorption and is passed in the stool, giving an absorptive efficiency of ~90%.
- This means that the average daily stool output is only about
  - 200 mL fluid, and
  - 50 g of food debris, desquamated mucosal cells, and bacteria.

➢ Balance "IN" (Absorption of Na^+ plus H_2O) Versus "OUT" (Secretion of Cl- Plus H_2O

- Net water absorption = H_2O influx across BBM of upper villus enterocytes, minus H2O secretion/ efflux across apical membrane of crypt enterocyte.
- The absorptive mechanisms in each segment of the gut differ, whereas chloride (Cl^-) secretion is found throughout the intestine.
- When secretion > absorption of H_2O → "diarrhea"

➢ Paracellular transport

- TJs (aka zona occludens [ZO]) are a network of strands and grooves that consist of
  - Membrane proteins (e.g., occludins, claudins, and junctional adhesion molecules [JAMs]).
  - These attach to a group of scaffolding proteins
    - Zonula occludens proteins (ZO-1, ZO-2, ZO-3), and
    - Multi-domain protein-1 (MUPP1)

- These scaffolding proteins are
  - Linked to the cytoskeleton of the enterocyte, which participate in vesicular transport via monomeric guanosine triphosphatase (GTPase) of the Ras superfamily (Rab3b), and
  - Participate and in the activation of signaling molecules that regulate the junction assembly (partition-defective protein)
    - PAR-3 and -6, and
    - Atypical protein kinase C (aPKC)
- Cadherins
  - Span the paracellular pathway across the zona adherens (ZA)
  - Responsible for cell-cell attachment and maintain cell polarity.
  - Bind to catenins, which are linked to the actin cytoskeleton by way of an additional family of molecules, including radixin, vinculin and α-actinin.
- Desmosomes
  - Cadherin-like molecules that are linked to intermediate filaments.
- Connexins
  - Gap junctions are an assembly of membrane spanning proteins called connexins.
  - Connexins allow the exchange of small molecules between neighboring enterocytes.

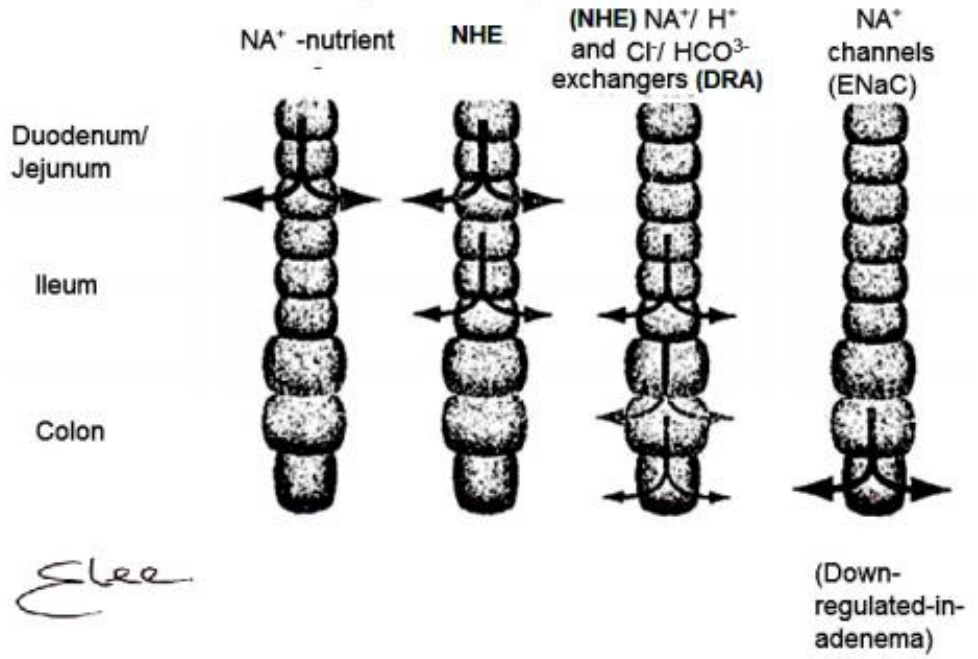
➢ Osmotic Gradients

- When solute exits across the BBM of the enterocyte and into the restricted of the lateral intercellular spaces, the fluid becomes slightly hypertonic.
- These osmotic gradients are sufficient to draw water from the intestinal lumen across the TJs.
  - This is called the “standing-gradient hypothesis”
- The junctions between epithelial cells become progressively ‘tighter’ from the proximal to distant intestine, so that the permeability to water becomes lower along the length of the small intestine.

➢ Sodium (Na^+) Transport

- Na^+ transport plays a major role in transcellular H_2O absorption.
- The negative cytoplasmic potential (~-40 mV) which arises from the basolateral membrane Na^+/K^+ ATPase acts as a driving force for Na^+ entry across the BBM.
  - Na^+ / nutrient- coupled transporters in the jejunum and ileum
  - Na^+ / H^+ exchangers (NHE) in the jejunum and ileum
  - Cl- / HCO_3- exchangers in the ileum and proximal colon down-regulated in adenoma (DRA)
  - ENaC (epithelial/ Na^+ channel) in the distal colon.

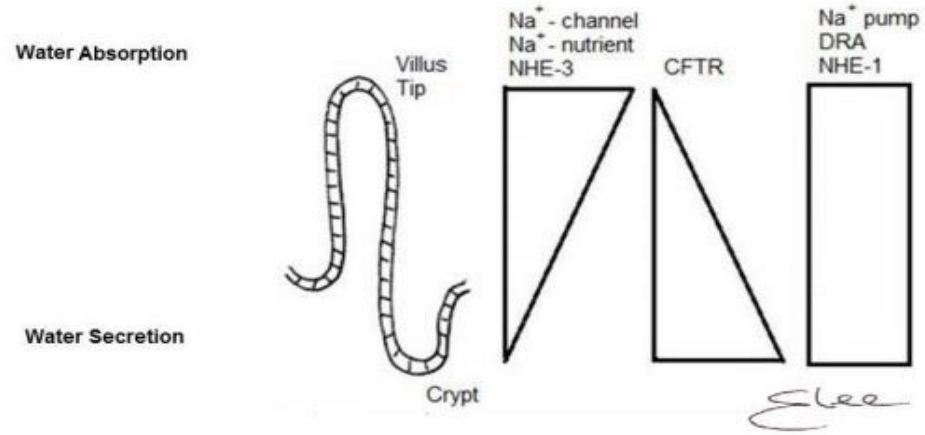
- Distribution of Na^+ Transporters Along the Small Intestine and Colon



Abbreviations: NHE plus DRA, parallel Na^+ - H^+ (NHE) exchanger plus Cl- HCO_3 - exchanger; DRA, down-regulated-in-adenoma [SLC 26A3])

Note: water absorption follows villus Na^+ absorption; water secretion follows crypt Cl- secretion

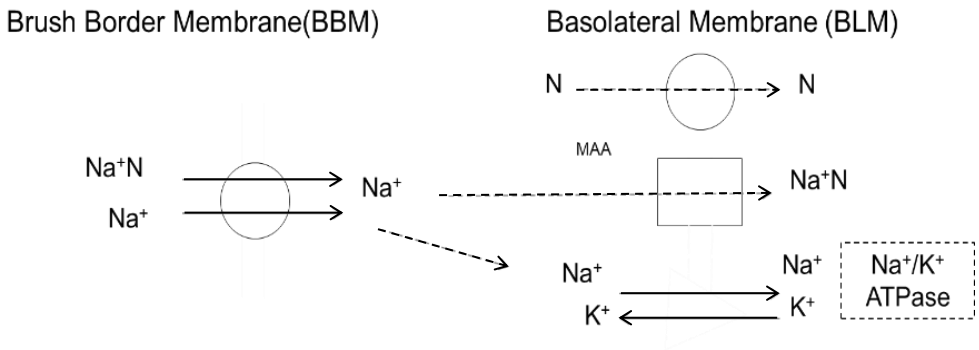
- Gradient of Na^+ Transporters Along Crypt-Villus Axis of the small intestine



Abbreviations: CFTR, cystic fibrosis transmembrane receptors; DRA, Cl- -HCO_3- exchangers; NHE, Na^+ / H^+ exchangers

Adapted From: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 11th Edition, 2020

- Na^+ - Nutrient Coupled Transporters in Jejunum and Ileum



Abbreviations: MAA, monosaccharide and amino acid transporter; Na^+N, sodium nutrient

Adapted from: Medical Physiology, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-3, page 938.

- BLM Na^+ - K^+ ATPase, Negative Membrane Potential
  - The Na^+ - K^+ ATPase in the BLM of the small intestine and colon exchanges 3 Na^+ molecules into the interstitial space for 2 K^+ transported into the cell.
  - The lower intracellular Na^+ (about 15 mM or lower) generates an intracellular-negative membrane potential.
    - Thus, H_2O is absorbed by transcellular BBM and by paracellular TJ processes

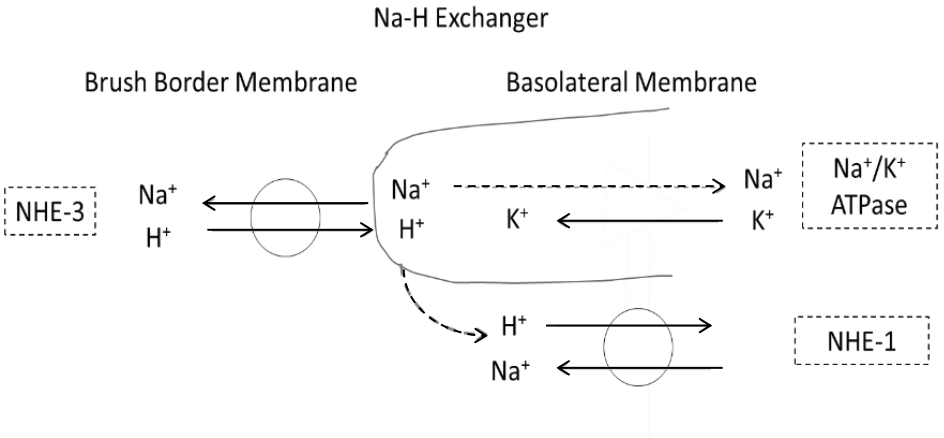
- Na^+ - Nutrient Coupled Transporters in Jejunum and Ileum
  - The movement of Na^+ and H_2O with glucose, as mediated by BBM SGLT1, is the basis of the benefit of ORS (oral rehydration solutions).
  - The relative amount of Na^+ and H_2O which moves through this water channel.
  - "…about 175 molecules of water can be transported per ion or mole of solute." (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 10th Edition. Saunders/Elsevier, Philadelphia, 2016, page 1718).
  - ↑ glucose in lumen → ↑ PKC / ↑ MAP kinase → ↑ GLUT2 in BBM → H_2O absorption

Abbreviations: MAP kinase, integrin-activated protein kinase; PKC, protein kinase

- Gradient and BLM Na^+ / K^+ ATPase Paracellular Movement of H_2O
  - The nutrients and electrolytes which have crossed the BBM
    - Diffuse across the cytosol to the BLM (basolateral membrane) → produce the osmotic and electrochemical gradients to provide for the passive absorption of H_2O through the tight junctions (TJs)

- Oral Rehydration Solution
  - This electrochemical gradient drives the downhill entry of Na^+ from either the apical or basolateral side of the enterocyte (i.e., across the BBM or BLM).
  - When the intestinal villus enterocytes absorb solutes such as glucose, water is also absorbed by transcellular aquaporins and by paracellular processes (across TJs).
  - This forms the basis for the use of ORS (oral rehydration solutions) for persons with diarrhea (glucose plus Na^+ in water greatly accelerates the absorption of water).

➢ Na^+ / H^+ Exchangers (NHE) in Jejunum and Ileum

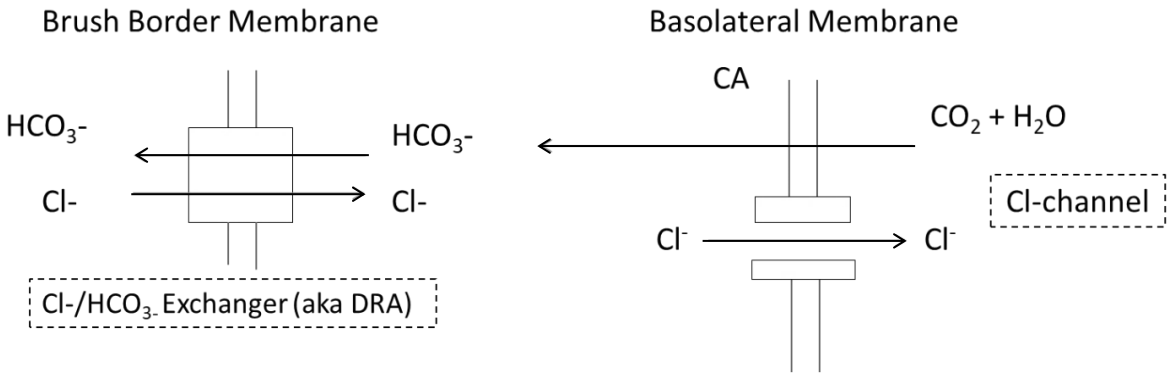


Abbreviations: N, nutrient; NHE, Na^+ /H^+ exchanger

Adapted from: Medical Physiology, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-3, page 938.

  - With food intake, the gastric H^+ -stimulated secretin released from the duodenal S cells → pancreatic duct cell secretion of HCO_3^- rich fluid into the lumen.
  - This ↑ HCO_3 - in the lumen of the proximal small bowel, and the ↑intracellular H^+ → BBM NHE (Na^+ -H^+ exchangers, NHE-2 and NHE-3).
  - The energy for NHE-2/ -3 arises from the intracellular Na^+ gradient created by the BLM Na^+ / K^+ pump (aka Na^+, K^+ ATPase)
  - The nutrient - Na^+ pumps are also energized by the Na^+ / K^+ pump in the BLM of the enterocytes.
  - Na^+ crosses the BBM of the enterocyte, down an electrochemical gradient.
  - K^+ channels help maintain the electrochemical gradient.
  - The NHE in the BLM regulates the intracellular H^+ (pH_i) and has a much lesser role in creating a Na^+ gradient.

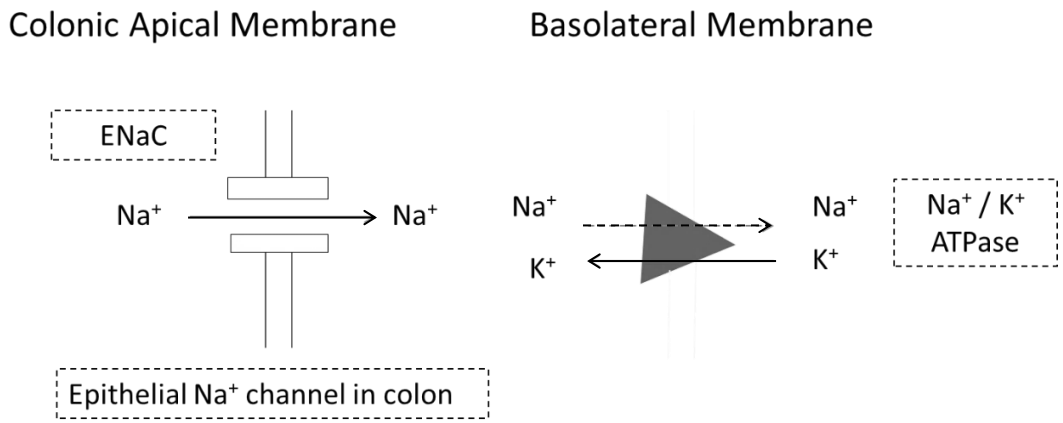
- Cl^- - HCO_3^- Exchangers (DRA) in Ileum and Proximal Colon, plus NHEs



Abbreviations: CA, carbonic anhydrase; DRA, down-regulated in adenoma

Adapted from: Medical Physiology, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-3, page 938.

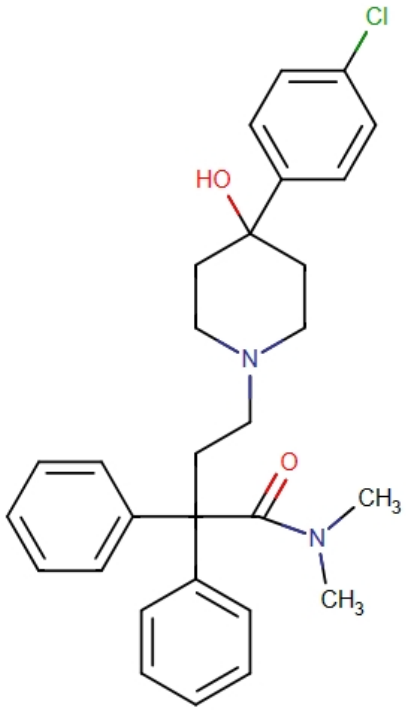
- Epithelial Na^+ Channel (ENaC) in Distal Colon



Adapted from: Medical Physiology, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-3, page 938.

- Antidiarrheal Drugs

- **Loperamide** (Imodium®)



- Indication
  - Diarrhea
    - 4 mg po AC, or
    - 4 mg after first loose BM, then 2 mg after each further loose BM to a maximum of 16 mg/day

- Mechanism of action
  - Anticholinergic effect → ↑ transit time / slows GI transit → ↑ "dwell time" for absorption of Na^+/H_2O

- Pharmacokinetics
  - Absorption
    - Well-absorbed from the GI tract
    - Undergoes extensive first-pass metabolism to form metabolites that are excreted in the bile
    - ↓ loperamide actually reaches the systemic circulation
    - Drug bioavailability is less than 1%.

- Following 2 mg capsule po, plasma concentrations of unchanged drug were below 2 ng/mL.
- Tmax ~5 h after po capsule administration and 2.5 h after the liquid formulation of the drug
- Volume of distribution
  - Large volume of distribution
  - Highly lipophilic, but does not cross the blood-brain barrier and generally acts peripherally
- Metabolism
  - Extensively metabolized
  - Primary metabolic pathway is oxidative N-demethylation mediated by CYP2C8 and CYP3A4, to form N-desmethyl loperamide.
  - CYP2B6 and CYP2D6 play a minor role in loperamide N-demethylation.
- Route of elimination
  - Loperamide and its metabolites in the systemic circulation undergo biliary excretion.
  - Excretion of the unchanged loperamide and its metabolites mainly occurs through the feces.
  - Only 1% of an absorbed dose excreted unchanged in the urine
- Half-life
  - Apparent elimination half-life of loperamide is 10.8 h with a range of 9.1-14.4 h
- Clearance
  - NA

➢ Contraindications/precautions

- Known hypersensitivity to domperidone or its products
- Note: Drug interactions
  - ↑ risk of AEs when given with ketoconazole

- GI
  - Diarrhea +/- abdominal pain
  - Severe, acute, bacterial (enterotoxin producing), infections including C. difficile infection (CDI)
  - Megacolon

➢ Adverse effects (AEs)

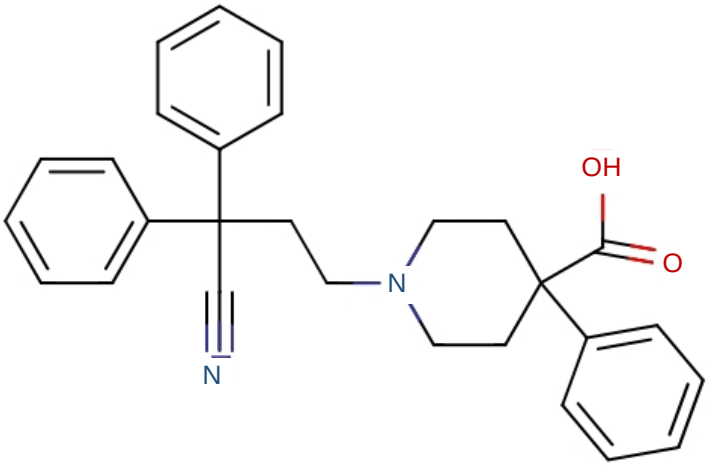
- CNS
  - Fatigue/somnolence
  - Dizziness
- GI
  - Pain, abdominal
  - Nausea/vomiting
  - Dry mouth (xerostomia)
- Endocrine
  - Hyperglycemia

➢ Drug-drug interaction

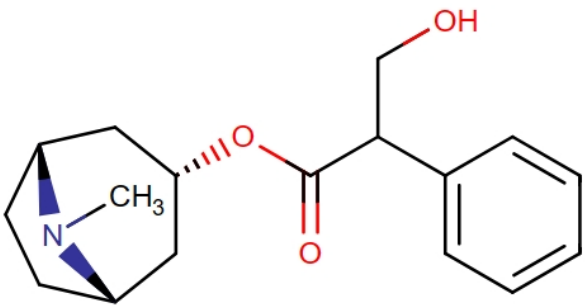
- ↑ risk of K^+ tablets causing pill damage to GI mucosa (due to ↓ transit time → ↑ exposure time of K^+ tablets to damage GI mucosa)

- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Safe

- **Diphenoxylate Hydrochloride / Atropine Sulphate** (Lomotil®)



Diphenoxylate Hydrochloride



Atropine Sulphate

- Indication
  - Diarrhea
    - Tabs 2 po q.i.d., or
    - 10 mL po q.i.d., to maximum of 20 mg/d

- Mechanism of action
  - Blocks acetylcholine release from presynaptic opioid receptors in the enteric nervous system to peristalsis
  - Crosses the blood brain barrier → produces central effects as well as effects on the enteric nervous system
  - Diphenoxylate Hydrochloride
    - Activating peripheral opioid receptors in the small intestine and thereby inhibiting peristalsis
    - Research has suggested that non-opioid receptor pathways exist. This explains its potent antidiarrheal effects despite only limited opioid action
  - Atropine Sulphate
    - Atropine binds to and inhibits muscarinic acetylcholine receptors, competitively blocking the effects of acetylcholine and other choline esters
    - Antagonizes the effects of acetylcholine on tissues innervated by post-ganglionic cholinergic nerves, such as smooth muscle, cardiac tissue, exocrine glands and the central nervous system.
    - Also acts in less innervated smooth muscle that responds to endogenous acetylcholine

- Pharmacokinetics

- Diphenoxylate Hydrochloride
  - Absorption
    - ↑ percentage absorbed, and absorption occurs rapidly
    - Plasma Tmax achieved within 40-60 min
  - Volume of distribution
    - NA
  - Metabolism
    - Metabolism occurs by hydroxylation to form an inactive metabolite.
  - Route of elimination
    - Both drug and metabolites are excreted, mainly as conjugates, in urine and feces.
  - Half-life
    - Elimination T1/2, 24 h
    - Appearance T1/2, 0.82 h
  - Clearance
    - NA

- Atropine Sulphate
  - Absorption
    - IV atropine follows a non-linear pharmacokinetic model at doses between 0.5 and 4 mg
    - IM atropine is well absorbed in the GI tract and rapidly delivered to systemic circulation
      - Adults given 1.67 mg atropine IM, Cmax 9.6 ng/mL and Tmax 3-60 min
      - Bioavailability, 50%
      - Cmax of atropine are higher in women than men (15%)

- Volume of distribution
  - Atropine is distributed throughout the body.
  - Following IV administration, total apparent volume of distribution 1.0-1.7 L/kg
- Metabolism
  - Mainly metabolized by enzymatic hydrolysis in the liver
  - Major metabolites of atropine are noratropine, atropine-n-oxide, tropine, and tropic acid.
  - The metabolism of atropine is inhibited by organophosphate pesticides
- Route of elimination
  - ~13-50% excreted unchanged in the urine
  - In healthy volunteers given IV atropine, 29% tropine was excreted in urine, along with 15% of an unidentified metabolite
- Half-life
  - Following IV and IM doses of atropine, T1/2 ~2-4 h
  - In geriatric patients (65-75 yr), IV atropine has a longer T1/2 (10 h)
  - T1/2 of atropine is slightly shorter (~20 min) in women than in men
- Clearance
  - Total clearance of IV atropine 5.9-6.8 mL/min/kg
  - Exercise before/after IM administration ↓ clearance of atropine

➢ Contraindications/precautions

- Known hypersensitivity to diphenoxylate, atropine, or their components
- Note adverse effects / drug-drug interactions
- GI
  - Diarrhea
    - Severe, acute, bacterial (enterotoxin producing), including C. difficile infection (CDI)
  - Megacolon
  - Jaundice, obstructive
    - May precipitate hepatic encephalopathy

➢ Adverse effects (AEs)

- CNS
  - Dizziness
  - Sedation/somnolence
  - Euphoria

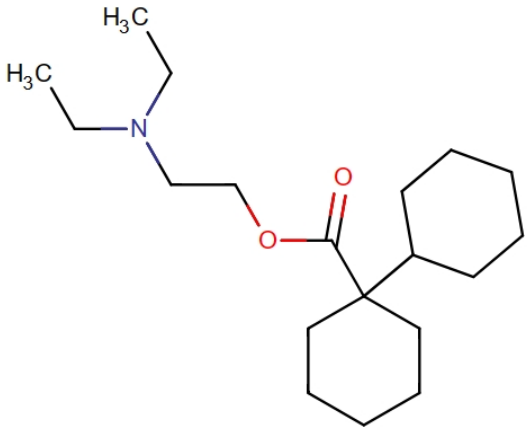
➢ Drug-drug interaction

- Anticholinergic effects of Lomotil® slows GI transit and of K^+ tablets → mucosal ulceration

➢ Peripartum

- Pregnancy
  - Safe
- Lactation
  - Safe

- **Dicyclomine hydrochloride**



➢ Indication

- Diarrhea
  - Dicyclomine 10-40 mg po q.i.d. prn

➢ Mechanism of action

- Direct antimuscarinic activity of the M1, M3, and M2 receptors; and partially through antagonism of bradykinin and histamine
- Non-competitively inhibits the action of bradykinin and histamine, resulting in direct action on the smooth muscle, and ↓ strength of contractions seen in spasms of the ileum

➢ Pharmacokinetics

- Absorption
  - Bioavailability of dicyclomine has not been determined
  - Likely well absorbed as the primary route of elimination is in the urine
  - Tmax 1-1.5 h
- Volume of distribution
  - Volume of distribution for a 20 mg po 3.65 L/kg
- Route of elimination
  - 79.5% eliminated in the urine and 8.4% in the feces
- Half-life
  - Mean plasma elimination T1/2 ~1.8 h

- **Cholestyramine**
  - Binding luminal bile acids (BA) to ↓ pressure of excess BA from ileum to colon to ↓ activity if cGMP and to ↓ secretion of Cl-/Na^+/H_2O
    - Please see next section for further details.

BILE SALT ASSOCIATED DIARRHEA

- The understanding of the enterohepatic circulation (EHC) bile acids is of use to understand the pathophysiology of the complications of interrupting the EHC, such as from ileal disease resection, cholestatic liver diseases, biliary tract disorders, and small intestinal bacterial overgrowth (SIBO).
  - As well, this provides an understanding of using bile salt binding agents, or bile salt supplementation.

➢ Component of the Enterohepatic Circulation (EHC) of Bile Acids (BA)

- Hepatocytes
  - Synthesis
  - Canalicular membrane (CM)
  - Sinusoidal membrane (SM)
- Biliary tract and gallbladder
- Jejunum/ileum
- Microbiome
- Colon
- Maintains the critical micelle concentration (CMC [of BA]) in the lumen of the proximal intestine → facilitates the absorption of lipids.
- Contributes to homeostasis of Chol/BA pool
- BA-dependent / independent flow
- The reabsorption of bile acids mainly from the ileum, their return to the liver, resecretion by the hepatocytes, and return to the lumen of the small intestine represents the EHC.

➢ Function of Bile Acids

- Liver
  - ↑ hepatic secretion of cholesterol (CH) and phospholipids (PL)
  - ↑ bile water flow (choleretic effect)
- Intestine
  - ↑ solubilisation of CH, triglycerides (TG), PL, fatty acids (FA), and fat-soluble vitamins (FSV)
  - Interact with pancreatic colipase to ↑ activity of lipase
- Mucosal defense
  - Jejunum
    - Bacteriostatic
  - Ileum
    - ↑ expression of antimicrobial genes
- Stones
  - Gallbladder
    - ↓ formation of calcium stone
  - Kidney
    - ↓ formation of oxalate stone

- Metabolic function
  - Regulate the enterohepatic circulation (EHC)
  - Signal nuclear and G-protein-coupled receptor → helps to maintain homeostasis of CH, TG, FA, glucose and energy
  - Possibly important in pathogenesis of non-alcoholic liver disease/steatohepatitis (NAFLD/NASH)

- Bile Acids and Bile Salts
  - Bile acids (BA)
    - Protonated
      - H-BA
    - Neutral
      - BA ‘BA
    - Deprotonated
  - Conjugation
    - BA are conjugated
      - Glycine, taurine (BA-Z)
      - Sulphate, gluconate (BA-Y)
  - Terminology
    - Bile acids
      - H-BA
      - BA
    - Bile Salts
      - BA^-
      - BA-Z
      - BA-Y

- BA Metabolism
  - Size of BA pool
    - 2 g to 4 g (50 to 60 mmol per kg body weight)
  - Cycles of BA pool
    - 2x to 3x per meal
    - 6x to 10x per day
  - Absorption of BA per day
    - 10 to 30 g (pool size x number of cycles)
    - Absorption efficiency >95%
  - Colonic loss of BA per day
    - 200 to 600 mg
    - Some BA metabolism results from the luminal microbiome
  - Hepatic synthesis of BA per day to match daily fecal losses
    - >> 95%

- Hepatocyte Synthesis of Primary (1^o) BA

Hepatocyte	Synthesis of Bile	
CH →	Primary bile acids	Cholic acid (CA) (3 OH-) Chenic acid (CDCA)* (2 OH-)

  - 7-α hydroxylase (rate controlling enzymes, CYP7A1)

*Chenic acid, aka chenodeoxycholic acid (CDCA)

- Daily synthesis of 1º BA by liver balances daily loss of BA into the colon
  - ~ 500 mg of BA synthesized daily
  - ~ 500 mg of BA lost in colon daily

- The Liver Zones and EHC

Liver, Zone	BA Absorption	BA Secretion
Zone I, periportal	During fasting	Recycle BA
Zone III, pericentral (aka perivenous)	During feeding	Newly synthesized BA

➢ Synthesis

- Hepatocytes
  - Cholic/chenic BA synthesized in hepatocytes from cholesterol (CH)

    ↓ 7α-hydroxylase
  - 1º cholic/chenic BA

    ↓
  - Conjugated to glycine (adults) / taurine (children)

    ↓
  - Binding proteins / vesicles to traffic canalicular membrane (CM)
  - Conjugated BA cross CM by
    - Bile salt export protein (BSEP)
    - Multidrug resistance associated protein -2

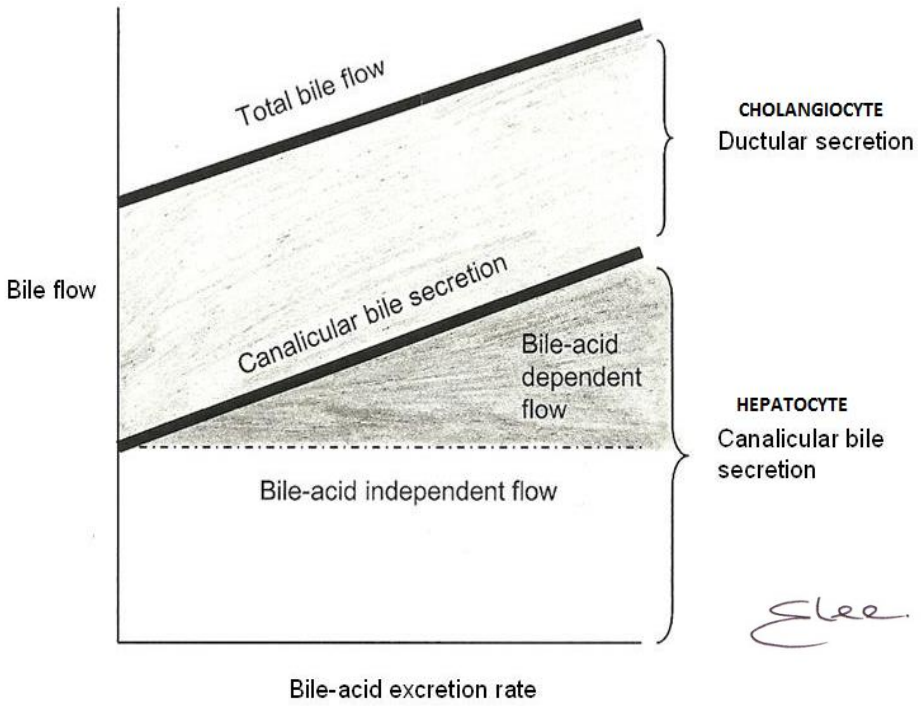
    } Common hepatic duct (CHD; exposure to cholangiocytes)

- Cholangiocytes
  - Secretion of Cl-/H_2O → dilute hepatic bile by way of
    - Bile acid dependent flow (BADF) and
    - BA independent flow (BAIF)
  - Basolateral membrane (BLM, cholangiocytes)
    - Transporters
      - Na^+/K^+ ATPase, Na^+/K^+ exchangers
      - Na^+/H^+ exchangers (NHE)
      - Na^+/HCO_3- cotransporter
      - K^+ channel

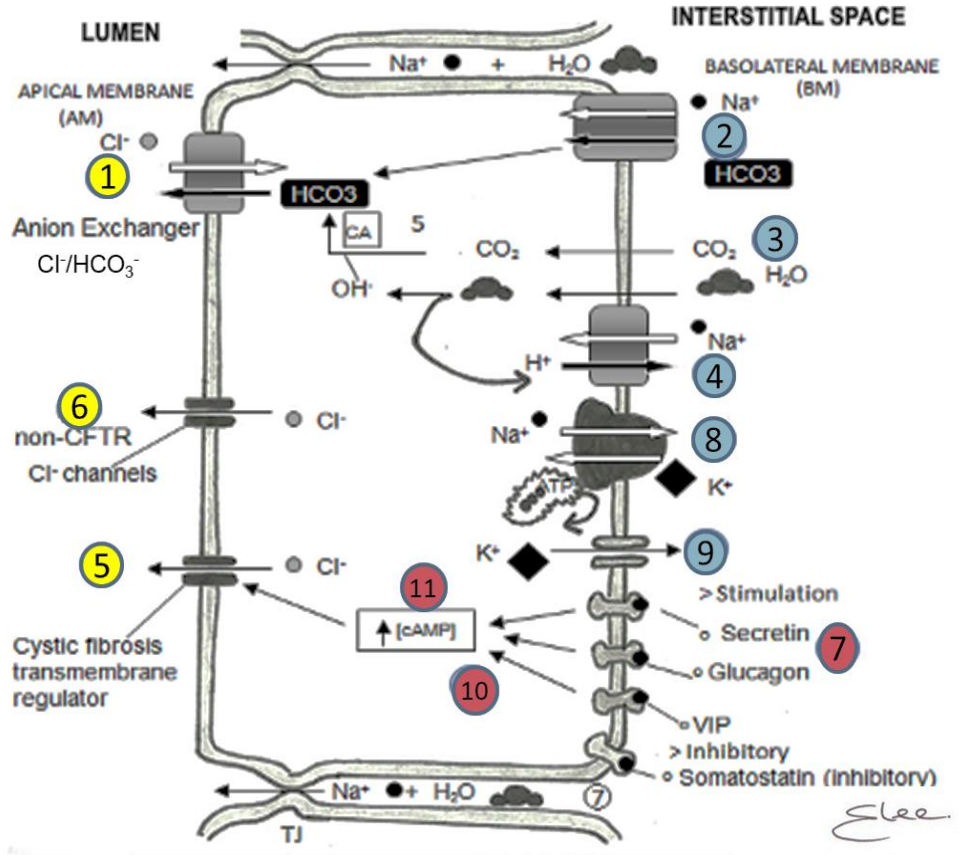
- Modifiers of intracholangiocytes
  - ↑ secretion
    - Glucagon
    - Secretin
    - Vasoactive inhibitory polypeptide (VIP)
  - ↓ secretion
    - Somatostatin (SST)
- Apical Membrane Transporters
  - Cl- channel
    - Cystic fibrosis transmembrane regulators (CFTR)
    - Non-CFTR
  - Anion exchanger, Cl-/HCO_3-)

➢ Bile Acid Independent and Dependent Bile Flow

- Basal
  - Bile acid independent secretion
    - Hepatocyte
- Stimulated
  - Bile acid dependent secretion
    - Hepatocyte CM
    - Cholangiocytes ductular



Cholangiocytes Secretion of Salt and Water



Abbreviations: CA, carbonic anhydrase; CFTR, cystic fibrosis transmembrane regulator; CHD, common hepatic duct; TJ, tight junction

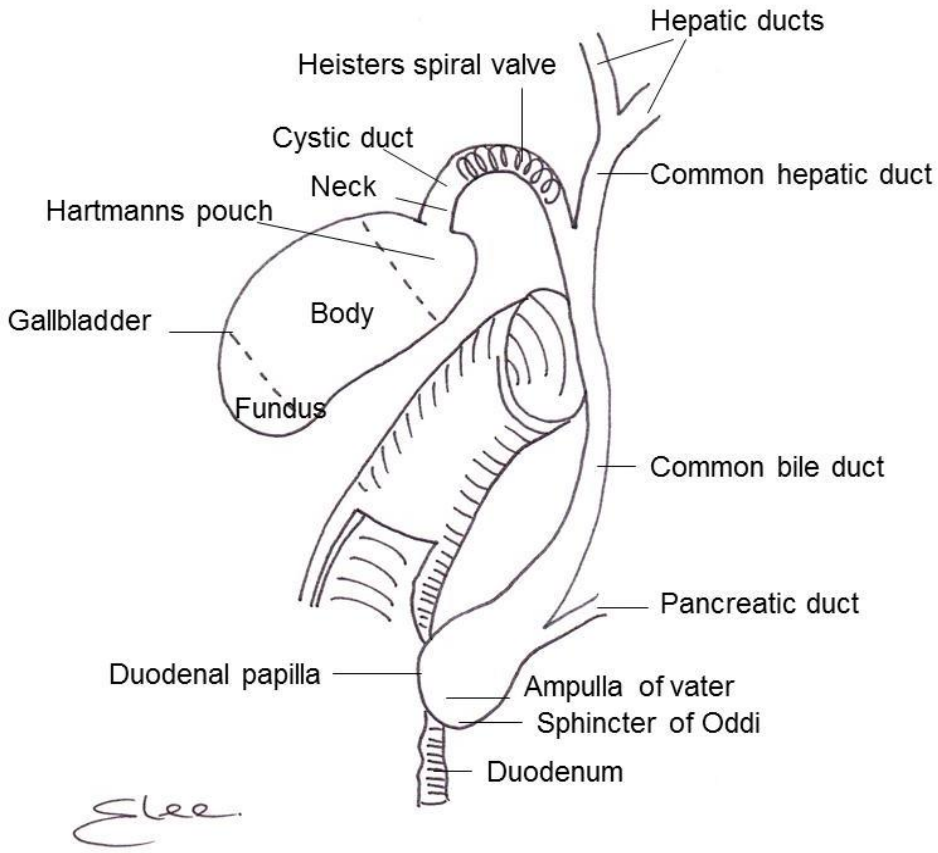
Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-11, page 996.

- Bile Flow
  - Common hepatic duct (CHD)
    → Common bile duct (CBD)
    → Gallbladder (GB)
    → Absorption of H_2O: ↑BA concentration in GB bile vs. hepatic BA
    → Timed contraction → release of concentration BA in response to cholecystokinin (CCK)

    - BA flow through the sphincter of Oddi and into lumen of duodenum

- Hepatic Bile Flow: Gallbladder (GB), Common Bile Duct (CBD)
  - Hepatic bile flows down common hepatic duct (CHD)
  - From CHD, dilute hepatic bile flows
    - ~½ into common bile duct (CBD)
    - ~½ into cystic duct and the into gallbladder (GB)
      - Concentrated bile from absorption of Na^+ / H_2O by GB epithelium

- Gallbladder Anatomy



Adapted from: Sherlock and Dooley, Figure 1.6, page 3, 11th Edition, 2002

- Bile Salt Micelles
  - Bile salts (BS)

  - Bile salts (BS)

↑[BS] —(Critical micellar concentration (CMC))→ BS micelles, simple —(FA, BG, PL, Chol)→ Mixed BS micelles (MBSM)

  - MBSM → BBM → Diffuse / CD36 (FAT) / FATP → Lipids in MBSM → Enterocyte cytosol
  - BBM → BSM, MBSM, Reform MBSM
  - Because of low rate of passive diffusion in jejunum lumen to shuttle lipids to BBM, return to lumen solubility more lipid (SBSM → MBSM)

  - Simple (SBSM) / Mixed Bile Salt Micelles (MBSM)
    - The concentration of BAs which is required to form the simple bile salt micelle (SBSMs) is known as the “critical micellar concentration” (CMC) of BAs.
    - These SBSM solubilize the lipid digestive products in the intestinal lumen (fatty acids [FA], B-glycerol [BG], phospholipids [PL], free cholesterol [CHOL]), forming mixed BSM (MBSM).

  - MBSM, FAT, FABT
    - MBSM diffuse across the unstirred water layer (UWL) on the luminal side of the jejunal enterocyte brush border membrane (BBM).
    - The lipids solubilized in the BBM are absorbed by
      - Passive diffusion
      - Carrier-mediated uptake by FAT (CD36) and FATP
    - MBSM → SBSL → shuttles back jejunal lumen to solubilize more lipids → MBSM → jejunal enterocyte BBM
      - The 1^{o} / 2^{o} BA are poorly absorbed in the jejunum (jejunal enterocytes lack FAT/FATP → this maintains a high luminal concentration of BA (CMC)
    - The microbiome metabolizes a small proportion of these 1^{o} BAs, cholic and chenic acid

- Microbiome
  - Deconjugation
  - Dehydroxylation

1° BA (Liver) → 2° BA (Lumen) ⇢ 3° BA (UDCA)

Cholic (CHO) ⇢ Deoxycholic (DCA)

Chenic (CHE) ⇢ Lithocholic (LCA)

Digestion, Absorption, and Metabolism of Lipids (TAG, CH, PLs)

- Fatty Acids (FA): BBM
  - Hepatic bile (dilute) → Gallbladder (GB, concentrated) $\xrightarrow{CCK}$ Simple micelles (SM) $\xrightarrow{CK}$ GB contraction: GB bile empties into lumen of duodenum
  - ↑BA concentration to CMC → concentrated BA → mixed micelles by solubilizing fatty acid (FA), monoglyceride (MG), phospholipid (PL), Cholesterol (CH)
  - MM diffuses through UWL to intestinal BBM
    - → CD36
    - → FATP4

    Transporters, low fat diet
    - → Passive diffusion
      - High fat diet
    - Crosses BLM into lymphatics
  - Intra enterocyte-binding of FA
    - FABP1 binding ligands
    - FABP2 binds FA

    Endoplasmic reticulum (ER): free fatty acids (FA) conversion to acyl-CoA → TAG synthesis → binding lipoproteins

➢ **Enterocyte Metabolism**

- Long Chain Fatty Acid (LCFAs; > 16 Cs)
  - MAG plus FA → DAG (1, 3 glycerol) + FA → TAG (1, 2, 3 glycerol fatty acyl-CoA mono-/diacylglycerol transferase)
- Medium Chain Fatty Acids (MCFA; 6-12 Cs)
  - MCFA-diffuse across BLM → bind to albumin in portal blood → uptake across hepatocyte sinusoidal membrane (SM) → hepatic oxidation/formation of VLDL
    - MCFA's different metabolism than LCFAs
      - No BA/micelles
      - No acetylation
      - No use of transporters/lymphatics

- Lysophospholipids (LPLs) →
  - Phospholipids (PLs)
  - Acyl transferase: LPCAT3 for esterification of lysophosphatidylcholine to phosphatidylcholine (PC)
  - Lumen – Solubilized mixed micelles (MM)
  - BBM – Passive uptake
  - Cytosol – LPL + FA (fatty acids)
    - Caveolin-1 containing endocytic vesicles → activation of protein kinase C2 (PKC 2) → traffics to endoplasmic reticulum (ER)
  - ER – Re-esterification
    - FA + LPL → phospholipids (PL)
    - FA + MA (monoacylglycerol) → TAGS (triacylglycerol [triglyceride])

- Cholesterol (CH)
  - Intracellular CH plus FA →
    - Esterified CH (E-CH)
    - Acyl-CoA cholesterol acyl transferase
  - Low CH Diet
    - SRBI
      → Activates MAP kinase → ↑ apo B trafficking to from TAG-rich lipoprotein
    - NPC11
      → Transport across BBM
      → Release of endocytic signal → interacts with numb protein to activate ER machinery
        - FABP2 binds FA
  - High CH Diet
    - Passive uptake of Chol/FSV
    - CH-HDL transported across BLM by ABCA1 into lymphatics
  - BLM
    - FA/CH bind to Apo 5 to diffuse to BLM
    - FA-LP diffuse across BLM into lymphatics
    - CH-LP (HDL) (an Apo-1) transported by ABCA1 in BLM

- Conjugation of 1º BA: BA-Z/BA-Y, CM-BSEP
  - The unconjugated 1º BA cholic and chenic acids are conjugated to the amino acids glycine (in adults) or taurine (in children)
  - When bile acids (BA) are conjugated in the liver to the amino acids (glycine and taurine), the conjugated BAs become more hydrophilic and less hydrophobic, so then passive absorption of the conjugated BA in the proximal intestine is less.

- BA-Z / BA-Y synthesized and conjugated in liver cytoplasm are attached to binding proteins → traffic in vesicular pathway to hepatocyte canalicular membrane (CM) → transported by
  - BSEP (bile salt export protein) into the common hepatic duct (CHD).
  - Multidrug resistance-associated protein-2 (MRP2)

- Reverse Cholesterol (CH) Transport
  - CH transported from blood, across BLM into enterocyte across BBM, and back into gut lumen.
    - Called direct transintestinal cholesterol excretion (TICE)
      - Accounts for ~25% of fecal Chol
    - Influenced by nuclear receptor FXR / PPARγ

Abbreviations: ABCA1, ATP-binding cassette transporters A1; BBM, brush border membrane; CH, cholesterol; ER, endoplasmic reticulum; FSV, fat soluble vitamins; FXR, farnesoid x receptor agonist; MG, monoglyceride; MM, mixed micelle; SRB1, scavenger receptors class B type 1; SM, simple micelle; PPARγ, peroxisome proliferation activated receptor γ; TAG, triacylglycerol (triglyceride)

- Enterocyte Endoplasmic Reticulum (ER), Golgi Apparatus (GA)
  - Esterified TAGs, E-CH, PLs →
    - Cytosolic lipid droplets (CLD) → enlargement of CLD by perilipins
      - CLD lipophagy by autophagosome-mediated lysosome acidic lipase (LAL) → to ER
  - Prechylomicron transport vesicles (PCTV) → budding of PCTV → fatty acid binding protein (FABP1) → ER protein →
    - TAGs/OGs, CE, PL bind to
    - Lipid binds to Golgi apparatus membrane binding proteins
      - RBET
      - VT II A
      - Syntoxins
      - SNARE (PCTC soluble n-ethylmaleimide-sensitive factor attachment protein receptor

      } Fusion of PCVT with Golgi
  - PCVT plus GA bind to Apo-A1 —glycosylated apo B-48→ ↓chylomicron to BLM → exocytosis → intercellular spaces / lymphates

- Gallbladder (GB): Function
  - Stores hepatic bile
  - Concentrates hepatic bile (absorption of H_2O)
  - CCK released from food in the duodenum
    → Contraction of smooth muscle in wall of gallbladder
    → Release of concentrated gallbladder bile into common bile duct (CBD), and then through sphincter of Oddi) into duodenum

- Small Intestine: Luminal Bacteria and Deconjugation of BA
  - The content of bacteria in the intestinal lumen (microbiome) increases from the proximal to the distal small intestine
    - Jejunum 10^{-3} organisms/HPF (high power field)
    - Ileum 10^{-8}
    - Colon 10^{-12}
  - Bacteria in the terminal ileum and colon deconjugate bile salts (BA-Z) to form bile acids (H-BA).
    - Deconjugation → Ileal absorption of BA (passive diffusion much less efficient than by ASBT)
  - Bacteria also
    - Dehydroxylate (7α-dehydroxylation) the primary bile acids secreted by liver (cholic and chenic acids) → secondary (2^o) bile acids (BA) deoxycholic (DCA) and lithocholic (LCA), respectively.
  - The 2^o BA may be dehydroxylated again by intestinal bacteria into the tertiary (3^o) bile acids.
    - 2^o /3^o / deconjugated BA are less efficiently absorbed by ASBT.

Secondary (2^o) and Tertiary (3^o) Bile Acids

- 2^o bile acids (BA)
  - Formed by dehydroxylation of 1^o BA by bacterial action
  - Deoxycholic 2 OH^-
  - Lithocholic 1 OH^-
- 3^o bile acids (BA)
  - Formed from 2^o BA by further bacterial dehydroxylation
  - Enteric bacteria also epimerize the 7α-hydroxy group of chenic acid (CDCA) → UDCA (ursodeoxycholic acid) 3α, 7β-dihydroxy BA)
- 1^o, 2^o, 3^o BA recycle in EHC

- EHC and the Colon
  - About 95% of BA in the lumen of the intestine are reabsorbed and recycled to the liver, representing the high efficiency of the EHC.
  - The ~5% of the luminal bile acids that are not reabsorbed pass into the colon.
  - Colonic bacterial 7α-hydroxylate produce 2^o from 1^o bile acids:
  - CA → DCA (50% absorbed by colon)
  - CDA → LCA / UDCA

- BA Reabsorption
  - As the 1º/2º/3º BAs pass by peristalsis along the length of the small intestine → ↓ exogenous/ endogenous lipids to be absorbed
  - The BAs need to be reabsorbed.
  - 95% of 1º/2º/3º BA are reabsorbed by the ileocytes
    - ~5% are spilled into colon

- Ileum – ASBT
  - Once the lipids have been absorbed in the proximal small intestine, the BA pass into ileum.
  - Conjugated bile acids (BA-Z) are actively transported across the ileocyte BBM by ASBT (apical sodium bile acid transporter).
  - ~95% of luminal BA are taken up into the ileocyte cytosol by ASBT (the remaining ~5% are spilled into the colon)

- Ileum – FXR / FGF19, OCTα/β
  - BA bind in ileocyte cytosol to BA-FXR / FGF19
  - The BA-FXR / FGF19 complex is transported across the basolateral membrane (BLM) of the ileocyte by OSTαβ and then into the portal vein (PV) blood → SM of hepatocytes
  - BA-FXR / FGF19 are transported by sodium taurocholate cotransporting polypeptide (NTCP) in the hepatocyte sinusoidal membrane (SM)

- Liver: NTPC, 7α-hydroxylase, FXR/FXF19
  - The 1º / 2º/ 3º BAs which are taken by the hepatocyte sinusoidal membrane (SM) transporter NTPC and mix with newly synthesized BAs.
  - The FGF activated a nuclear bile acid receptor → initiates a phosphorylation cascade → transcriptional repression of gene which encodes cholesterol 7α-hydroxylase → ↑ hepatocyte synthesis of 1º BA in liver from CH.
  - Rate of conversion of CH to BA determined by 7α-hydroxylase activity (rate-limiting steps in EHC) and FXR/FGF19

↓BA absorption → ↑ 7α hydroxylase (CYP7A1) → ↑ cholesterol conversion to BA to replate BA lost through ↓ BA absorption

  - Activity of 7α-hydroxylase (CYP 7A1) determined by amount of ileocyte FXR/FXF19 in portal blood returning to liver.
    - FXR/FXF19 determined by ileocyte cytoplasmic [BA]

Control of EHC of BA

- ↓BA absorption into ileocyte by ASBT → ↓ BA – FXR/FGF19 complex → ↓ BA – FXR/FGF12 in PV → ↓ uptake across hepatocyte SM by NTCP → ↓ hepatic cytosol BA-FXR/FGF19 → ↓ inhibition / ↑ activity of CYP 7A1 / 7α hydroxylase → ↑ conversion of CH to BA to restore BA lost by normal spillage of BA into colon from 5% non-absorption of BA by ileocytes.

➢ Clinical Correlation

- Loss of Ileal Function
  - In patients with ileal dysfunction or resection, there will be ↓ absorption of the BA across the BBM of the ileal enterocytes →
  - ↓ concentration of BA in the ileal enterocyte → ↓FXR / ↓FGF 19 formation and release →
  - ↓ FGF 19 → ↓ hepatic activation of FGFR4/β-klotho receptor → ↑7α-hydroxylase activity → ↑ synthesis of 1° BA from cholesterol
  - ↑ BA in lumen
    - ↑ spillage into colon → ↑ cGMP → ↑ secretion of Cl- / H_2O “diarrhea”

Abbreviations: BA, bile acid; cGMP, cyclic GMP; Cl-, chloride; FXR, farnesoid x receptor; FGF19, fibroblast growth factor 19; H_2O; water

- Surgical Resection
  - Loss of < 100 cm of terminal (ileum)
    - If there is only mild lose of ileal absorption capacity, such as from resection of less than 100 cm of the terminal ileum (as would often be done in persons with Crohn disease), there will be
      - A small decrease of FGF 19, FGFR4/β-klotho → ↑activity of 7α-hydroxylase which may be sufficient to increase primary BA synthesis enough so that CMC of BA is maintained → no fat malabsorption.
      - Small ↑/loss of BA into colon → water diarrhea
  - Loss of > 100 cm terminal ileum
    - Loss of BA into the colon is so great, that the ↑activity of 7α-hydroxylase cannot produce sufficient 1° BA (rate-limitation), CMC is not maintained, and
      - There will be fat malabsorption (steatorrhea)

- Inherited Transporter Defects in EHC
  - ASBT
    - Primary bile acid metabolism (PBAM)
  - BSEP (↓ bile acids)
    - BRIC syndrome, type 2
    - PFIC type 2
    - Intrahepatic cholestasis of pregnancy (ICP)
  - F1C1
    - Benign (type 1) recurrent intrahepatic cholestasis (BRIC) syndrome
    - Progressive familial intrahepatic cholestasis (AFIC) [amino phospholipids]
  - MDR3
    - Low phospholipid-associated cholelithiasis (LPAC)
    - Intrahepatic cholestasis of pregnancy (ICP)
    - MDR3 (ABCB4) deficiency (amine phospholipids) [PFIC type 3]

- Sinusoidal Membrane (SM)

	Solute	Transporter	Disease
Entry	BA- OA-	ASBT	RS
Exit	BA-	OSTαβ MRP2 MRP4	PBAM DJS

- Canalicular Membrane (CM)

	Solute	Transporter	Disease
Exit	APL	FICI (ATP8B1)	BRIC, T1; PFIC, T1
	BA-	BSEP (ABCB4)	BRIC, T2; PFIC, T3; ICP
	OA-	MRP2 OATP1B1 OATP1B3	DJS SLCO1B1 SLCO1B3
	CHOL	ABC G5/G8	-
	PC	MDR3 (ABCB4)	LPAC, PFIC, T3; ICP

➢ Inborn Errors of Bilirubin Metabolism

Gene Abnormality	Disorder	Defective Transporter
○ MRP2 (ABCC2)	− Dubin-Johnson Syndrome (DJS)	▪ Organic ion conjugate
○ OATP1B1 (SL01B1)	− Rotor syndrome (RS)	▪ Organic ion conjugate
○ ASBT (SLC10A2)	− Primary bile acid	▪ Bile acids
○ OSTB (SLC51B)	− Malabsorption (PBAM)	

Modified from: Sleisenger and Fordtran's Gastrointestinal and Liver Disease 2020, Edition 11th

- Cholangiocyte Transport of Bile Acids (BA-)
  - Into cholangiocyte from bile duct lumen − ASBT
  - Out of cholangiocyte into portal blood − MRP3 − OSTαβ

Abbreviations: ASBT, apical sodium bile salt transporter; BA, bile acid; H^+, hydrogen; UDCA, ursodeoxycholic acid

- Cholangiocyte Secretion of Cl-, HCO_3- and H_2O
  - Cl- out CFTR (cystic fibrosis transmembrane)
  - Cl- in − AE2 (anion exchange
  - HCO_3- out − HCO_3- isoform 2; Cl-
  - H_2O out AQ (aquaporin isoforms)

- Cholestasis
  - With rapid bile salt transport into and out of the cholangiocytes through the periductular capillary plexus (cholehepatic shunt) →
  - ↑ secretion of HCO_3- by AEs → ↑H_2O movement through aquaporin isoforms to ↑secretion of bile (cholestasis)

- Choleretic Effect of ursodeoxycholic acid (UDCA)
  - HCO_3-, this rapid reabsorption / UDCA → ↑ flow of bile/water (choleresis)

➢ Aide to Memoire: BA Transport Proteins

Cell Type	BBM/SM	BLM/CM	Cytosol
○ Ileocyte	– ASBT (apical sodium bile acid transporter)	▪ OST αβ (organic solute transporter)	– FXF19 (fibroblast growth factor 19) – FXR (farnesoid X receptor)
○ Hepatocyte	– NTCP (Na^+-taurocholate cotransporting polypeptide)	▪ BSEP (bile salt export pump)	
○ Cholangiocyte	– ASBT	▪ OST α/β	
○ Renal proximal tubular cell	– ASBT	▪ OST α/β	

Abbreviations: ASBT, apical sodium bile acid transporter; BBM, brush border membrane of ileocyte; BLM, basolateral membrane of ileocyte; CM, canalicular membrane; SM, sinusoidal membrane

❖ **Bile Salt Binding Agents**

- **Cholestyramine** (Questran®)

➢ Indication

- ○ Bile salt wastage syndrome
- ○ C. difficile infection
- ○ Hypercholesterolemia
- ○ Pruritis from cholestasis

➢ Mechanism of Action

- ○ Binding of bile acids in intestinal lumen → ↓ ileal absorption → interruption of enterohepatic circulation → ↓ delivery of excess bile salts into colon → ↓ cGMP → ↓ secretion of Cl-/H_2O.

➢ Pharmacokinetics

- ○ Absorption
  - − Not absorbed from the GI tract following oral administration
- ○ Volume of distribution
  - − NA
- ○ Metabolism
  - − Bile acids

- Route of elimination
  - Cholestyramine resin adsorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the feces
- Half-life
  - 6 min

➢ Contraindication/precautions
- Known hypersensitivity to cholestyramine, bile salt binding agents, or any components of their formulation.
- Adverse effects / drug-drug interactions (warfarin toxicity)
- Biliary tract obstruction, complete
- Colon obstruction / impaction

➢ Adverse effects
- GI
  - Nausea/vomiting
  - Abdominal pain
  - Flatulence
  - Constipation/diarrhea
  - Deficiency of fat-soluble vitamins (A, D, E, and K)
- Blood
  - Hypoprothrombinemia
    - Bleeding disorders
    - Clotting disorders

➢ Drug-drug interaction
- ↑ effect of warfarin to ↑ INR
- ↓ effect of
  - Amiodarone
  - Leflunomide
  - Raloxifene
  - Thyroid hormones

➢ Peripartum
- Pregnancy – Safe
- Lactation – Safety not known

- **Colestipol**
  - Colestipol has similar characteristics to cholestyramine, with additional adverse effect of hepatoxicity

GASTROENTERITIS

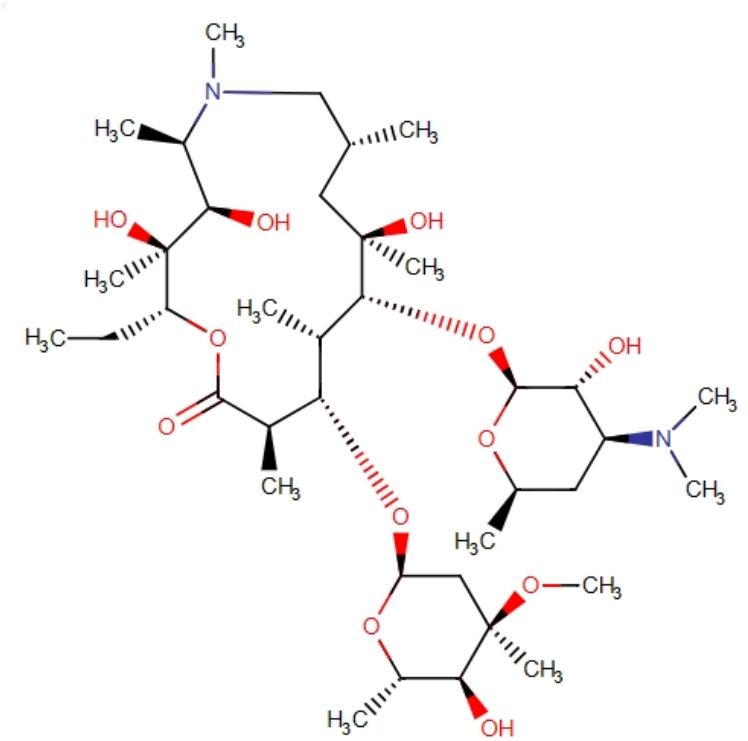
- Commonly Causative Microorganisms

	Antibiotic Sensitivity
○ E. Coli	– Ciprofloxacin – Trimethoprim (TMP) / Sulfamethoxazole (SMX; Bactrim®)
○ Shigella	– Azithromycin – Ciprofloxacin – TMP/SMX (Bactrim®)
○ Salmonella	– Amoxicillin – Ciprofloxacin – Levofloxacin – TMP/SMX (Bactrim®) – IV ▪ Cefotaxime ▪ Ceftriaxone
○ Campylobacter	– Ciprofloxacin – Erythromycin
○ Yersinia	– Ciprofloxacin – TMP/SMX (Bactrim®) – IV Ceftriaxone
○ Vibrio cholerae	– Azithromycin – Ciprofloxacin – Doxycycline – Erythromycin – Tetracycline
○ Clostridium difficile (to be discussed in detail later)	– Metronidazole – Vancomycin

➢ Antibiotics used for various enteric organisms

Organisms	Campylobacter	E. Coli	Salmonella	Shigella	Vibrio cholerae	Yersinia
○ Azithromycin	+			+	+	
○ Ceftriaxone / Cefotaxime (IV)			+			+
○ Ciprofloxacin	+	+	+	+	+	+
○ Doxycycline					+	
○ Erythromycin	+				+	
○ Levofloxacin			+			
○ Tetracycline					+	
○ TMP / SMX		+	+	+		+

- **Azithromycin**



- Mechanism of action
  - Inhibit bacterial protein synthesis by preventing the transit of aminoacyl-tRNA and the growing protein through the ribosome.

- Pharmacokinetics
  - Absorption
    - Bioavailability of azithromycin is 37% following oral administration.
    - Absorption not affected by food
    - Macrolide absorption in the intestines is believed to be mediated by P-glycoprotein (ABCB1) efflux transporters, which are known to be encoded by the ABCB1 gene
  - Volume of distribution
    - Azithromycin po is widely distributed in tissues with an apparent steady-state volume of distribution of 31.1 L/kg
    - Measured in the tissues higher than in plasma or serum
    - The lung, tonsils and prostate are organs have shown a particularly high rate of azithromycin uptake
    - Concentrated within macrophages and polymorphonucleocytes, allowing for effective activity against Chlamydia trachomatis
    - Concentrated in phagocytes and fibroblasts contributing to distribution to inflamed tissues
  - Metabolism
    - Eliminated by the liver
  - Route of elimination
    - Biliary excretion, primarily as unchanged drug, is a major route of elimination.
    - Over a 1 wk period, ~ 6% found as unchanged drug in urine
  - Half-life
    - Terminal elimination T1/2: 68 h
  - Clearance
    - Mean apparent plasma clearance 630 mL/min (following single 500 mg po and IV dose)

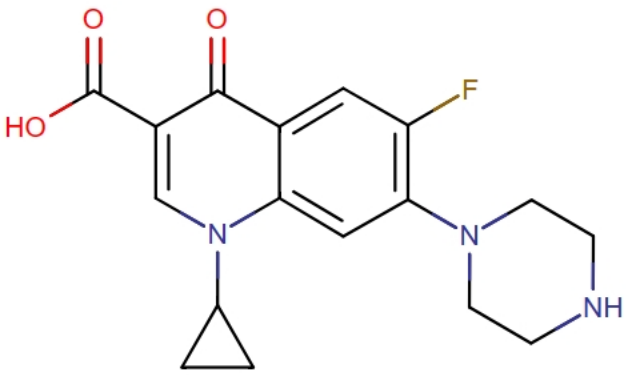
- Contraindication/precautions
  - Known sensitivity to azithromycin or any component in their formulation
  - Adverse effects / drug-drug interaction
  - Hepatic/renal dysfunction
  - CNS
    - QTc dysfunction

- Adverse effects
  - CVS
    - ↑ QTc prolongation
  - GI
    - Nausea/vomiting
    - Abdominal pain
    - Diarrhea / CDI / PMC
    - Cholestatic jaundice
  - Skin
    - Angioedema
    - Pruritis
    - Steven-Johnson syndrome (SJS)

- Drug-drug interaction
  - ↑ QTc risk when used with
    - Anti-arrhythmic class IA/III
    - Cisapride
    - Chloroquine
    - Droperidol
    - Erythromycin
    - Flecainide
    - Haloperidol
    - Methadone
    - Pentamidine
    - Phenothiazines
    - Pimozide
    - Ranolazine
    - Ziprasidone

Abbreviations: CDI, Clostridium difficile infection; PMC, pseudomembranous colitis; SJS, Steven-Johnson syndrome

- **Ciprofloxacin** (Cipro®)



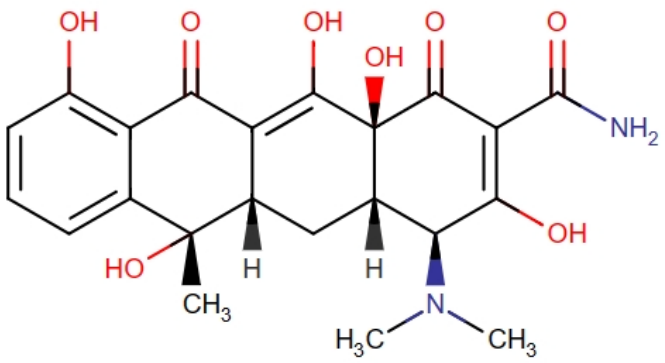
- Mechanism of action
  - Targets the alpha subunits of DNA gyrase prevents it from supercoiling the bacterial DNA which prevents DNA replication
- Pharmacokinetics
  - Absorption
    - 250 mg po reaches an average Cmax of 0.94mg/L, Tmax 0.81 h with an average area under the curve of 1.013L/h*kg
    - Oral bioavailability 70-80%
  - Volume of distribution
    - 3 compartment distribution model with a central compartment volume of 0.161L/kg and a total volume of distribution of 2.00-3.04 L/kg
  - Metabolism
    - Primarily metabolized by CYP1A2 or oxociprofloxacin and sulociprofloxacin make up 3-8% of the total dose each
    - Ciprofloxacin is also converted to the minor metabolites desethylene ciprofloxacin and formylciprofloxacin. These 4 metabolites account for 15% of a total oral dose.
  - Route of elimination
    - 27% recovered unmetabolized in urine compared to 46% of IV dose
    - Collection of radiolabelled ciprofloxacin resulted in 45% recovery in urine and 62% recovery in feces
  - Half-life
    - Average T1/2 of 250 mg oral dose was 4.71 h and 3.65 h following a 100 mg IV dose
  - Clearance
    - Average renal clearance after a 250 mg po is 5.08 mL/min*kg
    - Following a 100 mg IV dose
      - Average total clearance is 9.62 mL/min*kg
      - Average renal clearance is 4.42 mL/min*kg
      - Average non renal clearance is 5.21 mL/min*kg
- Contraindication/precautions
  - Known sensitivity to ciprofloxacin or any component in their formulation
  - Adverse effects / drug-drug interaction
  - CNS – ↑ myasthenia gravis-associated weakness
  - MSK – Tendonitis
    – Tendon (Achilles) rupture

- Adverse effects
  - GI
    - Nausea/vomiting
    - Diarrhea
    - ↑ rate of gastric emptying
    - Hepatotoxic (↑ALT/ ↑AST)
  - GU
    - ↑ Cr_s (↑ serum creatinine)
  - Skin
    - Rash

- Drug-drug interaction
  - ↓CYP1A2 ↑/↓toxicity
    - Cisapride
    - Imipramine
    - Ondansetron
    - Warfarin
- Peripartum
  - Pregnancy – Safe
  - Lactation – Do **not** use

- **Erythromycin** (please see previous section)

- **Tetracycline (doxycycline)**



  - The characteristics (contraindications/precautions, adverse effects / Drug-drug interactions are similar for tetracycline and for doxycycline
    - Additional features for doxycycline and noted in brackets)

- Mechanism of action
  - Passively diffuses through porin channels in the bacterial membrane and reversibly binds to the 30S ribosomal subunit, preventing binding of tRNA to the mRNA-ribosome complex, and thus interfering with protein synthesis.

- Pharmacokinetics
  - Absorption
    - Bioavailability < 40% when administered IM, 100% IV, and 60-80% po (fasting adults).
    - Food and/or milk reduce GI absorption of oral preparations of tetracycline ≥ 50%
  - Volume of distribution
    - NA
  - Metabolism
    - Not metabolized
  - Route of elimination
    - Concentrated by the liver in the bile and excreted in the urine and feces at high concentrations in a biologically active form
  - Half-life
    - 6-12 h
  - Clearance
    - NA

- Contraindication/precautions
  - Known sensitivity to tetracycline/doxycycline or any component in their formulation
  - Adverse effects / drug-drug interactions
  - Pregnancy
  - Sunlight/ UV light (doxycycline)
  - Hepatic / renal dysfunction
  - History of or predisposition of
    - Candidiasis
    - ↑ ICP (intracranial pressure e.g., papilledema, pseudotumour, cerebri [doxycycline])

- Adverse effects
  - CNS
    - Headache
  - CVS
    - Pericarditis
  - GI
    - Abdominal pain
    - Hepatotoxicity
    - Nausea/vomiting
    - Pancreatitis
    - Pill esophagitis
  - Blood
    - Anemia, hemolytic
    - Neutropenia
    - Thrombocytopenia
  - MSK
    - Arthralgias

- Skin
  - Discoloration
  - Erythema multiforme (EM)
  - Photosensitivity
  - Rash
  - Steven-Johnson syndrome (SJS)

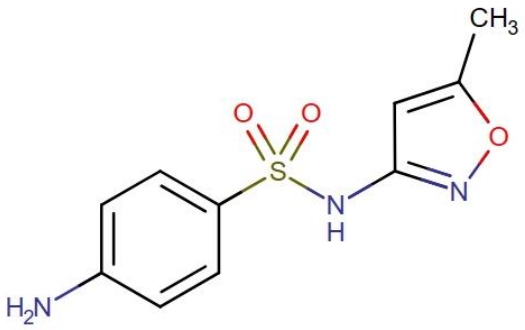
➢ Drug-drug interaction

- ↑ blood concentrations / ↑ toxicity of
  - Barbiturates
  - Carbamazepine
  - Rifabutin
  - Rifampin
- ↑ QT prolongation when used with
  - Amiodarone
  - Cisapride
  - Droperidol
  - Phenothiazines
  - Pimozide
  - Quinidine
  - Ranolazine

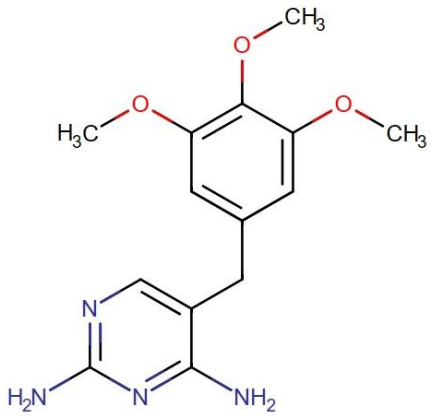
➢ Peripartum

- Pregnancy – Safe
- Lactation – Safety uncertain

- **Trimethoprim-Sulfamethoxazole** (TMP/SMX; Bactrim®)



Sulfamethoxazole



Trimethoprim

➢ Mechanism of action

- Sulfamethoxazole inhibits conversion of p-aminobenzoic acid to dihydropteroate.
- Trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate
- Trimethoprim-sulfamethoxazole synergistically blocks sequential steps in bacterial folate metabolism, which leads to bactericidal effect.

➢ Pharmacokinetics

- Sulfamethoxazole
  - Absorption
    - Rapidly absorbed following oral administration with bioavailability of 85-90%.
    - Tmax ~1-4 h following po administration
    - Cmax at steady-state is 57.4 - 68.0 µg/mL
  - Volume of distribution
    - Volume of distribution following a single oral dose 13 L
    - Distributes into sputum, vaginal fluid, middle ear fluid, breast milk, and the placenta
  - Metabolism
    - Mediated primarily by arylamine N-acetyltransferase (NAT) enzymes, responsible for acetylation of sulfamethoxazole at its N4 position
    - May also undergo oxidation at its C5 and N4 atoms, the latter of which is catalyzed by CYP2C9
    - Glucuronidation of the N4 atom, likely mediated by unspecified UGT enzymes, is an additional minor route of metabolism
    - None of the identified metabolites appear to carry antimicrobial activity
    - Hydroxylamine metabolite generated via oxidation by CYP2C9, may be further converted to a more reactive nitroso- metabolite
  - Route of elimination
    - Occurs primarily via glomerular filtration and tubular secretion in the kidneys, with urine concentrations generally considerably higher than plasma concentrations
    - Approximately 84.5% of a single oral dose of sulfamethoxazole is recovered in the urine within 72 h (~30% is free sulfamethoxazole and remainder is N4-acetylated metabolite)
  - Half-life
    - Average serum T1/2 is 10 h and may be increased in patients with severely impaired renal function
  - Clearance
    - Oral and renal clearance estimated as 1.2 ± 0.2 and 0.22 ± 0.05 L/h, respectively

- Trimethoprim
  - Absorption
    - Steady-state concentrations are achieved after ~3 d of repeat administration
    - Average Cmax 1 µg/mL with Tmax 4 h following the administration of a single 100 mg dose
    - Follow first-order pharmacokinetics as a single 200 mg dose results in serum concentrations approximately double that of a 100 mg dose
    - Steady-state AUC of orally administration ~30 mg/L·h
  - Volume of distribution
    - Extensively distributed into various tissues following po administration
    - Distributes well into sputum, middle ear fluid, and bronchial secretions
    - Distributes efficiently into vaginal fluids, with observed concentrations approximately 1.6-fold higher than those seen in the serum

- May pass the placental barrier and into breast milk
- Sufficiently excreted in the feces to markedly reduce and/or eliminate trimethoprim-susceptible fecal flora

- Metabolism
  - Undergoes oxidative metabolism to a number of metabolites
  - The most abundant of which are demethylated 3'- and 4'- metabolites, accounting for approximately 65% and 25% of the total metabolite formation, respectively
  - Minor products include N-oxide metabolites (<5%) and benzylic metabolites in even smaller quantities
  - The parent drug is considered to be the therapeutically active form.
  - Biotransformation appears to involve CYP2C9 and CYP3A4 enzymes, with CYP1A2 contributing to a lesser extent
- Route of elimination
  - ~10-20% of an ingested dose is metabolized, primarily in the liver, while a large portion of the remainder is excreted unchanged in the urine
  - Following oral administration, 50-60% excreted in the urine within 24 h, ~ 80% of which is unchanged parent drug
- Half-life
  - T1/2 8-10 h, but may be prolonged in patients with renal dysfunction
- Clearance
  - Following oral administration, the renal clearance variably reported between 51.7 - 91.3 mL/min

➢ Contraindication/precautions

- Known sensitivity to TMP or SMX, or any component in their formulation
- Adverse effects / drug-drug interaction
- Folate deficiency / megaloblastic anemia
- Severe liver/kidney disease

➢ Adverse effects

- GI
  - Nausea/vomiting
  - Anorexia
- Skin
  - Urticaria

➢ Drug-drug interaction

- CYP2C8/9 metabolized drugs toxicity
  - BCG vaccine
  - Dofetilide
  - Methenamine
  - Procaine

- Peripartum
  - Pregnancy – Safe
  - Lactation – Do **not** use

- Further information on metronidazole, vancomycin and fidaxomicin as given in the following section on the treatment of C. difficile infection (CDI).

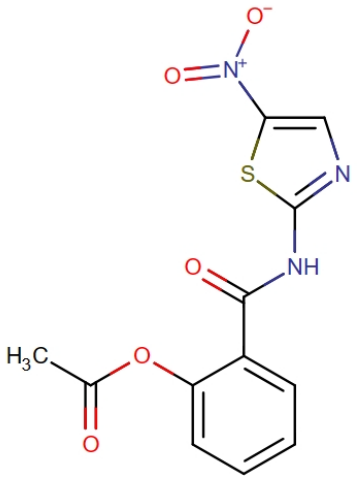
❖ **Candidiasis**

- **Fluconazole, Caspofungin, Clotrimazole**

Please see previous chapter on infectious esophagitis

❖ **Cryptosporidium hominis**

- **Nitazoxanide**



- Indication (GI context)
  - Gastroenteritis, infections – Cryptosporidium hominis

- Mechanism of action
  - Disrupt energy metabolism in anaerobic microbes by inhibition of the pyruvate: ferredoxin/flavodoxin oxidoreductase (PFOR) cycle

- Pharmacokinetics
  - Absorption
    - Relative bioavailability of the suspension compared to the tablet was 70%.
    - When administered with food
      - Tablet: AUC ↑2x, Cmax ↑ 50%, and
      - Oral suspension AUC ↑45-50%, Cmax ↑≤ 10%

- Volume of distribution
  - NA
- Metabolism
  - Initial reaction in the metabolic pathway of Nitazoxanide is hydrolysis to tizoxanide, followed by conjugation, primarily by glucuronidation to tizoxanide glucuronide.
  - When oral suspension was ingested with food, the AUC of tizoxanide and tizoxanide glucuronide ↑ ~50% and the Cmax ↑ <10%
- Route of elimination
  - Tizoxanide is excreted in the urine, bile and feces
  - Tizoxanide glucuronide is excreted in urine and bile
  - Approximately 2/3 of the oral dose of nitazoxanide is excreted in the feces and 1/3 in the urine
- Half-life
  - 7.3 h
- Clearance
  - Nitazoxanide is cleared in the urine and feces
  - Metabolite, tizoxanide, is also found in the urine, plasma, and breastmilk
  - Drug is not found unchanged in the urine

➢ Contraindication/precautions
- Known hypersensitivity to nitazoxanide or any component in their formulation
- ↓ hepatic / ↓ renal function
- Biliary tract disease
- Immunodeficiency / HIV infection
- Diabetes mellitus

➢ Adverse effects
- CNS
  - Headache/dizziness
- GI
  - Nausea/vomiting
  - Abdominal pain
  - Diarrhea

➢ Drug-drug interaction
- Nitazoxanide → ↑ blood concentration / toxicity
  - Phenytoin
  - Warfarin

➢ Peripartum
- Pregnancy
  - Safe
- Lactation
  - Safety **not** known

❖ **Whipple Disease** (Tropheryma Whipplei infection)

➢ Treatment

- Induction of remission
  - Ceftriaxone
    - 2 gm IV od (10 to 14 days)
  - Penicillin G
    - 6 to 24 million units IV daily, plus
  - Streptomycin
    - 1 gm IM od
- Long-term (for at least 1 yr)
  - Trimethoprim/sulfamethoxazole (TMP-SMX)
    - 160/800 mg po b.i.d.
  - For other antibiotic choices, please see Maiwald M et al., Gastrointestinal and Liver Disease, 11th Edition, 2020

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Tropheryma (T) whipplei is sensitive to tetracycline-type antibiotics, but this is not recommended for use.

- Give the reason why tetracycline is not recommended for use to treat T. whipplei
  - T. whipplei may invade the CNS, and tetracycline does not cross the blood brain barrier, and should not be used
  - Curiously, T. whipplei may occur just in the CNS
    -In either case, use TMP-SMX for CNS Whipple disease

❖ **Clostridium Difficile Infection (CDI)**

- Initial therapy
  - Supportive therapy
    - General management
    - Stop offending antibiotics
    - Contact precaution, especially hand hygiene using soap and water (not with alcohol-containing solutions which do **not** disinfect the C. difficile spores)
    - IV rehydration, as needed
- Antibiotics (bacteriostatic)
  - Metronidazole 500 mg po t.i.d., or 250 mg po q.i.d., for 10 to 14 days
  - If metronidazole ineffective and symptoms persist, vancomycin 125 mg po q.i.d., for 10 to 14 days
    - Risk of VRE (vancomycin-resistant enterococci) is similar with both metronidazole and vancomycin.

- If patient requires antibiotics for non- C. Difficile indication, continue metronidazole or vancomycin ("concomitant antibiotics") for 1 wk after other antibiotics for non- C. difficile infection are stopped.
- Repeat stool cultures
  - Not indicated if symptoms subsided (50% will have C. difficile spores for up to 6 wks in persons who have become asymptomatic)
  - Not indicated to treat C. difficile spores
  - May be an asymptomatic carrier

- Relapse/recurrent
  - ~20% of C. difficile diarrhea patients relapse or recur after initially successful treatmentwith metronidazole or vancomycin.
    - Because post-infectious IBS (irritable bowel syndrome) may present with similar symptoms, repeat testing of stool for C. difficile toxin is appropriate.
  - Recurrence rates
    - Antibiotic
      - Continuous ~30%
      - Pulse ~15%
      - Taper ~45%
    - Timing
      - Usually occurs within 3 to 12 wk of index CDI
    - Of those with 1 recurrence, at least 25% will have a second recurrence
    - ½ due to relapse from original strain of C. difficile
    - ½ due to reinfection with a different strain

- **Severe CDI**

➢ Guidelines
  - Suggested guideline parameters
    - WBC > 20,000 cells/μL
    - Serum creatinine ≥ 1.5 x pre-infection level
    - Scoring system (maximum 8 points)
      - One point each for
        - Age. > 60 yr
        - > 38.3 ^{o}C
        - WBC > 15,000 WBC/μL within 48 hours of enrollment
        - Serum albumin < 2.5 mg/dL
      - Two points each for
        - Pseudomembranous colitis (PMC) on endoscopy
        - Admission to ICU
    - Severe disease ≥ 2 points

➢ Complications
  - Patient
    - Shock
    - Death (within 30 d)

- Colon
  - Megacolon
  - Perforation
  - Need for colectomy
  - Risk of complications for the hypervirulent stain of C. difficile, NAP (north American Pulsed Field type I), 11%

➢ Risk factors

- Age > 65 yr
- Need for concomitant antibiotics (antibiotics for medical condition, plus antibiotic for CDI)
- Co-morbidities (e.g., associated IBD)
- ↓ host immune response (low anti-toxin antibody levels
- Exposure to asymptomatic carriers

Note: Recurrence of CDI after initial treatment with metronidazole does **not** necessarily signify metronidazole resistance.

➢ Pathophysiology

- "…. reintroduction of normal {bowel] flora via donor feces corrects the imbalance [in a perturbed ecologic…. Microbiota] and restores phylogenetic richness, therapy enablingrecovery of normal bowel function and health."

➢ Treatment

- Mild/moderate severity
  - Repeat vancomycin or metronidazole (usual treatment)
  - For severe disease, the cure rate for vancomycin (VAN) is superior to metronidazole (MET)

VAN	MET
97%	76%

  - If patient with severe CDI is NPO (such as with megacolon or ileus), consider use of
    - Vancomycin by enema, 500 mg in 100 mL normal saline q8h
    - Add metronidazole 500 mg IV q8h

Abbreviations: NPO, nil per OS (translation, nothing by mouth)

- Associations with metronidazole failure
  - Transfer from another hospital
  - CDI on hospital admission
  - Recent use of cephalosporin

- Intermittent (pulse) therapy
  - Antibiotic-free interval allows C. difficile spores to germinate, and to becomesusceptible to being destroyed by next interval dose of antibiotic
  - Sequential therapy
    - Vancomycin, followed by rifaximin for 14 days (88% response) previous exposure torifaximin may cause rifaximin resistant C. difficile infection
  - Fidaxomicin (bactericidal)
    - 200 mg po b.i.d. for 10 to 14 days
- Anion-binding resins
  - Adjuvant therapy with tapered vancomycin
  - Cholestyramine or colestipol
- Probiotics
  - Inconclusive results
- Monoclonal antibodies (mAb)
  - Adjuvant (Ad) to antibiotics (Ab), to reduce rate of recurrence

	Ad + Mab	Ad
Rate of recurrence	7%	25%

  - Intravenous immunoglobulin IVIG) – no proven benefit
- Fecal only
  - Transplantation of stool (fecal bacteriotherapy, aka fecal microbiota transplantation[FMT])
  - ↑ evidence that this is beneficial for recurrent CDI
- For C. difficile infection (and even for the virile NAP1 / BI / O27 strain), primarycure rate with FMT is ~90%, regardless of whether the FMT is administered po by NG tube orEGD, or pr retention enema
  - Using ~second FMT or FMT plus antibiotic will yield an even high rate of eradication
  - Has been useful in severe CDI complicated by toxic regression
  - FMT appears to be safe, oven in persons who are immunocompromised
- Fecal Microbiological Transplantation (FMT)
  - Altered bacteroides / firmicutes ratio is associated with obesity.
  - Frozen stool works as well as fresh stool for R. C. difficile
  - ↓ bifidobacterium → ↑ bacteroides → T1DM
  - Sweeteners → Δ microbiome → ↑ gluten intolerance
    ↓
    ↑ organisms which ↓ permeability
  - "Super donor"
    Ethanol-producing microbes may relate to development of NASH
  - Some microbes → ↑ glucose absorption → ↑ TG
  - Diet choline → TMA → hepatic FMOs → TMAO → atherosclerosis
  - Antibiotics in infancy may lead to obesity
  - Lactobacilli are growth enhancers (↑ BMI)
  - Avoid using obese stool doners.

- IBD
  - Loss of diversity of microbiome in UC, CD, which falls further with ↑ IBD activity.
- NAFLD
- Gut microbiome affects → ↑ firmicutes in obesity

- Surgical
  - Indications
    - Worsening of patient's condition
      - Age ≥ 65 yr
      - Systemic inflammatory response syndrome SIRS)
      - Multiorgan failure
      - Peritoneal signs
    - Colon
      - Megacolon
      - Severe ileus
      - Microperforation
      - Necrotizing colitis
    - Laboratory
      - WBC ≥ 20,000 WBC/μL, and/or
      - Plasma lactate, between 2.2 and 4.9 mEq/L
  - Procedures
    - Subtotal colectomy and ileostomy, secondary closure of ileostomy with ileorectal anastomosis
    - Diverting loop ileostomy, and colonic lavage (intraoperative PEG solution; post-operative autograft flushes of vancomycin into the ileostomy

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Because CDI is a common and serious complication of hospitalization and poor hand hygiene, including poor contact precaution by staff, alcohol-based hand sanitizers are being increasing placed in/outside patient rooms.

- Give why this practice may be challenged.
  - C. difficile spores are destroyed by soap and water
  - Washing with alcohol allows spores to survive, germinate and potentially cause more CDI

Clinical Caution

- Recurrence of symptoms after treatment for initial CDI does not automatically mean disease related to CDI, even if stool cultures are positive by stool toxin assay.
- Vancomycin given po or pr (by enema) is absorbed through the inflamed colonic mucosa in CDI, so that it is important to monitor serum creatinine for renal toxicity of this antibiotic.

Suggested Algorithm to Approach to Patient with CDI

- Mild-moderate WBC < 150,000/μL, or Cr_s <

↓

Metronidazole 500 mg po t.i.d. for 10-14 d

- WBC > 15,000/ μL, or Cr_s <

↓

Vancomycin 125 mg po q.i.d. for 10-14 d

↓

Plus megacolon / ileus sepsis / shock

↓

Vancomycin 500 mg po / NG, plus metronidazole 500 mg po IV q8h
+/- Vancomycin pr

Recurrence #1: Same as above initial therapy

↓

Recurrence #2: Vancomycin tapered +/- pulsed, or fidaxomicin 200 mg po b.i.d. for 10 days, or Fecal microbiota transplant (FMT)

↓

Recurrence ≥ 3: Fidaxomicin 20 mg po b.i.d. for 10 days, or FMT

↓

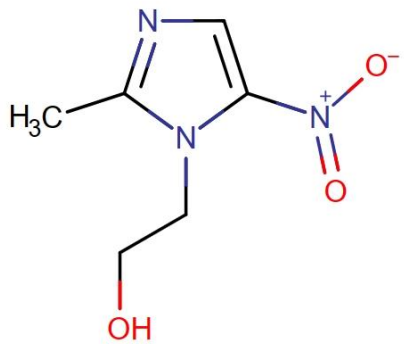
Failure to resolve despite optimal therapy
Megalocolonileus

↓

Total colectomy

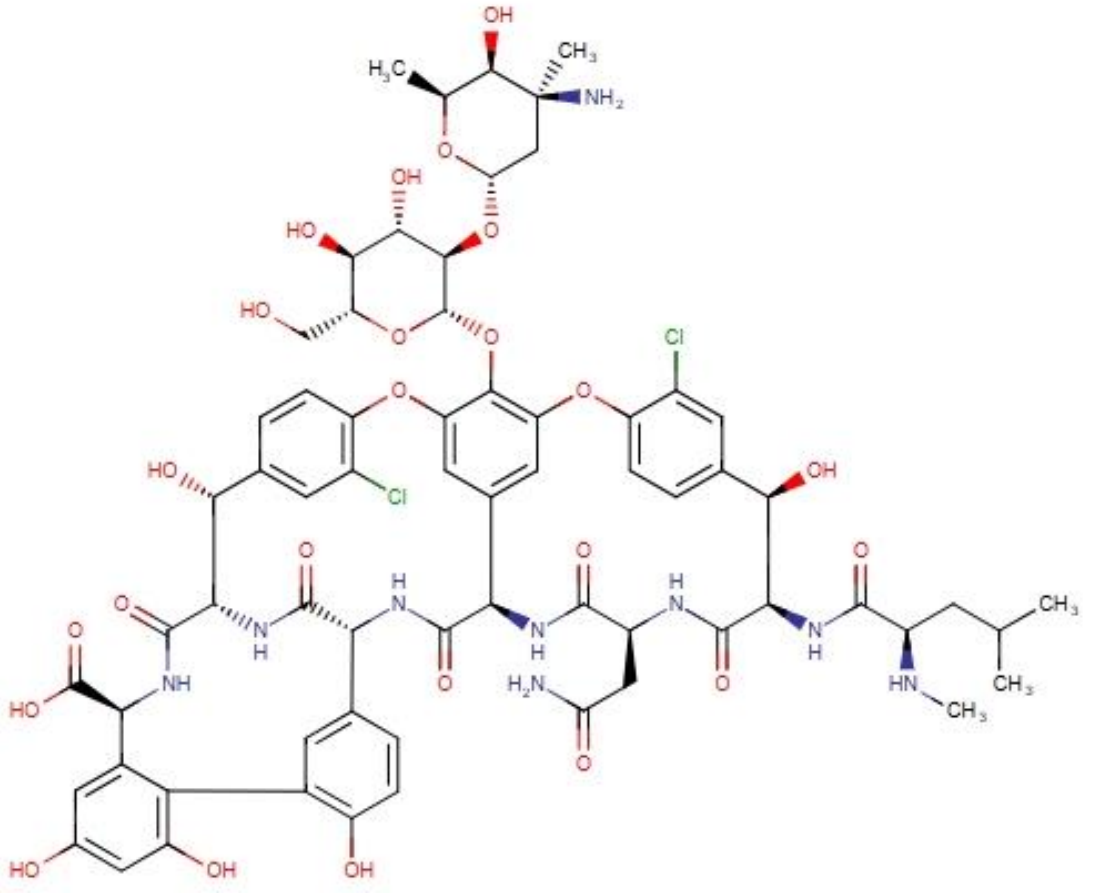
http://www.idsociety.org/up;oadedFiles/IDSA/Guidelines-Patient_care/PDF_Library/cdif/2010a.pdf

- **Metronidazole** (Flagyl®)



Please see previous section on Infections

- **Vancomycin**



- Indication (in GI context)
  - C. difficile infection
- Mechanism of action
  - ↓ cell wall synthesis by binding to the D-Ala-D-Ala terminal of the growing peptide chain during cell wall synthesis, → ↓ transpeptidase, →↓ further elongation / cross-linking of the peptidoglycan matrix.
- Pharmacokinetics
  - Absorption
    - Poorly absorbed from GI tract, however systemic absorption (up to 60%) may occur following intraperitoneal administration
  - Volume of distribution
    - Volume of distribution varies between 0.4-1 L/kg

- Metabolism
  - Since ~75-80% of the drug is excreted unchanged in the urine after the first 24 h following administration, there is seemingly no apparent metabolism of the drug
  - The concentration of vancomycin in the liver tissue and bile 24 h after administration is below detection limits
- Route of elimination
  - In the first 24 h, ~75-80% is excreted in urine by glomerular filtration
- Half-life
  - T1/2 in normal renal patients is ~6 h (range 4-11 h)
  - In anephric patients, the average T1/2 of elimination is 7.5 d
- Clearance
  - Mean plasma clearance ~0.058 L/kg/h

➢ Contraindication/precautions
- Known hypersensitivity to vancomycin and its products
- Adverse effects / drug-drug interactions
- Renal failure
- Hearing loss / deafness

➢ Adverse effects

Allergy	– Anaphylaxis
CNS	– Ototoxicity
CVS	– Hypotension/flushing
GI	– Nausea/vomiting
GU	– Nephrotoxicity
Blood	– Neutropenia
Skin	– Red skin rash
Face / upper body	– Red neck syndrome – "Red man" (person) syndrome

Clinical Gem
- Red person syndrome occurs when vancomycin is given too quickly by IV.

Clinical Ruby

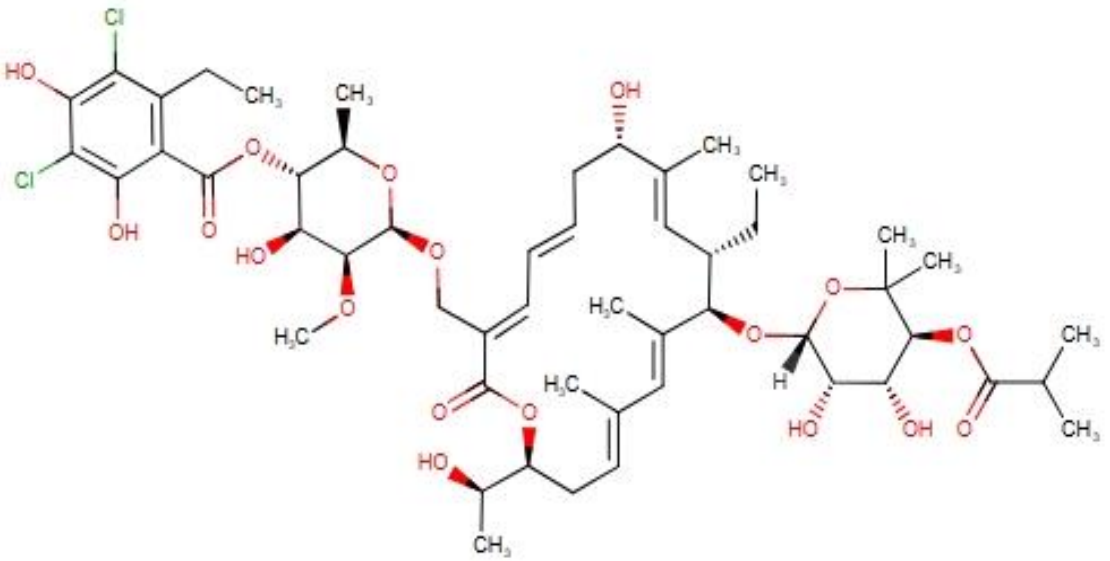
- Many persons given antibiotics will develop diarrhea
  - Only some of these patients will develop pseudomembranes (pseudomembranous colitis)
    - Only some persons with antibiotic-associated diarrhea +/- pseudomembranes will have CDI proven on presence of toxins
- In the patient with diarrhea and pseudomembranes are seen on colonoscopy, they may have CDI.
- In the patient with diarrhea and no pseudomembranes are seen on sigmoidoscopy, they may still have pseudomembranes in the non-visualized right colon.
- In the patients with diarrhea and C. difficile organisms in the stool, their diarrhea cannot be considered to be the result of CDI unless the cultured organisms produce toxins A/B.

➢ Drug-drug interaction

- When used with
  - Acyclovir
  - Cidofovir
  - Ganciclovir
  - Tenofovir

} ↑ nephrotoxicity

- **Fidaxomicin** (Dificid®)



- Indication
  - C. difficile infection
    - Minimal systemic absorption and a narrow spectrum of activity
    - Active against Gram positive bacteria, especially clostridia.

- Mechanism of action
  - Binds to and prevents movement of the "switch regions" of bacterial RNA polymerase.
  - Switch motion occurs during the opening and closing of the DNA:RNA clamp, a process that occurs throughout RNA transcription but is especially important in the opening of double-stranded DNA during the initiation of transcription.

- Pharmacokinetics
  - Absorption
    - Following single dose of 200 mg fidaxomicin po in healthy adults,
      - Cmax of fidaxomicin and its main metabolite OP-1118 were 5.20 ± 2.81 ng/mL and 12.0 ± 6.06, respectively.
      - Median Tmax is 2 h
      - Systemic absorption of fidaxomicin following oral administration is minimal.10
  - Healthy adults with high-fat meal versus under fasting conditions, Cmax of fidaxomicin and OP-1118 were decreased by 21.5% and 33.4%, respectively
    - This effect is clinically insignificant as the therapeutic action does not depend on drug concentrations in the systemic circulation.
  - Volume of distribution
    - There is limited information on the volume of distribution of fidaxomicin
    - Mainly confined to the GI tract when orally administered
  - Metabolism
    - Fidaxomicin po is transformed to its main and pharmacologically active metabolite, OP-1118, via hydrolysis at the isobutyryl ester.
    - Cytochrome enzymes are not involved in the metabolism
    - Biotransformation is mediated by gastric acid or enzymatic activity of intestinal microsomes
  - Route of elimination
    - Following oral administration, fidaxomicin is mainly excreted in feces
    - > 92% of the dose was recovered in the feces as either the unchanged parent drug or metabolites
    - Healthy adults, approximately 0.59% of oral dose (200 mg) administered was recovered in the urine as the main metabolite, OP-1118
  - Half-life
    - Following a single dose of 200 mg fidaxomicin po in healthy adults, the elimination T1/2 was ~ 11.7 ± 4.80 h.
  - Clearance
    - Limited information only

- Contraindication/precautions
  - Known hypersensitivity to fidaxomicin or any components of the formulation.
- Adverse effects
  - GI
    - Nausea/vomiting
    - Abdominal pain
    - GI bleeding
- Drug-drug interaction
  - None known

❖ Other treatments of CDI

- Probiotics
  - The data on clinical efficacy of probiotics is difficult to interpret because of
    - Wide variability in products used
    - Selection of patients, and
    - Evaluation of outcomes etc.
  - Please refer to recent review for outline of limitations to interpretation of data.
    - The best data is for maintenance of antibiotic induced remission of pouchitis (Systemic Review and Meta-analysis of published data 2012-2022)
  - Prevention
    - Antibiotic-associated diarrhea
    - Candidiasis, oral
    - Chemoradiation-induced diarrhea, prevention
    - Clostridium difficile associated diarrhea
    - H. pylori eradication therapy, prevention
    - Necrotizing enterocolitis
    - Post-operative sepsis
    - Pouchitis
    - Traveler's diarrhea
  - Treatment
    - Irritable bowel syndrome
    - Ulcerative colitis
    - Hepatic encephalopathy
  - Maintenance
    - Ulcerative Colitis
    - Pouchitis

Quigtej EMM. Sleisenger and Fordtran's Gastrointestinal and Liver Disease- Pathophysiology, Diagnosis, Management. 11th Edition, 2020, Chapter 130, pages 2187-2191.

- Stool Transplantation
  - Mixed results in UC, depending upper route of delivery (nasoduodenal vs. enema), donor

− Nasoduodenal	Clinical remission	wk 12	NS
− Enema	Remission	wk 6	24% vs. 5%
− Colonoscopy then enema	Steroid-free remission	wk 8	24% vs. 8%

Abbreviation: NS, non-significant

  - Negative results in Crohn disease
  - C-difficile overall efficacy prevents recurrent CDI, stool administered into
    - Stomach, small intestine, 81%
    - Colon, rectum, 93%

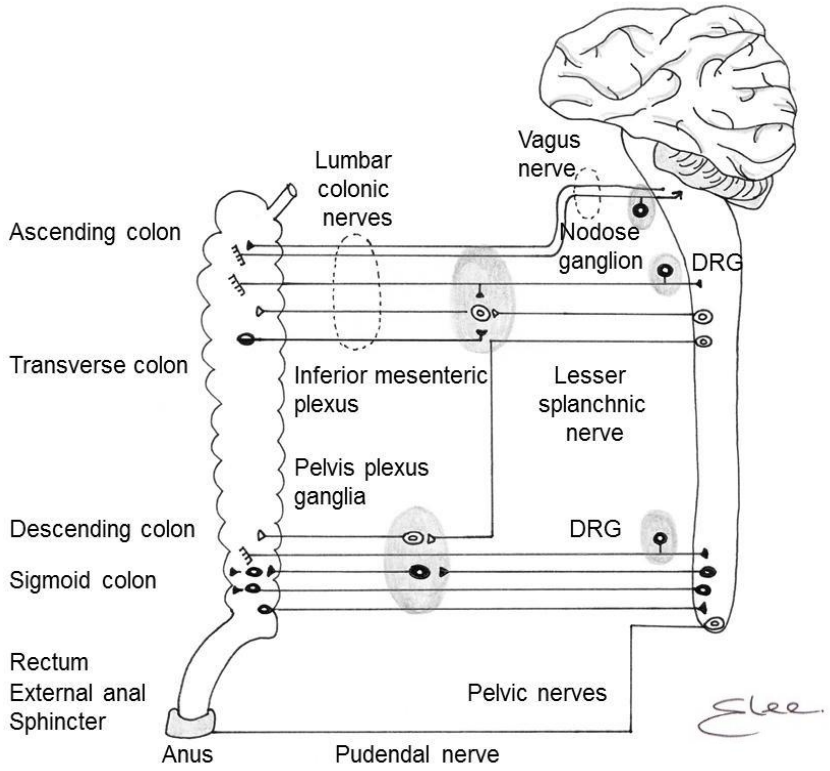
	Prevention of Recurrent CDI
Nasoduodenal infusion	81%
− Vancomycin	31%
− Vancomycin plus bowel lavage	23%

  - Single IMT vs. multiple IMTs
    - Cure rate 75% vs. 100%

COLON

MOTILITY AND DEFECATION

- Innervation of the Colon



Abbreviations: DRG, dorsal root ganglia

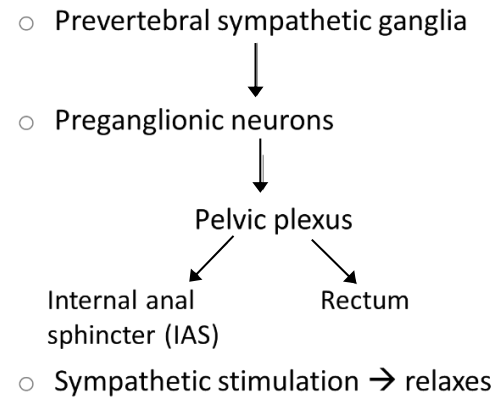
Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 10 Edition, 2016, Figure 100-3, page 1700.

- Efferent (Motor) Parasympathetic
  - Dorsal motor nucleus (DMN) in brainstem
    - ↓ Vagus nerve (CN X)
  - Nuclei in the sacral spinal cord
    - ↙ Lumbar colonic nerves
    - ↓ Enteric Nerves in Colonic Wall
    - ↘ Pelvic plexus ganglia (PPG) and nerves
      - Internal anal sphincter (IAS)
      - Rectum
  - Parasympathetic stimulation → contracts

- Parasympathetic Innervation
  - ↓ muscle activity
  - ↓ blood flow
  - ↓ secretion
  - ↑ contraction of IC (ileocecal) function and IAS (internal anal sphincter)
  - Anal sphincters

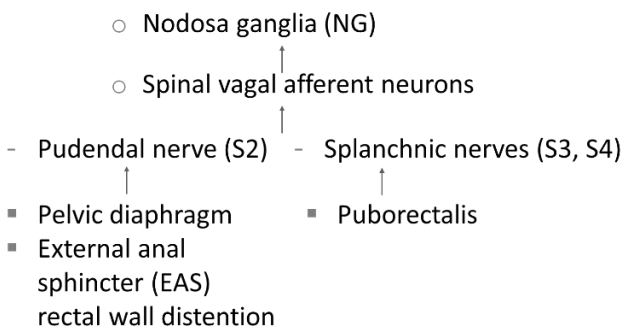
IAS inhibitory innervation	EAS stimulatory innervation
− Lumbar sympathetic − Sacral parasympathetic	− Pudendal nerve

- Efferent (Motor) Sympathetic



  - Sympathetic stimulation → relaxes

- Sensory Afferents



- Interstitial Cells of Cajal (ICC)
  - ICC-MP
    - Myenteric plexus (MP)
      - Pacemakers for rapid oscillations in myenteric potential oscillations (MPOs) of circular and longitudinal muscle
  - ICC-SM
    - Submucosal plexus (SM)
      - Pacemakers for high amplitude, slow waves
  - ICC-IM
    - Intramuscular (IM), between circular and longitudinal muscles
      - Integrates pacemaker activity and neuronal inputs to smooth muscle

➢ Motor Neurons

- Excitatory
  - Acetylcholine (Ach)
  - Tachykinins
    - Substance P (SP)
    - Neurokinin A (NKA)
- Inhibitory
  - Adenosine triphosphate (ATP)
  - Nitric oxide (NO)
  - Pituitary adenyl cyclase-activating peptide (PACAP)
  - Vasoactive intestinal polypeptide (VIP)

➢ Tonic Electrical Slow Waves and Colonic Peristalsis

- The pacing of the regular rhythmic contractions in the small/large intestine is by way of electrical slow waves
  - q6 sec in the small intestine
  - q10 sec in the colon
- The movement (transit, aka craniocaudal translocation) of feces is more marked in the colon than is the mixing.

➢ Motor Activity of Colon

- MMCs move food to ileocecal valve
- Monophasic, ileal propagating pressure plus inhibition of phase contractions of the ileocecal junction, pumps chime into the cecum within 90 min of a meal
- Cecal filling triggers proximal colonic propagating contractions

- Rhythmic myoelectric activity from layer of middle of circular smooth muscle Intramuscular, between circular and longitudinal muscles
  - MPOs (myenteric potential oscillations)
    - arise from myenteric plexus
    - 10-12 per min
    - MPO-related contractions summate to result in longer and stronger contractions
  - Slow waves
    - Arise from submucosal border of inner circular muscle
    - 2-4 per min
- Unlike small intestine (where slow waves propagate predominantly from the mouth and towards the anus) in the colon, slow waves propagate over short distances both up and down the colon.

- Proximal: segmentation
  - Motor activity in the proximal colon (cecum, ascending and transverse colon) are controlled by
    - Myogenic, neurogenic (vagus and pelvic nerves) and hormonal factors.
  - Mixing (non-propulsive segmentation caused by slow wave activity, creating haustra), and peristalsis (mass movements, propulsion distally of fecal material)
  - Transit
    - After eating and the entry of food into the duodenum, there is release of cholecystokinin (CCK).
    - CCK increases the neutrally mediated motor function of the ileum and the colon (especially the sigmoid colon), known as the “gastrocolic reflex”.
    - This gastrocolic response occurs with intake of 300 kcal, especially from fat
      - May result from the food-induced effects on 5-HT3 receptors on vagal afferent
    - Flow from the stomach to the cecum takes 1-2 h, but flow from the cecum to the rectum takes 5-7 d.
    - Transit through the transverse and descending colon is relatively faster than through the rest of the colon.

- Distal: Mass Movements
  - Motor activity in the distal colon is mostly segmentation (mixing), until a mass peristalsis fills the rectum and the process of defecation is begun.
  - A lump of feces will move quickly over several centimetres, then stop for a while, then propel forward again
    - These are called “mass movements”.
  - The intermittent rhythmic contractions that cause the mass movement of feces are neurogenic, initiated by extrinsic innervation, and are not linked to electrical slow waves.
  - The mass movements occlude the colonic lumen, push in the caudal direction and gradually fill the rectosigmoid bowel.

- Rectum
  - Transit through the transverse and descending colon is relatively faster than through the rest of the colon.
    - Myenteric potential oscillations (MPOs) and slow waves in colon
      - Non propagating waves mix stool
      - Excitatory motor neurons cause MPOs to summate and lead to HAPCS (high-amplitude propagating contractions)
    - The HAPC overcomes the RMC (rectal motor complex)
    - The rectum fills, and dilates to accommodate the stool bolus
    - Stretching of the rectal wall
      - Simultaneously activates an enteric descending inhibitory reflex to relax the IAS
      - Extrinsic reflex pathway to contract EAS
    - As the rectum distends further, the signal of discomfort and the need to defecate is transmitted centrally.
  - Feces enter the rectum, the rectum expands, and the sensory mechano- and chemoreceptors are stimulated, giving the sensation of "the urge to purge".
  - Rectal compliance increases, and the rectum continues to receive stool.
  - Rectal mucosa and myenteric plexus are myelinated and unmyelinated nerve fibers which mediate
    - The defecation reflex (viscero-visceral, rectoanal contractile and sympathetic)

- Defecation
  - EAS relaxes
  - Sit on toilet
    - Strain (Valsalva maneuver)
    - Perineum (anorectal junction) descends
    - ↑ ARA (anorectal angle)
  - Straining → diaphragm moves down (Valsalva maneuver)
    - Levator ani relaxes
      - Puborectalis
      - Pubococcygeus
      - Iliococcygeus

      } Rectum straightens out ($90^o \rightarrow 130^o$)

    - Ingestion, digestion and absorption of food
    - MMCs more food to ileocecal valve
    - Monophasic, ileal propagating pressure plus inhibition of phase contractions of the ileocecal junction, pumps chime into the cecum within 90 mm of a meal
    - Cecal filling triggers proximal colonic propagating contractions
    - MPOs and slow waves in colon
      - Non-propagating waves mix stool
      - Excitatory motor neurons cause MPOs to summate and lead to HAPCS (high-amplitude propagating contractions)

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- Conscious decision to follow the "urge to purge"
  - Relax EAS
  - Relax puborectalis ↑ ARA even more
  - Levator ani contracts
  - Perineum descends even more
  - Stool is "funneled" into the anal canal
  - Beginning one hour before defecation, there is
    - ↑ colonic phasic and tonic activity (gastrocolonic response)
    - ↑ frequency of propagating pressure waves (which represents the preparatory phase to defecation)
  - These propagating waves push stool into the rectum, and
    - Stimulate sacral spinal efferent mechanoreceptors
    - Activate an enteric descending inhibitory reflex (DIR) → ↓IAS / ↑EAS

- The mechanoreceptors cause the defecatory urge, and defecation can be postponed with
  - Receptive rectal accommodation (↑ rectal volume, with no ↑ intrarectal pressure) mediated by inhibitory nerves
  - Voluntary suppression of the defecatory urge
  - ↓ gastric emptying
  - ↓ small bowel transit
  - ↓ colonic transit (by ↓ proximal colonic propagating pressure waves)

- If defecation is not to be postponed, then there is
  - ↓ IAS pressure
  - Stool moves into upper anal canal
  - Anorectal junction descends with sitting
  - Rectum descends further with straining
  - Sitting and straining → ↑ anorectal angle (ARA) → relaxation of puborectalis
  - Levator ani muscles contract
  - Perineum descends
  - Stool moves further into anal canal
  - Voluntary ↓ EAS pressure
  - Successful expulsion of stool

➢ Physiology

❖ Fecal Continence

- Anatomical structures which provide the mechanisms for normal fecal continence.
  - Nerves - Pudendal nerve/sacral segments S2-S4 brain
    - The pudendal nerve has both afferent and efferent limbs, sensing stool entry into the rectum and delivering the impulse through the sacral nerves, spinal cord, to the brain
    - The efferent limb carries the sensation of distension which causes central pathways to send signals via the afferent limb to allow for conscious contraction of external sphincter to maintain continence.
  - Muscles
    - Internal anal sphincter (IAS)
    - External anal sphincter (EAS)

      ▪ The striated muscles of the pelvic floor (including the EAS) are supplied by motor neurons with cell bodies in the spinal cord and with axons that run in the pudendal nerves.
    - Levator ani complex:
      - The internal anal sphincter is tonically contracted providing continence at rest.
      - When stool enters the rectum the IAS relaxes, however, continence is maintained if consciously desired by contraction of the EAS.
    - The IAS returns to resting tone, the rectum demonstrates compliance allowing intrarectal pressure to decrease and the urge to defecate to pass.
    - The levator ani muscles
      - provide additional support to the EAS
      - form a sling around the anal canal
      - acute angle during rest
      - mechanical barrier for continence distends without substantial rise in pressure (thus not overwhelming resting anal tone)
      - Rectum - reservoir

- Internal anal sphincter (IAS)
  - 0.3 cm to 0.5 cm expansion of rectal smooth muscle.
  - The myotonically-produced tonic ring contraction involves the IAS.
  - The tone in the IAS is reduced or increased by neurogenic mechanisms → inhibitory and stimulatory motor nerves.
  - Receptors lead to reflex relaxation of internal anal sphincter (IAS).

- Anus and Anorectal Angle
  - Anus – 2 cm to 4 cm muscular tube, closed at rest
  - Anorectal angle
    - At rest, 90^{o}
    - Squeeze, 70^{o} (acute)
    - Defecation, 110^{o} – 130^{o} (obtuse)

- Tonic activity of IAS plus EAS (myotonically produced)
- Other anatomical components
  - Anal mucosal folds
  - Anal vascular cushions
  - Flap-like valve of puborectalis muscle

- External Anal Sphincter (EAS)
  - The striated and voluntarily innervated skeletal muscle of the external anal sphincter (EAS) surrounds the IAS.
  - External anal sphincter (EAS) – 0.6 cm to 1.0 cm expansion of levator ani muscles.
  - When the IAS relaxes and intraabdominal pressure is voluntarily increased, defecation occurs.
  - Once defecation occurs, the rectosigmoid colon empties, the defecation reflex is inhibited → ↑ EAS pressure → and the rectosigmoid is ready to be filled again with stool.

❖ **Rectal Manometry**

• Rectal Sensation	Balloon Volume (cc)
○ At first rectal sensation	~100
○ At defecation urge	~180

• Anorectal Sphincter Pressure	mmHg
○ Anorectal sphincter resting pressure	~58
○ Pressure squeeze during voluntary contraction	~130

- Defecation Reflex Disorders

Mechanism	%*
○ Dysfunction of anal sphincter	75
○ ↓ pudendal nerve function	50
○ ↓ rectal sensation	50
○ ↓ rectal compliance	40

*The approximate % contribution of the mechanisms for the development of fecal incontinence

CHRONIC IDEOPATHIC CONSTIPATION (CIC)

- Treatment

- Non-pharmaceutical
  - Treat underlying conditions
  - Bowel management programs, including fiber*
  - Psychological management
  - Avoid constipating medications
  - Exercise
  - Adequate water intake
  - Dietary measures
  - Biofeedback (pelvic floor retraining)
  - Total colectomy with ileorectal anastomosis

* Fiber supplement up to 30 g per day may be offered on a person-by-person basis.
  - In the absence of dehydration, ↑ water intake does not help constipation

- Pharmacological
  - There is a long menu of choices of treatments for CIC (chronic idiopathic constipation).
    - Expensive new agents have been developed, but these do **not** necessarily perform any better than polyethylene glycol, sodium, picosulphate, bisacodyl or lactulose.
  - The NNTs (number needed to treat) to prevent one patient failing to respond to therapy isbetween 3 and 6.
    - Compare the relative risks (RR) from RCTs reporting some old laxatives or new pharmaceuticals versus placebo:

	RR	95% CI
○ Older osmotic and stimulant laxatives	0.52	0.46-0.60
○ Newer pharmaceuticals with a big price tag		
– Prucalopride	0.82	0.76-0.88
– Lubiprostone	0.67	0.56-0.80
– Linaclotide	0.84	0.80-0.87

Abbreviations: CI, confidence interval; NNT, number needed to treat; RR, relative risk

- These newer agents were not studied extensively against the older laxatives.
- Because of the possible heterogeneity of the studies and the variable placebo response rates, the values of the relative risk (RR) or the number needed to treat (NNT) (if they had been reported) cannot be directly compared.
- It has been suggested that long-term use of the anthraquinone (e.g., cascara, senna) and bisacodyl laxatives may cause changes in the colon on diagnostic imaging (barium studies), and on histopathology; but
  - "Cathartic colon is an historic interact and is unlikely to be identified in current clinical practice." (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Saunders/Elsevier, Philadelphia, 2020).
- Brown discoloration of the mucosa may occur in ~70% of chronic users of cascara or senna laxatives (melanosis coli).

- **Manometric changes** in the colon that occur in persons with severe slow-transitconstipation
  - ↓ high amplitude of propagating pressure waves
  - ↑ frequency of low amplitude antegrade and retrograde propagating sequences
  - ↓ nighttime suppression of propagating sequences
  - ↓ colonic response to a high-calorie meal

- Approximate frequency of undesirable outcomes after colectomy performed for chronic constipation

Undesirable Outcomes	Approximate Frequency (%)
Abdominal pain	40
Small bowel obstruction	15
Reoperation	10
Fecal incontinence	10
Diarrhea	10
Recurrent constipation	10
Stoma dysfunction	5

Printed with permission: Müller-Lissner S. *Best Pract Res Clin Gastroenterol* 2007; 21(3): 473-84. (Table 1).

➢ Treatment

Mechanism of action of currently available OTC and prescription therapeutics approved for use in patients with CIC or IBS-C

Class	Drug	Mechanism of Action	Approved CIC/ IBS-C Indication	Efficacy	Adverse Events
○ Laxatives	Osmotic laxatives – PEG 3350 – Lactitol	↑ osmotic gradient → water/ electrolyte secretion into the intestinal lumen	CIC	▪ Improved stool consistency and frequency; ↓straining	▪ Abdominal pain and distention, diarrhea, nausea, flatulence, vomiting, bloating, electrolyte imbalances
	Stimulant laxative – Bisacodyl – Sennosides (anthraquinones)	↑ water and electrolyte secretion / peristalsis	Short-term constipation	▪ Improved stool consistency, frequency, and QoL; ▪ ↓ straining	▪ Diarrhea, abdominal pain, nausea, vomiting, headache
	Anionic surfactant – Docusate	↓ surface tension of the oil-water interface of the stool → ↑ water/fat to penetrate the stool	Occasional constipation	▪ Softened stool	-
○ NHE3 inhibitors	Sodium hydrogen exchanger isoform 3 (NHE3) – Tenapanor	↓ sodium absorption in the intestinal lumen → ↑ fluid secretion into the gastrointestinal tract → ↑ colonic transit	IBS-C	▪ ↓ abdominal symptoms (including pain)	Diarrhea

Class	Drug	Mechanism of Action	Approved CIC/ IBS-C Indication	Efficacy	Adverse Events
○Secretagogues	GC-C agonist – Plecanatide – Linaclotide	↑ intracellular cGMP → ion gradient that ↑ fluid secretion / ↓ colon nociception	CIC and IBS-C	▪ Improved stool consistency, frequency, and QoL; ↓ straining pain, discomfort, bloating and cramping	Diarrhea
	CIC-2 activator – Lubiprostone	↑ ion gradient → ↑ water and sodium secretions into the intestinal lumen	CIC and women with IBS-C	▪ Improved stool consistency and frequency ▪ ↓ straining bloating and pain	▪ Nausea, vomiting, abdominal cramping, diarrhea
○Prokinetics	5-HT4 agonist Prucalopride	↑ GI motility	CIC	▪ Improved stool consistency, frequency and QoL; ↓ straining	▪ Nausea, abdominal pain, diarrhea, headache
	Tegaserod		IBS-C in women < 65 yr without history of cardiovascular ischemic events	▪ Improved stool consistency and frequency, ↓ bloating and discomfort pain	▪ Nausea, abdominal pain, diarrhea, headache, and cardiovascular events

Abbreviations: 5-HT4, selective serotonin type 4; cGMP, cyclic guanosine monophosphate; CIC, chronic idiopathic constipation; CIC-2, chloride channel protein-2; GC-C, guanylyl cyclase-CC; IBS-C, irritable bowel syndrome with constipation; NHE3, sodium-hydrogen exchanger isoform 3; OTC, over the counter; PEG, polyethylene glycol; QoL, quality of life

Printed with permission: Sayuk GS, et al. Am J Gastroenterol 2022; 117: S6-S13 (Table 1).

Type of Constipation	Indication of Therapeutic Agent						
	OL	SL	AS	GC-CA	CIC-2A	NHE-3 I	5-HT4 I
• Indications							
○ Short term		+	+				
○ CIC	+			+	+		+(prucalopride)
○ IBS-C				+	+	+	+(tegaserod*)
• Outcomes							
○ Impaired stool							
− Consistency	+	+		+	+		+
− Frequency	+	+		+	+		+
− Softeners		+					
○ Straining stool	+	+		+	+		+
○ Bloating				+	+		+(T)
○ Cramping				+	+		
○ Pain						+	+(T)
○ Quality of life		+		+	+		+
• Adverse effects							
○ CNS							
−Headache		+					+
○ CVS events	+	+					+(T)
○ GI							
− Nausea/ vomiting	+	+					+
− Bloating/ distention	+				+		
− Pain/cramps	+	+			+		+
− Diarrhea	+	+		+	+	+	+
− Flatulence	+						
○ Electrolyte changes	+						

*Use for IBS-C in women < 65 yr, with no cardiovascular ischemic events

Abbreviations: 5-HT4 I, 5-hydroxytryptamine (serotonin) type 4 inhibitor; CIC-2A, chloride channel protein-2 activators; GC-CA, guanyl cyclase-C agonists; NHE-3 I, sodium (Na^+) / hydrogen (H^+) exchanger 3 inhibitor; OL, osmotic laxatives; SL, secretory laxatives; T, tegaserod

❖ **Bulk Agents**

- **Psyllium** (Metamucil®)

➢ Indication

- Constipation

➢ Mechanism of action

- Absorb excess water while stimulating normal bowel elimination

➢ Pharmacokinetics

- Absorption
  - < 10% of the mucilage gets hydrolyzed in the stomach, with formation of free arabinose
  - Intestinal absorption of the free arabinose is ~ 85-93%
  - Psyllium remains predominantly in the GI tract as a 'bulk' agent that passes largely unchanged throughout the gut
- Volume of distribution
  - When administered as intended largely undergoes little absorption into the body and plasma
- Metabolism
  - Remains largely in the gut as a 'bulk' agent that passes predominantly unchanged throughout the GI tract
  - There is little opportunity for marked absorption into or metabolism by the body
- Route of elimination
  - When administered as indicated is usually excreted in the faeces
- Half-life
  - T1/2 not formally documented at this time
  - Because psyllium husk is largely not adsorbed when administered, it is believed that the drug may not exhibit any kind of half-life
- Clearance
  - Largely undergoes little absorption into the body and plasma

➢ Contraindication/precautions

- Known sensitivity to psyllium/methylcellulose or other products

➢ Drug-drug interaction

- Not known

➢ Peripartum

- Pregnancy
  - Safe
- Lactation
  - Safe

❖ **Osmotic Agents**

- **Polyethylene Glycol (GlycoLax®, MiraLax®)**

➢ Indication

- Constipation
- Cleansing for bowel preparation for colonic procedure (e.g., colonoscopy); with electrolytes (GoLYTELY®)

➢ Mechanism of action

- Osmotic effect causes water to retain in the colon and produces a watery stool

➢ Pharmacokinetics

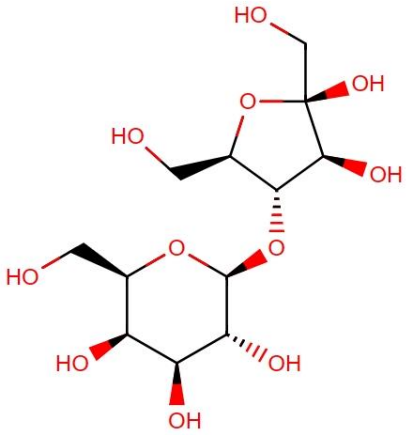
- Absorption
  - Following a 2-day split-dosing regimen of a suspension containing 140 g PEG 3350 po in healthy subjects, the mean Cmax was 2.7 µg/mL and the mean Tmax was 3 h.
  - Typically, PEG with a high molecular weight is poorly absorbed from the GI tract following oral administration
- Volume of distribution
  - Following a two-day split-dosing regimen of suspension containing 140 g of PEG 3350 po in healthy subjects, the mean volume of distribution was 48,481 L
- Metabolism
  - Metabolically inert laxative that does not undergo intestinal enzymatic degradation or bacterial metabolism
- Route of elimination
  - Following administration of suspension containing 140 g of PEG 3350 po in healthy subjects, up to 85-99% of the compound was excreted in the feces
- Half-life
  - Following a 2-day split-dosing regimen of suspension containing 140 g of PEG 3350 po in healthy subjects, the mean T1/2 was 4.1 h
- Clearance
  - There is limited information on the clearance rate of PEG

➢ Contraindication/precautions

- Hypersensitivity to polyethylene glycol (PEG) or its components
- Bowel obstruction

- Adverse effects
  - Abdominal pain / nausea
  - Bloating/distention
  - Excess flatulence
  - Diarrhea
- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Do **not** use

- **Lactulose** (Cephulac®)



- Indication
  - Constipation
  - Treatment/prevention of hepatic encephalopathy
- Mechanism of action
  - Non-absorbed disaccharide producing osmotic effect
- Pharmacokinetics
  - Absorption
    - After po administration. < 3% of lactulose solution is absorbed by the small intestine
    - The remaining unabsorbed lactulose reaches the large intestine where it is metabolized
    - Negligible quantities of unchanged lactulose or its metabolites are absorbed across the colon

- Volume of distribution
  - Negligible amounts of lactulose - metabolized or non-metabolized are absorbed into the body
  - Most lactulose administered subsequently remains predominantly around the GI tract area.
- Metabolism
  - Only metabolized in the colon by saccharolytic bacteria that are present there
  - The substance is broken down into lactic acid and small amounts of acetic and formic acid
  - Specific examples of bacteria that normally inhabit the large intestine that are capable of lactulose metabolism include Lactobacilli, Bacteroides, Escherichia coli, and Clostridia
- Route of elimination
  - Renal excretion of any lactulose that manages to be absorbed into the circulation has been determined to ≤ 3% and is generally complete within 24 h
  - Any unabsorbed lactulose is largely excreted with stool.
- Half-life
  - Renal excretion of any lactulose that manages to be absorbed into the circulation has been determined ≤ 3% and is generally complete within 24 h
  - Any unabsorbed lactulose is largely excreted with stool
- Clearance
  - Negligible amounts of lactulose (metabolized or non-metabolized) are absorbed into the body
  - Data regarding the clearance of lactulose is not readily available or accessible

➢ Contraindication/precautions

- Known hypersensitivity to lactulose
- Known intolerance to galactose – galactosemia

➢ Adverse effects

- GI
  - Abdominal pain / bloating
  - Distention / excess flatulence
  - Nausea/vomiting
- Endocrine
  - ↑ Na_s^+ (hypernatremia)
  - ↓ K_s^+ (hypokalemia)

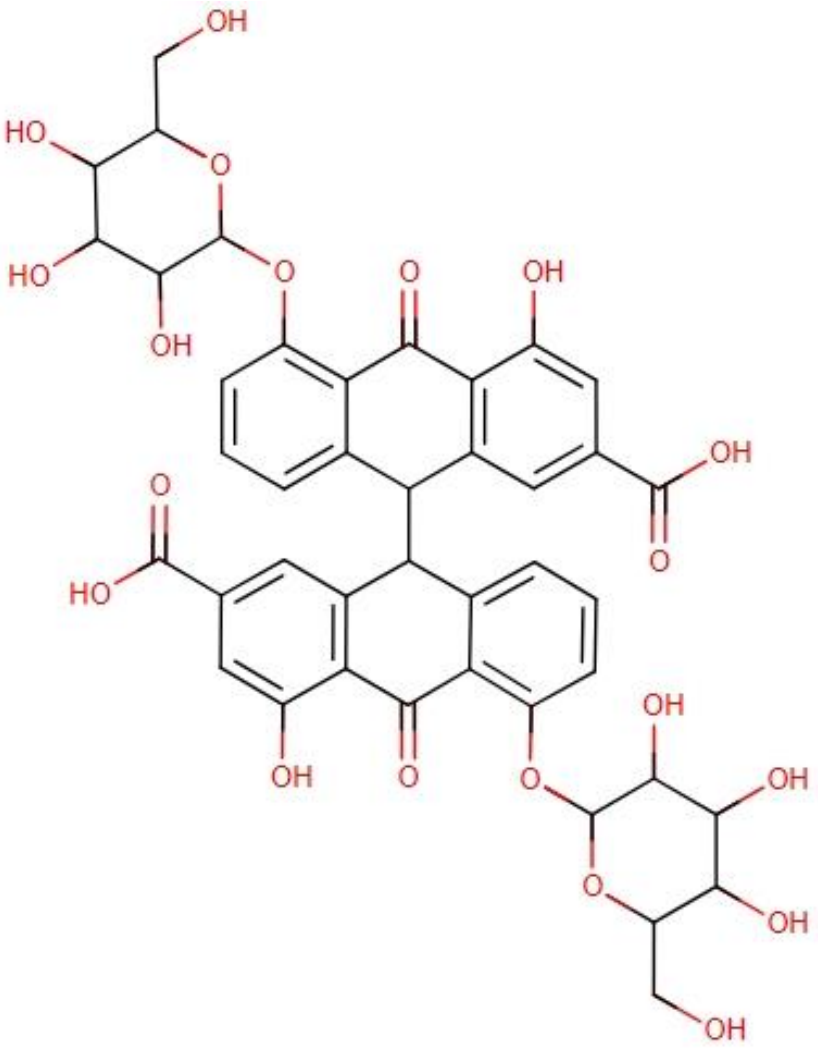
➢ Drug-drug interaction

- ↑ anticoagulant effect of coumadin

- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Not known

❖ **Stimulant Laxatives**

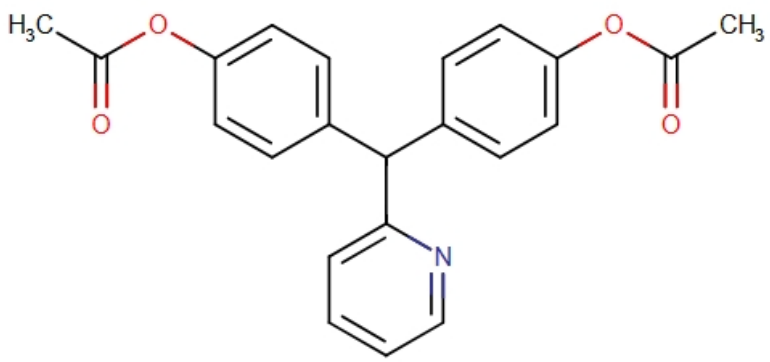
- **Senna** (Senokot®)



- Indication
  - Constipation
- Mechanism of action
  - Sennoside A and B, the components of senna, are metabolized by gut bacteria into the active metabolite, rheinanthrone
  - Rheinanthrone appears to ↑ cyclooxygenase 2 (COX2) expression in macrophage cells → ↑ prostaglandin E2 (PGE2) →↓ aquaporin 3 expression in mucosal epithelial cells of the large intestine → laxative effect by restricting water reabsorption by the large intestine→ ↑ fecal water content
  - Rheinanthrone also ↑ peristalsis in the large intestine
- Pharmacokinetics
  - Absorption
    - <10% is absorbed from the gut mostly in the form of the active metabolite rheinanthrone
  - Volume of distribution
    - Volume of distribution of radiolabelled IV sennoside B in rats was 0.802±0.124L/kg
  - Metabolism
    - Sennosides A and B are metabolised to sennidins A and B by gut bacteria.
    - Sennidins A and B are further metabolized to rheinanthrone by gut bacteria using beta-glucosidase
    - Rheinanthrone is absorbed into systemic circulation where 2.6% is metabolized to rhein and sennidins A and B via oxidation
    - Rheinanthrone is the major active metabolite of sennosides A and B which produces the laxative effect of the medication
    - Rhein is also an active metabolite known to have many protective effects
  - Route of elimination
    - 3-6% of metabolites are excreted in urine with some in bile
    - >90% of sennosides are excreted in the feces as polymers with 2-6% of the parent compounds excreted unchanged
  - Half-life
    - T12 of radiolabelled IV sennoside B in rats was 8.57±0.65 h
  - Clearance
    - Clearance of radiolabelled IV sennoside B in rats was 0.065±0.007 L/h/kg
- Contraindication/precautions
  - Hypersensitivity to anthraquinones or their components
  - GI
    - Abdominal pain, undiagnosed
    - Acute surgical condition
      - Appendicitis
      - Bowel obstruction
    - Bowel obstruction / fecal impaction

- Adverse effects
  - GI
    - Abdominal pain
    - Bloating/flatulence
    - Pseudomelanosis coli / cathartic colon
    - Diarrhea
  - GU
    - Nephritis
    - Coloured urine
  - Beware of possible laxative abuse
- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Safe

- **Bisacodyl** (Dulcolax®)



- Indication
  - Constipation
- Mechanism of action
  - Stimulate enteric nerves to cause peristalsis, i.e., colonic contractions
  - ↑ fluid and salt secretion

- Pharmacokinetics
  - Absorption
    - Bisacodyl po are only 16% bioavailable
    - A 10 mg enteric coated po tablet reaches a Cmax of 26 ng/mL with a Tmax of 8 h,
    - A 10 mg oral solution reaches a Cmax of 237 ng/mL with a Tmax of 1.7 h.10
    - A 10 mg suppository reaches a Cmax of 0-64 ng/mL
    - In lactating women, 10 mg bisacodyl po reaches a Cmax of 20.5-195 ng/mL, with a Tmax of 3-4 h
      - Geometric mean AUC after a single dose of 471 h*ng/mL
      - After multiple doses, the geometric mean AUC decreases to 311 h*ng/mL
  - Volume of distribution
    - Data not readily available
    - However, the volume of distribution of the active metabolite, BHPM, in lactating women is 181 L after a single dose and 289 L at steady state
  - Metabolism
    - Bisacodyl is deacetylated to the active bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) by an intestinal deacetylase
    - A small amount of BHPM is absorbed from the GI tract, and is glucuronidated before elimination
  - Route of elimination
    - The majority of bisacodyl is eliminated in the feces
    - 8-17.0% is eliminated in the urine as the active metabolite BHPM
  - Half-life
    - Data regarding T1/2 of bisacodyl is not readily available
    - T1/2 of BHPM, in lactating women was 7.3 h after a single 10 mg po and 10.0 h after multiple doses
  - Clearance
    - Data regarding the clearance of bisacodyl is not readily available.
    - Apparent plasma clearance of BHPM, in lactating women after a single 10 mg po is 272 mL/min and after multiple doses is 412 mL/min

- Contraindication/precautions
  - Known hypersensitivity to Bisacodyl or its components
  - Nausea/vomiting
  - Suspected bowel obstruction

- Adverse effects
  - GI
    - Abdominal pain
    - Diarrhea
    - Colonic inertia (atony)
    - Proctitis with use (suppositories)

- Peripartum
  - Pregnancy
    - Safe
  - Lactation
    - Not known

- **Castor Oil**

- Indication
  - Constipation

- Mechanism of action
  - Broken down to ricinoleic acid
    - Induces a strong laxative effect
    - Acts as an anionic surfactant that
    - ↓ net absorption of fluid
    - ↑ intestinal peristalsis
  - Ricinoleic acid interacts with EP3 prostaglandin receptors expressed on intestinal (and uterine smooth muscles) → smooth muscle contraction → defecation
  - Rarely the prostaglandin misoprostol is used to treat chronic constipation, making use of its adverse effect of diarrhea.
    - More frequently misoprostol may be used to ↓ risk of complications if NSAIDs to the gastric mucosa (gastroprotection).

- Pharmacokinetics
  - Absorption
    - After oral ingestion of castor oil, ricinoleic acid is released by lipases in the intestinal lumen and absorbed in the intestine
    - Findings from the rat study suggest that the absorption of castor oil is inversely related to the administered dose, but the absorption is virtually complete at small doses (4 g)
  - Metabolism
    - Hydrolyzed to glycerol and ricinoleic acid via pancreatic or intestinal lipase activity
    - Ricinoleic acid is metabolized systemically and the metabolites are excreted
    - Fatty acids are expected to be degraded by pancreatic and intestinal lipase
  - Route of elimination
    - Fecal recovery of radio-labelled castor oil ranged from 11.4% (for 10 g castor oil) to 86.0% (for 44.4 g castor oil)

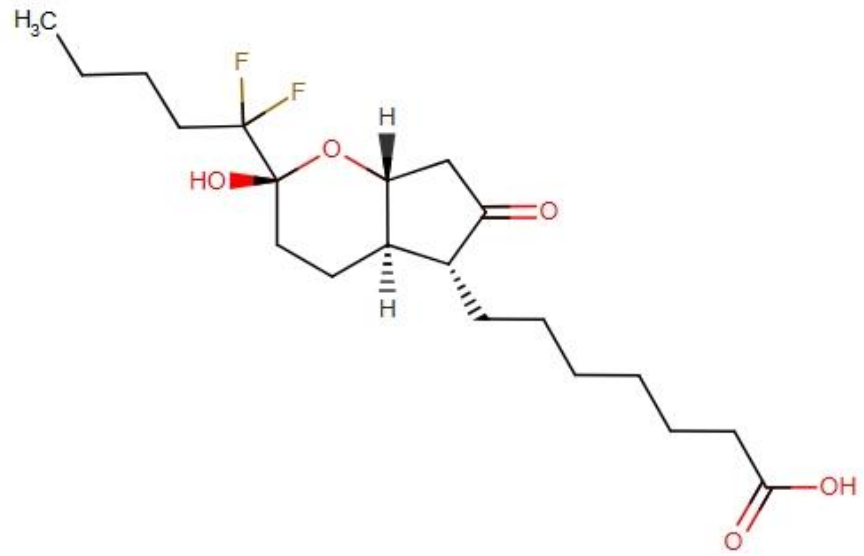
- Contraindication/precautions
  - Known hypersensitivity to castor oil
  - Pregnancy
  - GI
    - Obstruction
    - Appendicitis
    - Acute pain
    - Nausea/vomiting

- Adverse effects
  - GI – Abdominal pain / nausea / vomiting
  - MSK – Muscle cramps

- Peripartum
  - Pregnancy
    - Do **not** give
      - EP3 receptors evoke contraction of uterine smooth muscle → do **not** use in pregnancy/lactation.
  - Lactation
    - Do **not** give

CHLORIDE/WATER SECRETION

❖ Lubiprostone



- Indication
  - Constipation
- Mechanism of action
  - Specifically activating ClC-2 chloride channels (a normal constituent of the apical membrane of the human intestine) in a protein kinase A action independent fashion.
  - Activation of ClC-2 chloride channels causes an efflux of Cl- into the lumen → efflux of Na+ ions through a paracellular pathway to maintain isoelectric neutrality → water follows Na+ into the lumen in order to maintain isotonic equilibrium → ↑ intestinal fluid secretion.
  - Activates intestinal chloride channels → secretion of chloride and water into lumen of intestine → laxation
- Pharmacokinetics
  - Absorption
    - Has ↓ systemic availability following oral administration and concentrations in plasma are below the level of quantitation (10 pg/mL).
  - Metabolism
    - Rapidly and extensively metabolized by 15-position reduction, α-chain β-oxidation, and ω-chain ω-oxidation
    - These biotransformations are mediated by the ubiquitously expressed carbonyl reductase. M3, a metabolite of lubiprostone formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α-hydroxy and β-hydroxy epimers.

- Route of elimination
  - Peak plasma concentration ~1.14 h, with a majority of the drug excreted in the urine within 48 h.
  - Lubiprostone and M3 are only detected in trace amounts in human feces.
- Half-life
  - 0.9 to 1.4 h

➢ Contraindication/precautions

- Known hypersensitivity to lubiprostone or its components
- Bowel obstruction, mechanical/structural

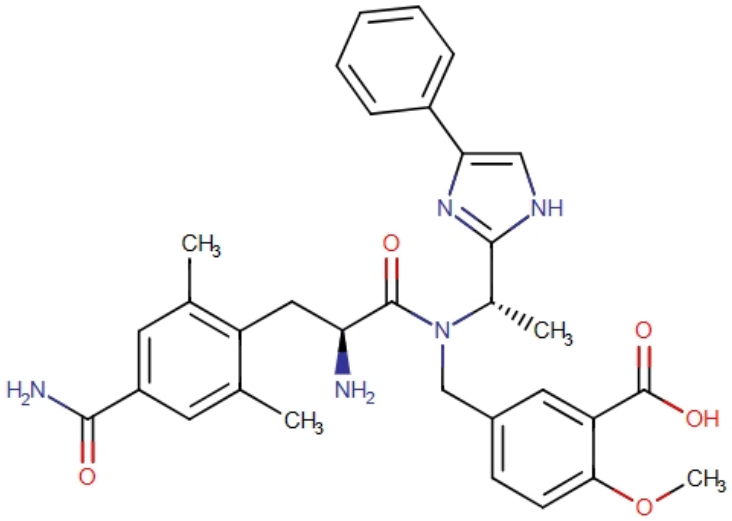
➢ Adverse effects

- CNS
  - Headaches
- GI
  - Abdominal pain / distention
  - Nausea
  - Flatulence
  - Diarrhea

➢ Peripartum

- Pregnancy
  - Safe
- Lactation
  - Safety not known

❖ **Eluxadoline** (Viberzi®)



- Indication
  - Constipation
- Mechanism of action
  - Opioid receptor (locally acting to ↓ pain/diarrhea)
    - Agonist
      - Mu and kappa receptors
    - Antagonist
      - Delta
  - Hypersensitivity to eluxadoline and its components
- Pharmacokinetics
  - Absorption
    - Oral absorption of eluxadoline is poor (~1%) due to poor GI permeability, and its zwitterionic nature leading to a negatively charged molecule across the GI pH range.
  - Metabolism
    - The metabolism is currently unclear; however, evidence suggests limited glucuronidation forms an acyl glucuronide metabolite that is then excreted into urine.
  - Route of elimination
    - 82% excreted in feces
    - <1% excreted in urine
  - Half-life
    - Mean plasma elimination T1/2, 3.7-6 h
- Contraindications/precautions
  - Liver
    - ↓ liver function
    - Alcohol abuse
  - Biliary tree
    - Sphincter of Oddi dysfunction (SOD)
    - Obstruction
  - Gallbladder
    - Cholecystectomy
    - ↓ dose (otherwise ↑ AEs)
  - Pancreas
    - Obstruction, pancreatic duct
  - Small bowel / colon
    - Obstruction, mechanical

- Adverse effects
  - CNS
    - Dizziness
    - Fatigue
    - Drowsiness
  - Lung
    - Asthma/wheezing
    - Bronchitis
    - Upper respiratory infection (URI)
  - GI
    - Abdominal pain / GERD
    - Nausea/distention
    - Constipation
    - ↑ liver enzymes (LES: ↑ ALT / ↑ AST)
  - Skin
    - Rash

- Drug-drug interaction
  - Alcohol
    - ↑ adverse effects
  - A long list of other drug-drug interactions due to ↑ serum concentration of eluxadoline

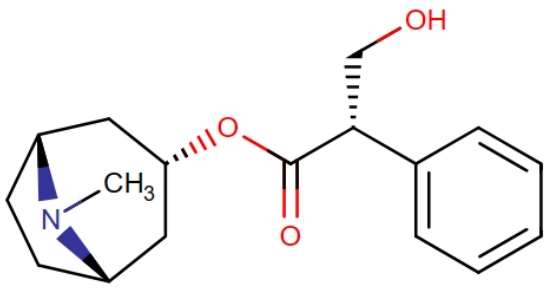
- Peripartum
  - Pregnancy
    - Paucity of data
  - Lactation
    - Paucity of data

IRRITABLE BOWEL SYNDROME (IBS)

- Treatment
  - Altered bowel habit – Please see previous sections on Diarrhea and on Constipation

❖ **Pain Reduction in GI Functional Disorders** (e.g., IBS)

- **Hyoscyamine Sulphate**



- Indication
  - Pain reduction in GI functional disorders, such as irritable bowel syndrome
    - 0.125-0.25 mg po q4h prn

- Mechanism of action
  - Tricyclic antidepressant (TCA)
    - May ↑ threshold for pain in CNS
  - Competitively and non-selectively antagonises muscarinic receptors in the smooth muscle, cardiac muscle, sinoatrial node, atrioventricular node, exocrine nodes, gastrointestinal tract, and respiratory tract

- Pharmacokinetics
  - Absorption
    - Completely absorbed by sublingual and oral routes, though exact data regarding the Cmax, Tmax, and AUC is not readily available
  - Metabolism
    - Largely unmetabolized, however a small amount hydrolyzed into tropine and tropic acid
  - Route of elimination
    - Mainly eliminated in the urine as the unmetabolized parent compound
  - Half-life
    - 3.5 h

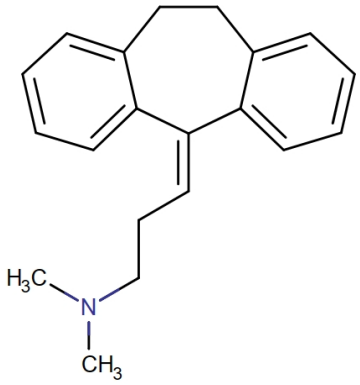
- Contraindication/precautions
  - Known hypersensitivity to imipramine or its components
  - Adverse effect / drug-drug interactions (e.g., use of monoamine oxidase inhibitor)
  - CNS – Do **not** use in period of recovery from a myocardial infarction

- Adverse effects (AEs)
  - CNS – Headache/dizziness
    – Somnolence
  - Lung – Asthma
  - Eyes – Blurred vision
  - CVS – Arrythmia / heart block
    – Palpations
    – Hypotension (orthostatic) / syncope
    – Myocardial infarction
  - GI – Constipation
    – Xerostomia
  - GU – Urinary retention
  - Endocrine – ↑ body weight

- Drug-drug interaction
  - CNS – ↑ risk of
    - When used with monoamine oxidase (MAO) inhibitors
      - Overstimulation / seizure / hyperreflexia Psychomotor activity
    - When used with pimozide
      - ↓ psychomotor activity
      - ↑ CNS depression
  - CVS – ↑ QT prolongation
    – Arrhythmias
  - GI – ↑ GI exposure
    – Ulcerative GI mucosal lesions with K^+ tablets

- Peripartum
  - Pregnancy
    – Use with caution (category D)
  - Lactation
    – Safe

- **Amitriptyline**



➢ Indication

- Pain reduction in functional GI disorders, such as irritable bowel syndrome (IBS)
  - 0.1 mg/kg po q1h, then increase dose slowly prn to maximum 150 mg/d

➢ Mechanism of action

- Tricyclic anti-depressant
  - Used in low dose for patients with IBS, is not acting as an antidepressant
- May ↑ threshold for pain in the central nervous system (CNS)
- ↓ reuptake of serotonin +/- norepinephrine by the presynaptic neuron → ↑ serotonin +/- norepinephrine in the CNS
  - Anticholinergic properties

➢ Pharmacokinetics

- Absorption
  - Rapidly absorbed following oral administration (bioavailability 30-60% due to first pass metabolism)
  - Tmax 2-12 h after po or IM administration
  - Steady-state plasma concentrations vary greatly and this variation may be due to genetic differences
- Volume of distribution
  - Apparent volume of distribution estimated after IV administration is 1221 L ± 280 L; range 769-1702 L (16 ± 3 L/kg)
  - It is found widely distributed throughout the body
  - Amitriptyline and the main metabolite nortriptyline pass across the placental barrier and small amounts are present in breast milk
- Metabolism
  - Metabolism occurs mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid
  - Other isozymes involved are CYP1A2 and CYP2C9
  - Metabolism of this drug is subject to genetic polymorphisms
  - The main active metabolite is the secondary amine, nortriptyline

- Route of elimination
  - Amitriptyline and its metabolites are mainly excreted in the urine.
  - Virtually the entire dose is excreted as glucuronide or sulphate conjugate of metabolites, with ~ 2% of unchanged drug appearing in the urine
  - 25-50% of a single po dose is excreted in urine as inactive metabolites within 24 h
  - Small amounts are excreted in feces via biliary elimination
- Half-life
  - Elimination T1⁄2 after po administration ~25 h
- Clearance
  - Mean systemic clearance 39.24 ± 10.18 L/h (range: 24.53-53.73 L/h)
  - No clear effect of older age on the pharmacokinetics of amitriptyline, although it is possible that clearance may be decreased

➢ Contraindication/precautions

- Known hypersensitivity to amitriptyline
- Adverse effects / drug-drug interactions
- Lactation / breast feeding
- Myocardial infarction, recovery phase
- Use of cisapride
- Use of monoamine oxidase inhibitors (MAOIs) within last 14 d

➢ Adverse effects (AEs)

- General
  - Fever/diaphoresis
  - Fatigue
- Eyes
  - ↑ intraocular pressure (↑ IOP)
  - Dilated/mydriasis
  - Blurred vision
- CNS
  - Anxiety/fatigue
  - Ataxia/extrapyramidal symptoms
  - ↓ cognition
  - Hallucinations
  - Headache/dizziness
  - Neuroleptic malignant syndrome
  - Peripheral neuropathy
  - Seizure
  - Seizures
  - Serotonin syndrome
  - Stroke
  - Suicidal ideation
- Ears
  - Tinnitus

- CVS
  - Arrythmias / AV block / tachycardia
  - Hyper-/hypotension (orthostatic, syncope)
  - Myocardial infarction / cardiomyopathy
- GI
  - Anorexia/nausea/vomiting
  - Black tongue
  - ↓ body weight
  - Constipation / diarrhea
  - Dry mouth / stomatitis / abnormal taste
  - Ileus
- GU
  - Urinary retention
- Blood
  - Eosinophilia
  - Myelosuppression
  - Purpura
- MSK
  - Tremor
  - Weakness
- Drug withdrawal syndrome on suddenly stopping drugs amitriptyline

➢ Drug-drug interaction

- CNS
  - Depression
    - Alcohol
    - Propoxyphene
    - Valerian
    - St. John's Wort
  - ↑ neurotoxicity
    - Lithium
  - Serotonin syndrome
    - SSRIs
- CVS
  - ↑ stimulation
    - Amphetamine
  - ↑ hypotension, orthostatic
    - Altretamine
    - MAOI
  - ↑ vasopressor effects
    - α/β agonists
    - Nilotinib
    - Gadobutrol
  - ↑ QTc prolongation
    - Alfuzosin
    - Artemether
    - Chloroquine
    - Ciprofloxacin
    - Dronedarone
    - Lumefantrine
    - Pimozide
    - Quinidine
    - Quinine
    - Tetrabenazine
    - Thioridazine
    - Ziprasidone

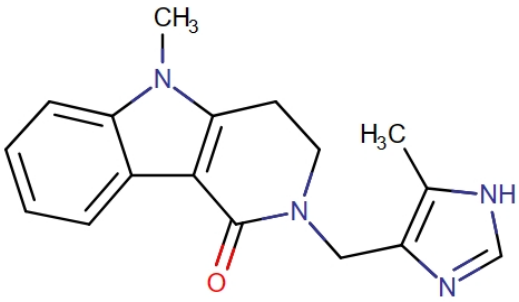
○ Blood	– ↑ anticoagulation effect coumadin (and other vitamin K antagonists)
○ ↑ serum concentration (↑ therapeutic effects and potential for ↑ adverse effects)	– Bupropion – Conivaptan – Cimetidine – Cinacalcet – Divalproex – Duloxetine – Grapefruit juice – Protease inhibitors – Quinidine – SSRIs – Terbinafine – Valproic acid
○ ↑ adverse effects	– β2-agonist – Desmopressin – Dexmethylphenidate – Methylphenidate – Metoclopramide
○ ↑ anticholinergic effect	– Pramlintide
○ ↑ hypoglycemic effect	– Sulfonylureas
○ ↑ risk of seizures	– Tramadol
○ ↓ serum concentration (↓ therapeutic effects) and potential adverse effects	– Acetylcholinesterase inhibitor – Iobenguane I^{123} – α2-agonists

Abbreviations: CNS, central nervous system; IBS, irritable bowel syndrome; IOP, intraocular pressure; MAOI, monoamine oxidase inhibitor; SSRIs, selective serotonin reuptake inhibitor

➢ Peripartum

- Pregnancy
  - Category D
- Lactation
  - Do **not** use

- **Alosetron** (Lotronex®)



➢ Indication

- Diarrhea/IBS without constipation, in women only
  - 0.5 mg po b.i.d. for 4 wk, then
  - 0.5 mg po b.i.d. prn

➢ Mechanism of action

- Serotonin (5-HT_3) receptor antagonist
- Inhibits activation of non-selective cation channels which results in the modulation of serotonin-sensitive GI motor and sensory processes

➢ Pharmacokinetics

- Absorption
  - 50-60%
- Volume of distribution
  - 65-95 L
- Metabolism
  - Hepatic, via microsomal cytochrome P450 (CYP)
- Route of elimination
  - Renal elimination of unchanged alosetron accounts for only 6% of the dose.
  - Extensively metabolized in humans.
- Half-life
  - 1.5 h
- Clearance
  - 600 mL/min

➢ Contraindication/precautions

- Known hypersensitivity to alosetron or its components
- Adverse effects / drug-drug interactions
- Used only in women without constipation (IBS-C)

- CNS
  - Headache
- GI
  - History of
    - Obstruction / perforation
      - Crohn disease
      - Diverticulitis
      - Ischemic colitis
      - Toxic megacolon
  - Abdominal pain
  - Chronic liver disease (GI dosing)
- Blood
  - Hypercoagulable state

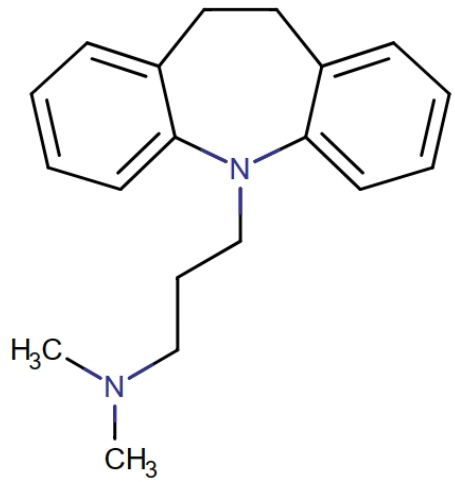
➢ Drug-drug interaction

- ↑ risk of alosetron AEs when used with fluvoxamine

➢ Peripartum

- Pregnancy
  - Category **D**
    - Do **not** use, or use with great caution
- Lactation
  - Safety **not** known

- **Imipramine**



➢ Indication

- IBS
  - Imipramine 10 mg od, increase dose to maximum of 100 mg/d, prn

- Mechanism of action
  - Inhibiting the neuronal reuptake of the neurotransmitters, norepinephrine and serotonin
- Pharmacokinetics
  - Absorption
    - Rapidly and well absorbed (>95%) after po administration
    - Primary site of absorption is the small intestine as the basic amine groups are ionized in the acidic environment of the stomach, preventing movement across tissues
    - Bioavailability ranges from 29-77% due to high inter-individual variability
    - Cmax 2-6 h following oral administration
    - Absorption is unaffected by food.
  - Volume of distribution
    - ↑ apparent volume of distribution of 10-20 L/kg
    - Drug is known to accumulate in the brain at concentrations 30-40x that in systemic circulation
  - Metabolism
    - Nearly exclusively metabolized by the liver
      - Converted to desipramine by CYP1A2, CYP3A4, CYP2C19
      - Desipramine is an active metabolite.
      - Both imipramine and desipramine are hydroxylated by CYP2D6
    - Minor metabolic pathways include dealkylation to form an iminodibenzyl product as well as demethylation of desipramine to desmethylimipramine and subsequent hydroxylation
    - < 5% of orally administered imipramine is excreted unchanged
  - Route of elimination
    - Primarily excreted in the urine with < 5% present as the parent compound
  - Half-life
    - Mean T1/2 of 12 h
    - Its active metabolite, desipramine has a mean T1/2 of 22.5 h
  - Clearance
    - Mean clearance of 1 L/h/kg
    - Active metabolite, desipramine has a mean clearance of 1.8 L/h/kg

❖ Other treatments of IBS

- Probiotics
  - The data on clinical efficacy of probiotics is difficult to interpret because of
    - Wide variability in products used
    - Selection of patients, and
    - Evaluation of outcomes etc.
  - Please refer to recent review for outline of limitations to interpretation of data.
    - The best data is for maintenance of antibiotic induced remission of pouchitis (Systemic Review and Meta-analysis of published data 2012-2022)

- Prevention
  - Antibiotic-associated diarrhea
  - Candidiasis, oral
  - Chemoradiation-induced diarrhea, prevention
  - Clostridium difficile associated diarrhea
  - H. pylori eradication therapy, prevention
  - Necrotizing enterocolitis
  - Post-operative sepsis
  - Pouchitis
  - Traveler's diarrhea
- Treatment
  - Irritable bowel syndrome
  - Ulcerative colitis
  - Hepatic encephalopathy
- Maintenance
  - Ulcerative Colitis
  - Pouchitis

Quigtej EMM. Sleisenger and Fordtran's Gastrointestinal and Liver Disease- Pathophysiology, Diagnosis, Management. 11th Edition, 2020, Chapter 130, pages 2187-2191.

- Stool Transplantation
  - Mixed results in UC, depending upper route of delivery (nasoduodenal vs. enema), donor

Nasoduodenal	Clinical remission	wk 12	NS
Enema	Remission	wk 6	24% vs. 5%
Colonoscopy then enema	Steroid-free remission	wk 8	24% vs. 8%

  - Negative results in Crohn disease
  - C-difficile overall efficacy prevents recurrent CDI, stool administered into
    - Stomach, small intestine, 81%
    - Colon, rectum, 93%

	Prevention of Recurrent CDI
Nasoduodenal infusion	81%
Vancomycin	31%
Vancomycin plus bowel lavage	23%

  - Single IMT vs. multiple IMTs
    - Cure rate 75% vs. 100%

CONSTIPATION IN PREGNANCY

- Causes / associations
  - Hormonal
    - Slow transit
  - Mechanical
    - Distended uterus
  - Medications
  - Lifestyle
    - Reduced exercise
    - Dietary changes
  - Pre-existing disease:
    - Chronic idiopathic intestinal pseudo-obstruction
    - Chronic slow-transit constipation
    - Irritable bowel syndrome
    - Congenital or acquired megacolon

- **FDA category*** (shown in brackets) of laxatives in pregnancy

Safe (B)	Caution (C)	**Unsafe** (D)
○ Bisacodyl	– Castor oil	-**Anthraquinones**
○ Bulking agents	– Docusate sodium	**-5HT4 agonists**
○ Glycerin	– Saline osmotic laxatives	**-Prostaglandins (misoprostol)**
○ Lactulose		
○ Polyethylene glycol (PEG)	– Senna	

* While the FDA category of pharmaceutical agents is no longer widely used, somephysicians find the use of these categories useful.

Adapted from: Cullen G, and O'Donoghue D. Best Pract Res Clin Gastroenterol 2007; 21(5): pg. 815.; and Thukral C, and Wolf JL. Nat Clin Pract Gastroenterol Hepatol 2006; 3(5): pg. 260.

- Treatments

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ULCERATIVE COLITIS (UC)

- Details of the pharmacological agents used for treatment of Ulcerative Colitis are given on the section on Inflammatory Bowel Disease (IBD) in the chapter on Small Intestine.

Drugs that are effective in UC but not in CD	Drugs that are effective in CD but not in UC
○ 5-ASA	○ Methotrexate
○ Cyclosporine	

Exception

- The ↓ risk of loss of effect of anti-TNF therapy due to the prediction of antibodies, low dose immunosuppressants are often added, such as AZA or MTX,
  - In this setting if a patient with UC is being placed on anti-TNF therapy, MTX may be added, not as primary therapy but rather as to supplement the benefit of anti-TNF.

MICROSCOPIC COLITIS

- Imodium 2 mg po, maximum 8/d
- Fecal incontinence is common
- ↑ risk of lung cancer and lymphoma
- Biopsy (bx)
  - R/L colon (R>L)
  - 3 bx from R, T, L colon
- ↑ lymphocytes > 20/100 epithelial cells (lymphocytic colitis)
- Subepithelial collagen band > 10 µm (collagenous colitis)

➢ Treatment

- Suggested algorithm

Check Rx list / stop offending medications (e.g., NSAIDs, PPIs)

↓

Antidiarrheals

- Imodium (adjunct) up to 8/d
- Lomotil
  - Max 4 tablets/d
    - Time dosing to when symptoms are worse

↓

Pepto-Bismol (RCT) histological response in some

↓ - Do **not** use bismuth long-term (neurotoxicity)

5-ASA or Cholestyramine

↓

Entocort 9 mg clinical/histological response
(Budesonide) 80% clinical response
65% histological response

Achieve remission ↓

Relapse in 50-75% in 1st yr after stopping budesonide

Maintenance ↓

Maintenance 6 mg po od

↓

Immunosuppression / biologicals

COLORECTAL CANCER (CRC)

- Molecular pathways to CRC
  - CIN
    - Chromosomal instability
      - "gain of function" mutation
  - Mismatch repair
    - Mutator phenotype
      - DNA mismatch/ repair
  - Hyper-methylation
    - CIMP+
      - Serrated phenotype (30% of polyps, esp. in R-colon)
    - Epigastric hypermethylation of MMR gene (e.g., MLN1) → CpG island hypermethylation phenotype
    - CpG region in gene → methylation → ↓ activity of gene MLN1 hypermethylation
    - BRAF mutation → MSI-N, CIMP+, CRCs
  - Lynch MMR genes
    - Germline (sporadic)
    - Not germline (not necessarily passed on)
  - Treatments vary for different genetic mutations
    - Germline mutation
    - Best to test CRC tissue
  - Microsatellite instability (MSI) – R. colon
  - Chromosomal instability (CI)
    - L. colon
    - CIN
    - APC mutations
    - K Ras mutations
  - Approximate doubling time of CRC 2 yr
    - "Fat" (obese)
    - Women
    - Hyperplastic polyposis syndrome
    - Dilated crypts
    - Serrated surface
    - 4% have malignancy

- Colorectal Cancer Screening
  - Family history CRC (25%)
  - Begin average risk person at age 45, q5-10 yr, depending upon findings of
    - Endoscopic type (pedunculated, sessile, sessile serrated)
    - Type (adenomatous, hyperplastic, hamartoma, juvenile polyps)
    - Subtype (tubular, villous, tubulovillous)
    - Size of polyp

- First Degree Relative (FDR) Screen

Index	Condition	Age	Frequency
1 FDR	CRC/AA	40 yr or 70 yr 40-50 yr	q5-10 yr q5-10 yr
≥ 2 FDR	CRC/AA	40-50 yr	q5-10 yr
≥ 1 FDR	CRC/AA	50 yr	q5 yr
≥ 1 FDR	AA	40-50 yr	

- ↑ #, ↑ distorted / disorganized
- Clusters
- Invasion
- Poor margins differ
- Malignant polyp
  - Margin ≤ 1 mm
  - Size of tumor (**not** size of polyps) > 2 (w) x 4 (d) mm
  - Shape, budding
  - Lymphovascular involvement

Abbreviations: d, depth; w, width

- Proximal extension of UC is a prediction of poor prognosis.

Risk of Cancer in Hamartomatous Polyposis Syndrome

Site	General Population Risk,[a] %	Syndrome Risk, %	Mean Age at Diagnosis, yr
○ PJS			
− Colorectal Cancer	4.3	39	42-46
− Stomach	<1	13	37-42
− Breast	12.9	32-54	37-59
− Ovarian (mostly SCTAT)	1.2	21	28
− Cervix (adenoma malignum)	<1	10-23	34-40
− Uterus	3.1	9	43
− Pancreas	1.7	11-36	41-52
− Testicular (Sertoli cell tumour)	< 1	9	6-9
− Lung	6.3	7-17	47
○ JPS			
− Colon	4.3	39	44
− Stomach	<1	5-21	54
○ CS			
− Breast	12.9	25-85	38-46
− Thyroid	1.3	3-38	31-38
− Uterus	3.1	5-28	25
− Kidney (renal cell)	1.7	15-34	40
− Colon	4.3	9-18	35
− Melanoma	2.3	6	3[b]
○ HMPS			
− Colon	4.3	Increased	-

Abbreviation: SCTAT, sex cord tumours with annular tubules

[a] National Cancer Institute Surveillance, Epidemiology and End Results Cancer Statistics Review 1975-2017. Lifetime risk (%) of being diagnosed with cancer by site 2017.
[b] Youngest age of onset

Printed with permission: Boland C, et al. Am J Gastroenterology 2020; 117(6): 846-864 (Table 3).

HEPATOBILIARY TREE

AUTOIMMUNE HEPATITIS

- Definition
  - Autoimmune hepatitis (AIH) is an immune disorder of the liver.
    - The cause of these immune changes is not known.
      - Treatment is directed at these immune changes, using corticosteroids and immunosuppressants such as azathioprine.

- Pathophysiology: MHC

- DRB1, APC, CD4+ – Th Cells
  - Possible environment antigenic peptide (molecular mimicry) → inciting antigen fits in the antigen-binding groove of the class II DR molecule of the MHC antigen presenting cells (in USA / Canada, usually DRB1 gene, susceptibility alleles DRB1*0301 and DRB1*0401) →
  - The DR molecule-antigen complex of the APC (antigen-presenting cell) interacts with the antigen receptor of CD4+ T-helper cells (1st signal).

- CD28, B7 – Th1/Th2
  - The CD28 molecule on the surface of CD4+ T-helper cell binds to the B7 ligand on the surface of the APC" (2nd signal)
  - CD4+ T-helper cells differentiate into Th1 or Th2 T-cells
  - The cytokine milieu of Th1 and Th2 cytokines is regulated

Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Saunders/Elsevier, Philadelphia, 2020

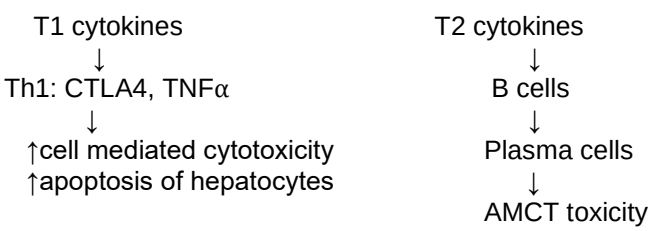
- Th1/Th2, NKT, Treg, Type 1/2 Cytokines
  - This balance between Th1 and Th2 may be disturbed by
    - ↓ intrahepatic natural killer T cells (NKT)
    - ↓ regulation of CD8+ T cell proliferation by
      - T-reg (T-regulatory CD4+ CD25+) cells
  - The cytokine pathways are increased by ↓ activity of Treg (T regulatory) cells
  - Th2 (type 2 cytokine) pathway of activated CD4+ T-helper cells causes differentiation of B cells into plasma cells
    - Plasma cells → ↑ production of immunoglobulin → antibody-mediated cellular toxicity (AMCT)
  - Hepatocyte damage is caused by
    - Cell-mediated cytotoxicity (regulated by type 1 cytokines)
    - Antibody-dependent cell-mediated (ADCMC; cytotoxicity (regulated by type 2 cytokines)

❖ CTLA4, TNF, FAS

- Th1 (type 1 cytokine) pathway of activated CD4+ t-helper cells are stimulated by polymorphism of
  - CTLA4 (the cytotoxic T lymphocyte antigen 4 gene)
  - TNF A*2 (TNF gene)
  - TNF receptor superfamily gene (FAS)
  - TNFRSF6 (FAS gene phenotype at position – 670)
- These polymorphisms and Th1 T-cells
  - Sensitize cytotoxic T cells
    - ↑ cell-mediated cytotoxicity
    - ↑ apoptosis of hepatocytes

➢ Overview

- Inciting antigen (molecular mimicry)
  ↓
- DR molecule of MHC antigen
  ↓
- CD28 on surface binds CD4+ Th
  ↓ ↓
  Th1 Th2
  ↓
  Balance disturbed
  ↓
- ↓NKT, ↓CD8+ perforation (Treg)
  ↓
- Hepatocyte damage: cytokines



Abbreviations: AMCT, antibody-mediated dependent cellular toxicity; APC, antigen presenting cells; MHC, major histocompatibility cells; NKT, natural killer T cells; Th, T helper cells; TNF, tumour necrosis factor; T reg, regulatory T cells; TRS, TNF receptor superfamily

➢ Treatment

- Asymptomatic Patients
  - ~40% of patients can be asymptomatic even if they have severe AIH
  - Of these 40% of patients who are asymptomatic, ~ 40% develop symptoms
    - Asymptomatic patients more frequently have concurrent immune disorders of thyroid/skin
    - Asymptomatic patients may improve without treatment, but the improvement is
      - Not predictable
      - Not complete
      - Not fast

      } Asymptomatic persons with AIH who are not treated have a ↓ 10 yr survival than do those who have severe symptomatic AIH (67% vs. 98%, respectively)

    Message: Even asymptomatic patients with AIH have a risk of death

- Achieving Remission of Acute / Acute severe (fulminant AIH)
  - Treat asymptomatic/mild AIH with abnormal liver biochemistry/histopathology
    - "Only the absence of laboratory or histological findings of disease activity is a justification for withholding treatment"

MCQ Ruby

- Give the reasons why AIH may be difficult to diagnose.
  - Differential diagnosis
    - Acute / acute severe and must be distinguished from
      - New onset of AIH
      - Chronic AIH plus acute flare
    - Treatment of AIH with immunomodulators
      - Acute AIH plus concurrent condition, e.g., viral hepatitis/toxic hepatitis
      - Viral hepatitis, then AIH
  - Diagnostic imaging in acute/severe AIH
    - ↑ INR in acute liver failure (ALF)
    - Heterogenies ↓ in hepatic attenuation on CT (in 65% of AIH, but only 5% of virus induced acute liver failure
  - Laboratory diagnosis
    - ANA ~1/3 are negative or weakly positive ≤ 1:40 tire
    - IgG ~ 1/3 are normal
  - Hepatic histopathology
    - Acute severe hepatitis is usually in the centre lobular area, not the peripheral area

- If MELD score < 40
  - Has not been shown to ↑ survival
- For MELD score > 40
  - Early liver transplantation (LT)

- First-line treatment regimens for induction of remission
  - "Head-to-head comparisons between the [following] endorsed regimens have not been performed, and the recommendations proposed with each new [professional association-endorsed treatment regimen] guidelines have been based mainly on weak clinical evidence."

AASLD Endorsed Combination regimen	AASLD-Endorsed Monotherapy Regimen	BSG/EASL-Endorsed Combination Regimen
○ Induction phase x 4 wk	○ Induction phase x 4 wk	○ Induction phase x 10 wk
− Prednisone or Prednisolone plus AZA 30 mg daily x 1 wk 20 mg daily x 1 wk 15 mg daily x 2 wk, plus	− Prednisone or Prednisolone 60 mg daily x 1 wk 40 mg daily x 1 wk 30 mg daily x 2 wk	− Prednisolone 0.5-1 mg/kg daily (e.g., patient weighing 60 kg) 60 mg daily x 1 wk 50 mg daily x 1 wk 40 mg daily x 2 wk 30 mg daily x 1 wk 25 mg daily x 1 wk 20 mg daily x 1 wk 15 mg daily x 2 wk 12.5 mg daily x 2 wk
− Azathioprine 50 mg daily	−	− Azathioprine 1-2 mg/kg daily start 2 wk after prednisolone 50 mg daily x 2 wk 100 mg daily thereafter
○ Maintenance phase:		
− Prednisone or Prednisolone 10 mg daily − Azathioprine 50 mg daily − Doses may be adjusted to response and tolerance	− Prednisone or Prednisolone 20 mg daily − Doses may be adjusted to response and tolerance − Preferred in patients with severe cytopenia, absent thiopurine methyl-transferase activity, azathioprine intolerance, or reluctance, or reluctance to use during pregnancy	− Prednisolone 10 mg daily − Azathioprine 100 mg daily − Doses may be adjusted to response and tolerance − All patients with thiopurine methyltransferase activity and azathioprine tolerance

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	Induction Interval, wk
○ Combination therapy of	
− AASLD: Prednisone / prednisolone plus azathioprine, started together BSG/EASL	4
− BSG/EASL: Prednisolone for 2 wk, then prednisolone, plus azathioprine	10
○ Monotherapy	
− AASLD: Prednisone / prednisolone; maintenance CS 20 mg/d, with doses adjusted to response/tolerance	4

➢ Indications

	AASLD Endorsed Regimen	BSG Endorsed Combination Therapy
○ Normal thiopurine methyltransferase (TPMT)	+	+
○ AZA tolerance	+	+
○ Obesity, diabetes, osteopenia	+	-
○ Emotional instability	+	

- AASLD-Endorsed Monotherapy Regimen
  - ○ Severe cytopenia
    - − WBC < 2.5 x 10^9 /L, or
    - − Platelet count < 50 x 10^9 /L
  - ○ Low/absent TPMT +
  - ○ AZA intolerance +
  - ○ Patient unwilling to use during pregnancy +

- Budesonide
  - ○ Pharmacology
    - − Synthetic glucocorticosteroids
    - − First-pass hepatic clearance > 90% (only ~10% of drug is absorbed and therefore has systemic glucocorticosteroids activity)
    - − ↓ proinflammatory cytokines IL01B, -2, -6, -8, TNF-α (tumor necrosis factor α)

- Comparison

Outcome	Comparisons of budesonide 3 mg t.i.d., plus azathioprine 1-2 mg/kg per day	Prednisone 40 mg/d tapered to 10 mg/d, plus azathioprine 1-2 mg/kg per d
− Normalization of ALT/AST	47%	18%
− Adverse effects	28%	53%
− Safety acceptable in cirrhosis	No	
− Development of ↓ bone density	No	Yes

  - Screen for osteoporosis (↓ bone mineral density (BMD) when corticosteroids started
  - If osteoporosis present or develops, use alendronate (a bisphosphonate)
  - If osteoporosis not present, use preventive measures
  - AS for all persons at risk for HAV/HBV infection or the complications, vaccinate for HAV/HBV infection.

- Azathioprine
  - Thiopurine methyl transferase (TPMT) activity measurement is strongly recommended for patients with inflammatory bowel disease (IBD, ulcerative colitis (UC) and Crohn disease (CD). The identification of ↓/0 TPMT activity mandates that azathioprine not be used at all, or only started in very low doses.
    - Even with normal TPMT activity, all patients on AZA thiopurine must have frequent/continued monitoring of WBC/platelet count to identify possible immunosuppression from non-TPMT metabolic pathways.
- However, in the consideration for the need for TPMT screening in all patients with AIH has been questioned
  - "…genotype and genotype screening for TPMT activity has not reduced the frequency of azathioprine-induced side effects in patients with AIH compared with unscreened patients.
    - Nor has the occurrence of azathioprine related side effects been associated with below-normal TPMT activity"
  - TPMT testing prior to azathioprine therapy is especially justified for patients with
    - Cirrhosis
    - Pre-existing cytopenia
- Azathioprine during pregnancy
  - IBD titration concludes azathioprine is safe to be taken during pregnancy and lactation
  - Hepatology literature suggests
    - Use of azathioprine should be individualized, or
    - Stop during pregnancy but maintain adjusted prednisone or prednisolone.
  - Dose adjustment may be particularly important if there is postpartum ↑ activity of AIH

❖ Response to attempt to achieve remission

- Achieving remission
- Definition of remission must be classified and collaborated as much more than symptoms
  - Symptoms → no symptoms
  - Biochemical abnormalities → normal biochemistry
    - Usually occurs in ~85% of AIH
    - Laboratory normality usually in 3-12 mon
    - ALT to < 50% of ULN< plus IgG < 12 g/L better prediction of normal histology than just biochemistry
  - Histopathological abnormalities → histological normality slower than biochemical normally by > 3-8 mon (8-12 mon for normal biochemistry, histological, normality or near-normal in 22 mon
    - Normal biochemistry does not mean likely
      - Normal histology
      - No progression or recurrence
      - Normal survival

MCQ Alert

- Treatment for AIH must continue beyond
  - Loss of symptoms
  - Loss of biochemical abnormalities
  - Presence of normal histopathology

- Do **not** consider stopping AIH therapy
  - For at least 3 yr
  - At least 2 yr after normal biochemistry
  - Normal biochemistry for 6 mon predicts normal histology, but
  - The only way to know if there is normal histology and that there is truly a low risk of recurrence if treatment is stopped, is to do a biopsy.
- Ultrasound / MR elastography plus biochemical normality as the best non-biopsy indicates of normal histopathology.
- All these predictors of normal histology
  - Biochemistry
  - Liver ultrasound elastography
  - Speed of recovery of ALT/IgG

- Incomplete response
  - Optimal treatment for 6 mon → incomplete response (normalization of biochemistry)
  - Differential
    - Incorrect drug regimen
    - Poor adherence
    - Incorrect dose
    - Drug toxicity / drug-drug interaction
  - Frequency
    - 14%
    - ↑ risk of AIH progression

- Treatment failure (despite compliance)
  - ↑ ALT, ↑ AST, ↑ IgG, ↑ bilirubin, or
    - Lack of improvement of blood work
  - Occurs in 9%

  } ▪ Within 3 mon

- Drug toxicity
  - Treatment ending complication with prednisone +/- azathioprine, 13%
  - Prednisone
    - Adverse effects over 2 yr, sometimes severe enough to require dose adjustment, 80%
  - Azathioprine (AZA)
    - Cytopenia
      - Usually residing with dose reduction, 46%
      - Drug stopped, 6%
      - Early resection causing AZA to be stopped, 5%
    - High risk of AZA-associated cytopenia in patients with cirrhosis
      - Direct AZA effect
      - Cirrhosis-associated hyperplasia
  - Budesonide-lower risk than prednisone for adverse effects, except
    - Patients with cirrhosis treated with budesonide have same risk of adverse effects as those treated with prednisone, including osteoporosis and portal vein thrombosis (PVT)

- Miscellaneous complications
  - Cirrhosis in treated patients ~25%
    - Even in persons with normal biochemistry
    - Especially in those who respond slowly to treatment, < 6 mon
  - Within 5 yr of treatment
    - Esophageal varices, 13%
    - Upper GI bleeding, 6%

- Hepatocellular cancer (HCC)
  - Annual rate, ~1% - 2%
  - Standardized
    - Incidence ratio of HCC in AIH, 23
    - Mortality rate, 42%
  - In patient with cirrhosis from AIH
    - Perform abdominal ultrasound (US) q6 mon (US plus AFP measurements also recommended)
- Enterohepatic malignancies
  - 5% overall

❖ Treatment withdrawal

- Warn patient that AIH recurrence is possible with cessation of treatment, even if symptoms, and histopathology have normalized and remained normal for 24 mon ("… no laboratory histologic assessment can confidently predict the absence of disease activity or relapse".
  - Against the background, cautiously consider the predictive value of these indications of continued remission after treatment withdrawal.
    - Biochemistry – AST < 1/2 ULN, IgG < 12 g/L (maintained remission for median of 28 mon (17-57)
    - Histopathology normal, relapse rate 28% vs. 76% for failure to normalize histopathology
- Protocols for treatment withdrawal
  - Corticosteroids
    - Gradual and monitored taper over > 6 wk
  - Azathioprine (AZA)
    - Continue full dose over half the withdrawal period, then reduce to half dose
    - If combination regimen, slowly taper both the prednisone and the azathioprine

❖ Treating Relapse after Treatment Withdrawal

➢ Definition

- After stopping treatment
  - ↑ ASL > 3x ULN +/- histopathology showing interference hepatitis

➢ Demography

- Relapse within 6 mon, 50%
  - Relapse within 3 yr, ~7%

} May be associated with progression to
- Cirrhosis, 10%
- Liver failure, 3%

➢ Treatment

- First-time treatment relapse (failure)
  - Of these who relapse and are retreated with the same regimen which predict the initial remission
  - If retreatment is with combination prednisone plus azathioprine (AZA), when biochemistry +/- histopathology are normal, begin taper of prednisone at rate of 10 mg/mon, and ↓ AZA 50 mg/mon.
    - Success of high dose prednisone retreatment
      - Improvement in most at 6 mon
      - Biochemical normalization in 2-9 mon in 35%
  - After one relapse, patients are retreated and maintained long term on prednisone +/- AZA, since
    - 70% of retreated patients who recur will have another recurrence after a second drug withdrawal
    - Drug-associated adverse effects, 70%
    - Progression to cirrhosis, 38%
    - Death from hepatic failure need for liver transplant (LT), 20%

MCQ Pearl

- Treatment after one relapse after treatment withdrawal is usually mentioned indefinitely.

  - Success of long term maintenance after treatment withdrawal
  - Safety of long-term maintenance therapy spontaneous relapse after 40-215 mon, median 76 mon, 10%.

- Second-time treatment relapse (failure)

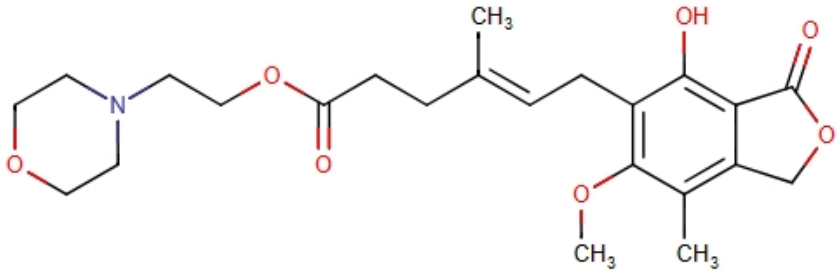
➢ Options

- The pharmacology of following classes of drugs is detected in the chapters on small intestine, Crohn disease, and in the chapter on Colon, ulcerative colitis.

- Budesonide
  - Efficacy
    - Biochemistry
      - Improvement, 67%
      - Normalization, 43%
    - Bone density
      - Stable/improved, 93%
      - The main advantage of budesonide is the prevention of bone damage
  - Failure
    - Budesonide dependence, 38%
    - Budesonide failure prednisolone started, 25%

- Theoretical reasons budesonide is unlikely to have superior efficacy compared to prednisolone for the use of
    - Prednisolone and budesonide have the same receptors
        - With the progression of AIH to the development of cirrhosis, the rapid clearance of budesonide, which ↓ adverse effects, becomes lost and clearance time approaches that of prednisolone.

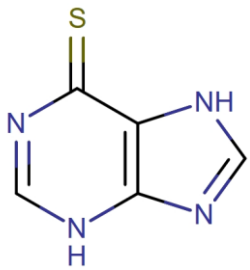
- Mycophenolate Mofetil



    - Purine antagonist, used as a substitute for azathioprine (AZA)
        - Intolerance
        - Non-response
        - Absent TPMT
        - Dose, 0.5 – 3 g/d plus glucocorticoids (GC), budesonide, or calcineurin inhibitors
    - Mechanism of action
        - Active metabolite of mycophenolate, mycophenolic acid (MPA), prevents T-cell and B-cell proliferation and the production of cytotoxic T-cells and antibodies
        - ↓ de-novo production of guanosine nucleotides, interfering with the synthesis of DNA, RNA, and protein required for immune cell production
    - Absorption
        - Rapidly absorbed in the small intestine
        - Cmax of its active metabolite, MPA, is attained 60-90 min following po dose
        - Average bioavailability of orally administered dose was 94%
        - In healthy volunteers, Cmax of 24.5 (±9.5) µg/mL.13
        - In renal transplant patients 5 d post-transplant, Cmax was 12.0 (±3.82) µg/mL, increasing to 24.1 (±12.1) µg/mL 3 mon after transplantation
        - The absorption of mycophenolate mofetil is not affected by food
    - Volume of distribution
        - 3.6 (±1.5) to 4.0 (±1.2) L/kg
    - Metabolism
        - Both po and IV administered mycophenolate mofetil is entirely metabolized by liver carboxylesterases 1 and 2 to mycophenolic acid (MPA), the active parent drug.
        - It is then metabolized by the enzyme glucuronyl transferase, producing the inactive phenolic glucuronide of MPA (MPAG)
        - The glucuronide metabolite is important, as it is then converted to MPA through enterohepatic recirculation.
        - Mycophenolate mofetil that escapes metabolism in the intestine enters the liver via the portal vein and is transformed to pharmacologically active MPA in the liver cells.

- Route of elimination
  - A small amount of drug is excreted as MPA in the urine (less than 1%).
  - When given orally, 93% is excreted in urine and 6% excreted in feces.
  - ~ 87% is found to be excreted in the urine as MPAG, an inactive metabolite
- Half-life
  - Average apparent T1/2 is 17.9 (±6.5) h after po administration and 16.6 (±5.8) h after IV administration.
- Clearance
  - Plasma clearance is 193 mL/min after a po dose and 177 (±31) mL/min after an IV dose
- Efficacy
  - Laboratory
    - Improvement, ~50% over 2 yr (about 20% lower in presence of cirrhosis)
    - Partial response, 32% (when used with prednisolone for first-line therapy, normalization occurred in 85%, usually within 3 mon)
  - Adverse effects
    - Dose reduction, 14%
    - Treatment ending, 9%
    - Serious, 3%
  - GC withdrawal, 40%

- 6-mercaptopurine (6-MP)



- Indication
  - Usually used for GI symptoms due to azathioprine at a dose of 1.5 mg/kg per d, or 25 mg, increasing to 50 mg
- Mechanism of action
  - Purine antagonist that competes with hypoxanthine and guanine for the enzyme Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) → convert to thioinosinic acid (TIMP), which is a false metabolite that is incorporated into DNA and RNA → block DNA and RNA synthesis.
- Absorption
  - Absorption of po dose is incomplete and variable, averaging ~ 50%
- Volume of distribution
  - Volume of distribution exceeded that of the total body water

- Metabolism
  - Hepatic degradation primarily by xanthine oxidase
  - Catabolism of mercaptopurine and its metabolites is complex
  - After po administration, urine contains intact mercaptopurine, thiouric acid (formed by direct oxidation by xanthine oxidase, probably via 6-mercapto-8-hydroxypurine), and a number of 6-methylated thiopurines.
  - The methyl thiopurines yield appreciable amounts of inorganic sulphate.
- Half-life
  - Triphasic: 45 min, 2.5 h, and 10 h
- Benefit
  - Symptom improvement, 75%
- Adverse effects
  - Treatment ending, 75%

- Cyclosporine (CyA) and Tacrolimus (TAC) (Calcineurin inhibitors)
  - Induction
    - Treatment failure/non-response to first-line therapies
  - Biochemical
    - Improvement →
      - CyA, 93%
      - TAC, 96%
    - Intolerance / no response
      - CyA, 7%
      - TAC, 2%

❖ Liver transplantation (LT)
  - First and second line treatment programs are successful in ~90% of patients with AIH
    - About 10% of AIH patients require LT
    - This represents lists 1 person per 10^6 (one million persons
  - Survival from LT for AIH (5 yr)
    - < 50 yr 78%
    - > 50 yr 61%
  - Post-LT AIH
    - 1 yr 10%
    - 5 yr ~40% (2 yr to 5 yr survival from post-LT AIH, ~95%)
    - Graft failure ~15%
    - AIH can recur after second LT!
  - De novo AIH after LT for non-immune liver diseases ~5%
    - Fibrosis, ~60%
      - Repeat LT (2 grafts) needed in ~10%
      - Repeat LT survival for AIH, 95% at 4 yr

➢ Prognosis

- Overall
- Unfortunately, the prognosis for African American with AIH is worse than in Caucasians/whites (mortality rate ~30% vs. 8%)
- There is no recommendation for one second-line treatment over another.

Outcome	Corticosteroids (CS)	Mycophenolate Mofetil plus CS/other	CyA	TAC	BUD
− Laboratory improvement	100%	~50%	93%	67%	67%
− Treatment failure / nonresponse / intolerance	0%	8%	~10%		25% (prednisolone started, ~25%; budesonide dependence, 38%

Abbreviations: CyA, cyclosporine; TAC, tacrolimus; BUD, budesonide

❖ **Overlap Syndrome Diagnosis and Treatment**

- AIH plus PBC (primary biliary cholangitis)

➢ Diagnosis

- AIH
  - − Biochemistry
    - ALT ≥ 5x ULN
    - IgG ≥ 2x ULN, or
    - SMH+ (smooth muscle antibody positive)
  - − Histopathology
    - Interface hepatitis, plus ≥ 1 of alone
- PBC
  - − Biochemistry
    - Alkaline phosphatase (AP) ≥ 2x ULN, or
    - GGTP ≥ 5x ULN
    - AMA+ (antimitochondrial antibody positive)
  - − Histopathology
    - Florid duct lesions

➢ Treatment

- Combination therapy (recommended by EASL)
- For AIH
  - − Prednisone/prednisolone 30 mg/d tapering to 10 mg/d, plus azathioprine 50 mg/d
- For PBC
  - − UDCA 13-15 mg/kg per day

- Individualized empiric therapies
  - Corticosteroids
    - Prednisone 10 mg/d plus azathioprine 50 mg/d
    - Budesonide 9 mg plus azathioprine 50 mg/d plus
    - UDCA 10-15 mg/kg per day
    - Budesonide plus UDCA as above but no azathioprine
  - Immunosuppressants
    - Cyclosporine, 3 mg/kg per day
    - Mycophenolate mofetil, 1-3 g/d
  - UDCA markers
    - 10-15 mg/kg per day

Treatment alert

- Two safety steps for use of
  - Measure thiopurine methyl transferase), plus
  - Perform vigorous and continued monitoring of WBC for leucopenia

- AIH plus PSC (primary sclerosing cholangitis)

➢ Diagnosis

- AIH
  - As above for AIH plus PBC
- PSC
  - Biochemistry
    - AMA-
  - Diagnostic imaging
    - MRCP strictures of bile ducts, fecal with dilation and possibly dominant stricture
  - Histopathology
    - ↓ bile ducts / ↑ bile duct damage
    - Obliterative fibrous cholangitis
    - Portal edema

➢ Treatment (AIH)

- Combination therapy (recommended by EASL, AASLD)
  - Prednisone/prednisolone 0.5 mg/kg

Abbreviations: AASLD, American Association for the Study of the Liver; EASL, European Association for the Study of the Liver

- Individualized empiric therapies
  - Prednisolone 20-80 mg/d, tapered to 7.5 – 10 mg/d, plus azathioprine 75-150 mg/d

- AIH plus unexplained cholestasis (may be PBC, AMA- or PSC, small duct disease)

➢ Diagnosis
  - AIH
    - As above for AIH plus PBC
  - Diabetes
    - AMA-
    - MRCP normal
    - Histopathology
      - ↓ bile duct / ↑bile duct damage

➢ Treatment (not the necessary data for a consensus recommendation for best practice)
  - Prednisone/prednisolone 10 mg/d, plus azathioprine 50 mg/d, plus UDCA 13-15 mg/kg per day

PRIMARY BILIARY CHOLANGITIS (PBC; previously called Primary Biliary Cirrhosis)

- Opioids must be used cautiously in patients with cholestasis (e.g., in persons with cholestasis treated with opiates which are suddenly discontinued).
  - In cholestasis, the endogenous opioids are not secreted, their levels in the blood are increased, and sudden withdrawal of even low doses of exogenous opioids represents sufficient to lead to opioid withdrawal syndrome.
- PBC may recur after liver transplantation (LT).
  - Risk factors for post-LT PBC
    - Age,male sex, use of tacrolimus post-LT

➢ Pathoimmunology

- Immune-mediated response to an unknown antigen (molecular mimicry)
- Activation of CD4+ and CD8+ T lymphocytes, B cells, and NK cells
- Aberrant polyclonal activation of B cells (↑ IgG, IgM)
- Breakdown of tolerance against mitochondrial antigens → production of autoantibodies against proteins on the inner membrane of mitochondria
  - Anti-mitochondrial antibody (AMA), in 95% of PBC patients) directed against the E2 component of
    - Pyruvate dehydrogenase complex (PDC E2)
    - PDC E1a subunit of PDC
    - E3 BP subunit of PDC
    - E3 BP subunit of PDC
    - Branched-chain of 2-oxo-acid dehydrogenase (BCO-ADC E2)
    - Molecular target is gene gp120 nucleoprotein p62
    - Anti-gp 210
      - AMA+PBC, 25%
      - Sensitivity AMA-PBC, 50%
      - Specificity, AMA+PBC, 99%, AMA-PBC, 25%
    - Gp210 and p62 associated with poor prognosis
    - Gp210 protein and AMA persist in serum after liver transplantation for PBC
  - Clinically for AMA, immunoblotting and enzyme-linked immunosorbent assay (ELISA) have excellent performance characteristics for AMA: > 90% for both sensitivity and specificity
  - These methods may detect AMA in persons who were negative by direct immunofluorescence testing
- PDC-E2 specific CD4+ lymphocytes interact with duct cells in the small intrahepatic bile ducts
- This interaction of CD4+ and CD8+ T cells in the small intrahepatic bile ducts
- This interaction of CD4+ and CD8+ T cell is facilitated by intracellular adhesion molecule (ICAM-1)
- Other antibodies:
  - Rheumatoid factor, 70%
  - Anti-smooth muscle, 16%
  - Anti-thyroid, 41%
- HLA class II molecular phenotype may be associated with PBC

- Clinical
  - Time course from no symptoms (asymptomatic) to symptoms
    - 40% in 5 to 7 yrs
    - 95% in 20 yrs
  - Development of esophageal varices (EV) ~ 30%
    - Bleeding of EV in 3 yrs ~ 12%
  - Metabolic Bone Disease
    - Osteoporosis (OP)
      - Defective bone formation
    - Osteomalacia
      - Defective bone mineralization
    - At diagnosis, 20% of PBC patients already have osteoporosis
    - Cumulative risk of fragility fractures – 10% to 20%
    - Presence and severity of OP ↑ with progression from stage 1 and 2 to stages 3 and 4 PBC
    - After liver transplantation (LT), for PBC
      - 50% develop a pathologic fracture within 1 mon
  - Factors that ↑ risk of bone disease in patients with chronic cholestatic liver disease.
    - General
      - ↓ physical activity
      - ↓ body mass index
      - Increasing age
      - Smoking
      - Female sex
      - ↓ sunlight exposure
      - Family history
    - Intake
    - ↓ Absorption -from cholestasis
      - ↓ Vitamin D and K
      - ↓ Calcium availability (steatorrhea)
      - ↑ Serum bilirubin
      - Genetically abnormal vitamin D receptor genotype
    - Requirements
      - Menopause/hypogonadism

Clinical Curiosities in PBC

- The commonly observed symptom of fatigue is an independent predictor of mortality, especially mortality from cardiac death.
- Gallstones occur in about 1/3 of persons with PBC.
- Recurrence of PBC after liver transplantation "does not seem to decrease survival" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1487).

MCQ ALERT

- Give the reason why patients with PBC but no cirrhosis may develop portal hypertension.
  - NRH (nodular regenerative hyperplasia) may be associated with PBC, and
    - NRH causes presinusoidal portal hypertension
- Give the reason why PBC patients with hypercholesterolemia do **not** have early onset of atherosclerotic disease.
  - The hypercholesterolemia in PBC is from HDL and not from LDL-cholesterol, so the risk of atherosclerosis is not increased.

➢ Pathophysiology (recurrence of PBC post-LT)

- AMA and other autoantibodies (e.g., ANA, anti-MND, anti-gb 210) are immunological makers for PBC, and they persist in the serum post-LT.
  - These autoantibodies do **not** cause the disease, but
    - Reflect continuing activity of B- and T-lymphocytes, as well as NK cells.
- The basic abnormality in the humoral and cellular response to an unknown antigen presumably continues
- Defects in immunological regulation may lead to bile duct obstruction in the allograft.

➢ Laboratory

- Diagnostic criteria for recurrent PBC after liver transplantation (LT) for PBC, as well as the important differential diagnostic considerations

Diagnostic Criteria for Recurrent PBC	Differential Diagnostic Considerations
○ LT for confirmed diagnosis of PBC ○ Persistence of serum AMA ○ Compatible Histopathology – Epithelioid granulomas – Portal inflammation – Lymphocytic inflammatory infiltrates – Lymphocytic cholangitis	▪ HCV infection with lymphocytic cholangitis ▪ Drug-induced liver injury (DILI) ▪ Acute cellular rejection ▪ Biliary obstruction ▪ Graft-vs-Host Disease (GVHD)

➢ Exclusion of differential diagnostic considerations

○ Interpretations: 2 of 4 diagnostic criteria = probable PBC; 3 of 4 = definite PBC

➢ Treatment

○ The details of the enterohepatic circulation of bile acids is considered in the chapter on the small intestine and bile acid associated diarrhea.
– Giving bile acids for treatment of PBC is understood from the addition of exogenous BA act through FXR (FGF19) to alter the activity of hepatocyte 7α-hydroxylase to ↓ endogenous synthesis of the primary bile acids, cholic and chenic acid.

○ The concentration of these primary BA in the BA pool lessens, and the unexplained detrimental effect of these BA on hepatocyte canalicular membrane and hepatocyte function which occurs in PBC becomes less
– The clinical biochemical and histological features of PBC improve.

○ UDCA (ursodeoxycholic acid)
– Used routinely in patients with stage 1 to 3 PBC
– 7-β epimer of chenodeoxycholic acid
– 13-15 mg / kg per day, with meals, taken od, or divided inti b.i.d.
– Take 2 h before or after bile acid binding agents, e.g., cholestyramine

○ Budesonide
– Non-systemic steroid
– 6 mg po od
– Used in stages 1 to 3 PBC
▪ Alone, or with UDC (requires more clinical data)
▪ Avoid use in stage 4 (↓ metabolism of budesonide → ↑adverse effects)

○ Nutrition
– Fat soluble vitamins

○ Treat associated
– Pruritis
– Steatorrhea
– Proximal renal tubular disease (type II)

- Pruritus
  - The mechanisms of the development of pruritus in PBC is unknown
    - The pruritic factor is not bile acids themselves,
  - However, binding bile acids with cholestyramine and ↑ their fecal excretion by diluting the bile acid pool with more hydrophobic UDCA may ↓ pruritus.
  - The antibiotic Rifampin induces CYP, and this presumably ↓ itching by acting on the release of endogenous opiates.
    - It is not clear what is the mechanism of the known anti-pruritic effect of
      - Antihistamines, 5-HT3 antagonists, selective serotonin reuptake inhibitors (SSRIs), or phenobarbital

➢ Treatment (pruritus in hepatic cholestatic syndromes)

- Treat the underlying cholestatic condition, including
  - Deficiencies of calcium, fat soluble, vitamin (A, D, E, K)
  - Cholestyramine 4 g po q AM, increasing to t.i.d., taken 2 h before or after other medications
  - UDCA may help to ↓ pruritus in PBC
- Skin care
  - Skin moisturizing emollient lotions
- Anti-histamine
  - Hydroxyzine 25 mg – 50 mg t.i.d. po
  - Cimetidine 300 mg t.i.d.
- Naltrexone
  - Opiate receptor antagonist – naltrexone 12.5 – 50 mg/d po
- SSRI
  - Sertraline (Zoloft®) 50 mg -100 mg / day
- Rifampin
  - 150 mg / day po in doses increasing to 10 mg / kg / day in 2 divided doses

- Beneficial outcomes for the use of UDCA in PBC
  - Probability of Developing Cirrhosis When UDCA used for PBC

	Stages at diagnosis of PBC		
	1	2	3
– After 5 yrs	4	12	59
– After 10 yrs	17	27	76

- All of following are reduced by UDCA
  - Clinical
    - Ascites
    - Death
    - Gastroesophageal varices
    - HCC risk
    - Liver transplantation
    - Mayo risk score
  - Laboratory
    - Biochemistry
  - Histopathology
    - Liver biopsy progression
    - Cirrhosis development

- Liver transplantation (LT)

SO YOU WANT TO BE A GENIUS HEPATOLOGIST!

- PBC recurs after liver transplantation (LT).
  - There are several risk factors for post-LT PPC (age, men, use of tacrolimus).

- Give the likely mechanism for the recurrence of PBC post-LT.
  - AMA and other autoantibodies (e.g. ANA, anti-MND, anti-gb 210) are immunological makers for PBC, and they persist in the serum post-LT. These autoantibodies do **not** cause the disease, but reflect continuing activity of B- and T-lymphocytes, as well as NK cells.
  - The basic abnormality in the humoral and cellular response to an unknown antigen presumably continues.
  - Defects in immunological regulation leads to bile duct obstruction in the allograft.

- The number of LT performed for PBC is falling, not because of a ↓ incidence or prevalence, but instead because of the favourable outcomes with using UDCA
- Survival rates for LT for PBC
  - 1 yr > 90%
  - 5 yr > 80%
- Organ allocation in PBC is established by risk stratification with the MELD (Model for End-stage Liver Disease) score
- See: http://mayoclini.org/meld/mayomodel6.html

- Risk of recurrence of PBC after LT
  - Median time ~ 4 yrs
  - ↑ with time: ~ 40% in 10 yrs post LT
  - ↑ risk of recurrence with
    - ↑ age
    - Men
    - Use of tacrolimus

➢ **AMA-Negative PBC**

- Symptoms, biochemistry, liver histology, clinical course, therapy and indications for liver transplantation are similar to AMA-positive PBC
- Human leukocyte antigen (HLA) alleles may be different in AMA- versus AMA + PBC, with possible loss of protective allele
- No difference in Treg (regulatory T cells / or t cell subgroups)
- Serology
  - Most have ANA or anti-smooth muscle (ASM) antibodies
  - 50% have anti-gp 210

➢ Prognosis (poor)

- Patient
  - Older age
  - Symptoms
  - Complications
    - Hepatomegaly
    - Ascites, edema
    - GE variceal bleeding
- Laboratory
  - ↑ AP, bilirubin, PT
  - ↓ albumin
- Histopathology
  - Cholestasis
  - Mallory hyaline
  - Fibrosis
  - Cirrhosis

Abbreviations: AP, alkaline phosphatase; PT, prothrombin time (aka, INR)
Please refer to Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 89.4, page 1482, for "Independent Predictors of Survival in Patients with Primary Biliary Cirrhosis in Various Clinical Trials".

- Prognosis (useful to select optimal timing for liver transplantation)
  - Simple: total serum bilirubin > 10 mg/mL
    - Life expectancy then is only 2 yrs
  - Sophisticated: Mayo Risk score for PBC: Please see http://www.mayoclinic.org/gi-risk/mayomodel2.html

VIRAL HEPATITIS

Hepatitis B Virus (HBV) **Infection**

- Transmission and Risk

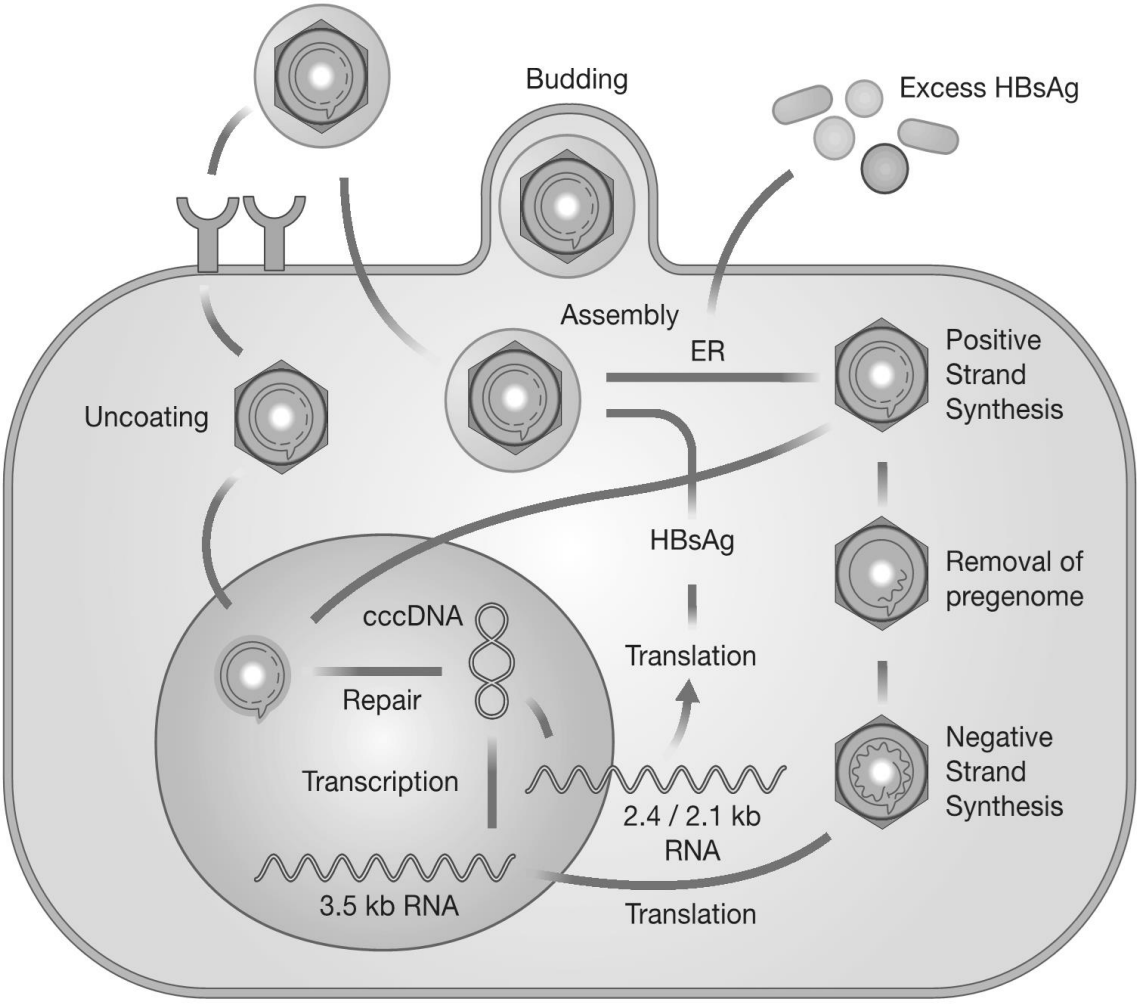
Geographical Area	Mode of Transmission	Life Risk of HBV Infection
NA, WE, SA, Au	– Horizontal person-to-person, young adults	< 20%
SEA, China, Africa	– Perianal – Horizontal, young children	60% to 80%

  - Once infected with HBV, men are more likely than women to remain persistently infected
  - Women are more likely
    - To be infected transiently and
    - To develop anti-HBs (antibody to hepatitis B surface antigen).

- Virology
  - HBV is a DNA virus which
    - Goes through an RNA intermediate
    - Requires an active viral reverse transcriptase / polymerase enzyme for encapsulation of viral RNA into a negative strand of viral DNA (reverse transcription) and
    - Conversion of this first HBV DNA strand into a second DNA strand of positive polarity
    - Has a high point mutation rate, low replication fidelity
    - A gene encodes HBsAg, a viral surface, envelop protein
  - HBeAg, HBsAg, HBcAg
    - The core gene has
      - Precore region → HBeAg
      - Core region → core proteins
    - The negative-strand HBV DNA is a template for the synthesis of a positive-strand.
    - The positive strand is incorporated into the maturing nucleocapsid.
    - The nucleocapsids are coated with the surface protein (HBsAg) in the endoplasmic reticulum (ER).
    - From the ER, the enveloped nucleocapsid bud off from the hepatocyte membrane, and enter the circulation.

➢ Pathophysiology

- Life cycle of HBV



  - The receptor for viral entry has not been identified, but studies have suggested that sodium taurocholate cotransporting polypeptide (NTCP) is likely to be the receptor for binding the HBsAg protein.

Printed with permission: Janssen HLA and Fung S. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 79, Figure 79.3, page 1219.

- Once inside the hepatocyte
  - The virus undergoes uncoating, and
  - The HBV genome enters the nucleus, followed by repair of the single-stranded DNA strand, and
  - Formation of the currently closed circular (ccc) DNA template.
  - Viral transcripts are formed for the HBsAg, DNA polymerase, X protein, and RNA pregenome
  - The pregenome and polymerase are incorporated into the maturing nucleocapsid, and
  - Removed after translation
- The surface protein enveloping process occurs in the endoplasmic reticulum (ER).
- The surface protein enveloping process occurs in the ER.
- Some of the non-enveloped nucleocapsid recirculates back to the nucleus, and the cycle begins again.
- Excess tubular and spherical forms of HBsAg are secreted in great abundance and outnumber complete virions in serum by a factor of 10^3 or more.

- The expression of HBV proteins and the release of virions precedes biochemical evidence of liver disease.
  - Large quantities of surface antigen can persist in liver cells of apparently healthy persons who are carriers.
  - HBV is therefore not directly cytopathic.
- Immune-modulated damage
  - An HLA class I restricted cytotoxic T-cell (CTL) response directed at HBcAg/HBeAg on HBV-infected hepatocytes.
  - ↑ expression / ↓ secretion of HBsAg.
  - A direct cytopathic effect of HBcAg expression in infected hepatocytes.
  - ↓ viral clearance by cytotoxic T lymphocytes (CTLs)
    - Liver damage from HBV is immune-mediated (not a direct hepatocyte cytopathic effect of HBV).
    - Cellular immune response
      - Innate and adaptive
  - CD4+ T cells produce antiviral cytokines which reduce the production of neutralizing

- Hepatocyte metabolism of HBV.
    - HBV uptaking into hepatocyte
        ↓
    - HBV uncoating
        ↓
    - Uptake into nucleus
        ↓
    - cccDNA transcription
        ↓
    - 2.4 kb RNA
        ↓ 3.5 kb RNA
    - Priming/encapsulation
        ↓
    - Translation
        ↓
    - Encapsulation
        ↓
    - Negative-strand synthesis
    - Assembly, budding, HBV exit from hepatocyte
        - Positive-strand synthesis
            - Removal of pregenome

- Adefovir
- Entecavir
- Lamivudine
- Tenofovir

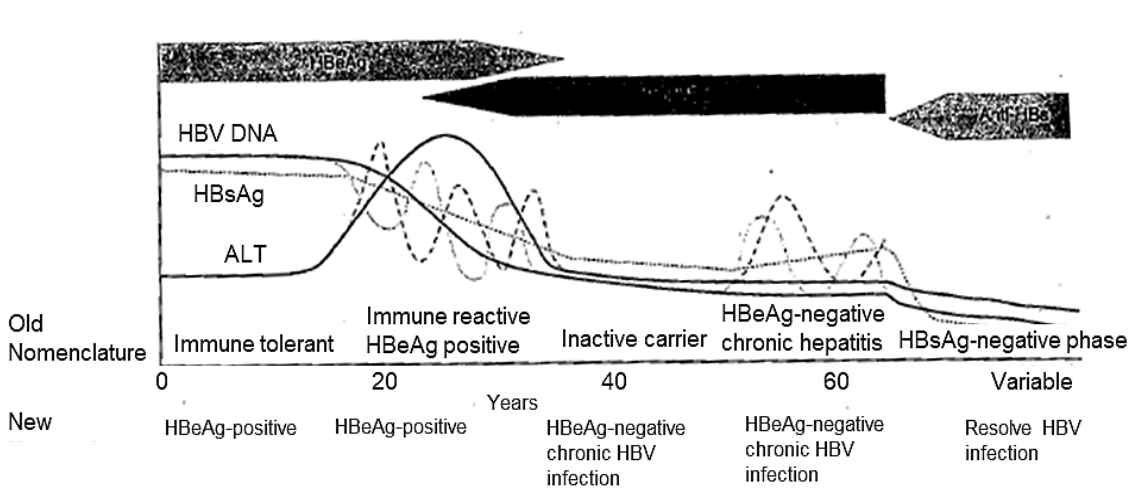
- Inhibitor of HBV +/- strand synthesis

- HCC Development in HBV
    - HBV infection contracted early in life may lead to chronic hepatitis, then to cirrhosis, and finally to hepatocellular cancer (HCC), usually after a period of 30 to 50 yr.
    - HBV may not be carcinogenic by a direct viral mechanism.
        - HBV may cause chronic liver cell damage with associated host response of inflammation and liver regeneration that continues for many years.
        - This pathological process, especially when leading to cirrhosis, may be carcinogenic, without involving a direct oncogenic action of the virus.

- No viral oncogene, insertional mutagenesis, or viral activation of oncogenic cellular genes has been demonstrated
- Risk of developing hepatocellular cancer (HCC)
  - HBV, ~4/100 patient years
  - For comparison HCV, ~2/100 patient years
- HBV is incorporated into cellular DNA (in 90% of HCC patients)
- Chromosomal insertion is random
- HBV is indirectly and directly carcinogenic
  - Cis-activation of cellular genes
  - Transcriptional activation of HBV x protein
  - Viral mutations
  - Activation of
    - Mitogen-activated protein kinase (MAP)
    - JAK/ STAT pathways (Janus kinase-signal transducer and activator of transcription)

➢ Laboratory

- Clinical Course



  - The relative time dimensions of each phase are shown
    - Note that there may be significant overlap of features among the various phases.

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- Diagnostic Criteria for each HBV Infection Phase

	HBeAg-positive		HBeAg-negative		HBeAg-negative
	Chronic HBV Infection	Chronic Hepatitis B	Chronic HBV Infection	Chronic Hepatitis B	Resolved HBV Infection
○ HBsAg	High	High/ intermediate	Low	Intermediate	Negative
○ HBV DNA	≥10^7 IU/mL	10^4 – 10^7 IU/mL	<2000 IU/mL	≥2000 IU/mL	Undetectable
○ ALT	Normal	Elevated	Normal	Elevated	Normal
○ Liver disease	None/ minimal	Moderate/ severe	None	Moderate/ severe	None
○ Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBsAg-negative chronic hepatitis	HBsAg-negative phase

- HBV Serology patterns

HBV Diagnosis	Serological Pattern
○ Acute hepatitis B (AHB)	− HBsAg+, HBeAg+, Anti-HBC IgM+ − Anti-HBc-IgM+, HBeAg+/-
○ Chronic hepatitis (CHB)	− Active viral replication ▪ HBsAg+, HBeAg+. Anti-HBe IgG+ − Heterotypic anti-HBs ▪ HBsAg+. Anti-HBs+, HBeAg+/-, anti-HBe+/- − Inactive HBV carrier (low HBV DNA) ▪ HBsAg+, anti-HBe+, anti-HBe+ − HBeAg- CHB, active viral replication (high HBV DNA) − Recovery (immunity) from/to HBV − Vaccination immunity ▪ Anti-HBs+, anti-HBc IgG+, anti-HBe+/- − False-positive (past infection) ▪ Anti-HBC+ ▪ Immunity, vaccination

- HBV Serological Patterns and HBV Disease Diagnosis

	HBsAg+	Anti-HBC	Anti-HBC IgM	Anti-HBC IgG	HBeAg	Anti-HBe
○	AHB		+		+	
○	CHB					
	− Viral replication					
	− Low HBV DNA					
	− Heterotrophic anti-HBS	+		+	+/-	+/-
	− Recovery	+				+/-
	− Vaccination	+		+		

Source: Papdakis MA and McPhee SL. Current Medical Diagnosis and Treatment. Chapter 16, Freedman LS. 2020. Adapted from Table 16-5, page 698

➢ Differential diagnosis of hepatitis flares (HBV reactivation) in persons with chronic hepatitis B.

Cause of Flare	Comment
• Therapy	
○ Spontaneous	− Factors that precipitate viral replication − Loss of immune control are unclear
○ Immunosuppressive	− During or shortly after withdrawal of the agent (preemptive antiviral therapy is required)
○ Antiviral therapy for HBV	
− Interferon	▪ Within the first 3 mon of initiating therapy with interferon in 30% of patients and may herald HBeAg seroconversion in some patients
− Nucleos(t)ide analog	
− During treatment	▪ Improve medication adherence
− Antiviral resistance	▪ Agents that have a low genetic barrier to resistance such as lamivudine and telbivudine ▪ Confirm genotypic resistance with resistance testing
− Off treatment	▪ Clinical relapse (re-elevation of serum ALT levels and re-appearance of HBV DNA in serum in those previously virally suppressed)

Cause of Flare		Comment
○ Coinfection with	− HCV	▪ HBV may be suppressed in HCV-coinfected patients ▪ HBV reactivation in co-infected patients undergoing DAA therapy for HCV infection
	− HDV	▪ HBV is usually suppressed in HDV coinfected patients ▪ ↑ risk of liver disease progression
	− HIV	▪ The direct toxicity of ART, or ▪ With immune reconstitution (HBV increases the risk of anti-retroviral drug hepatotoxicity)
○ Other liver disease		− Alcohol overuse − Autoimmune liver disease − Drug and toxin-induced liver injury − NAFLD

Abbreviations: ART, antiretroviral therapy; HBeAg, hepatitis B e antigen

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- High-risk anticipated evidence for developing of HBV infection (HBV in > 10% if cases)

	Drug Exposure
○ HBsAg+ / anti-HBc+, or HBsAg-/Anti-HBc+ patients	− B cell depleting ▪ Ofatumumab ▪ Rituximab
○ HBsAg+ / anti-HBc+	− Anthracycline derivatives ▪ Doxorubicin ▪ Epirubicin − Prednisone ▪ 10 mg to 20 mg /d, or ▪ > 20 mg/d of adequate corticosteroids per d for ≥ 4 wk

- Moderate risk (HBV, 1% to 10%)

○ HBsAg+ / anti-HBc+, or HBsAg-/Anti-HBc+ patients	− Tumour necrosis factor alpha inhibitor ▪ Adalimumab, certolizumab, infliximab ▪ Other cytokine/integrin inhibitors − Abatacept, natalizumab, ustekinumab, vedolizumab ▪ Tyrosine kinase inhibitors − Imatinib, nilotinib

- HBsAg+ / anti-HBc+
  - Prednisone < 10 mg/d or equivalent corticosteroids for ≥ 4 wk
  - Immunosuppressive therapy: sensitive HBV DNA test (Strong recommendation; moderate-quality evidence
  - Prednisone
    - 10 mg to 20 mg per day or equivalent corticosteroid
    - > 20 mg per day or equivalent corticosteroid per day for ≥ 4 wk
  - Anthracycline derivatives epirubicin, doxorubicin

- Low risk: HBV, < 1%
  - HBsAg+ / anti-HBc+, or HBsAg-/Anti-HBc+ patients
    - "Traditional immunosuppressive drugs
      - Azathioprine
      - 6-mercaptopurine
      - Methotrexate
      - Corticosteroids (intraarticular)
    - Any dose corticosteroids po per day for ≤ 1 wk
  - HBsAg+ / anti-HBc+
    - Prednisone < 10 mg or equivalent per day for ≥ 4 wk

Risk of HBV_R	Anti-viral Prophylaxis	Duration of Antiviral Prophylaxis after Stopping Immunosuppression	Alternate to Drug Prophylaxis: No Prophylaxis
High > 10%	Yes	≥ 10 mon	-
Medium 1% to 10%	Yes	≥ 6 mon	+*
Low < 1%	No		+

*No recommendation made for HBV DNA monitoring as an alternate to anti-viral prophylaxis (knowledge gap)

- Do **not** use anti-HBs status to grade antiviral prophylaxis for all risk groups (weak recommendation: very low-quality evidence)
- Drug prophylaxis
  - Antiviral drugs with high barrier to resistance (weak recommendation; moderate quality evidence), especially in patients receiving immunosuppression (strong recommendation; moderate quality evidence).

Risk	Strength of Recommendation	Evidence Quality
High	Strong	Moderate
Medium	Weak	Moderate
Low	Weak	Moderate

- Risk of HBV reactivation (HBV_R) with Immunosuppressive drug
  - Azathioprine (AZA)
    - HBV_R
      - Monotherapy AZA or 6-MP (mercaptopurine) dose ≤ 2.5 mg/kg < 1%
      - Patient who is HBsAg negative, anti-HBc positive, 6-MP < 0.1%

- Methotrexate, < 1%
- Corticosteroids
  - Long term use in
    - HBsAg positive carrier > 10%
    - HBsAg negative, anti-HBc positive, much lower than 10%
- Biologics, 1% to 10%
  - Rituximab HBsAg-positive/-negative, anti-HBc positive > 10%
    - Additive/effect of other chemotherapy drugs used for non-Hodgkin lymphoma synergistic → use anti-viral prophylaxis to ↓ risk of HBV_R

- Prophylaxis
  - Use drugs with high barrier to resistance for prophylaxis against HBV_R (e.g., entecavir)
    - The authors of this guideline conclude that "…the cost of testing [for HBV_R] is likely outweighed by the benefits [of anti HBV prophylaxis] when the baseline not for reactivation is moderate (≥ 1%, < 10%) or high (> 10%)

Hepatitis B Viral Reactivation *(HBV_R)*

➢ Definition of terms
- Acute exacerbation or flare of hepatitis B
  - Intermittent increase of aminotransferase activity to >10 × ULN and >2 × baseline value

- Azathioprine (AZA), 6-mercaptopurine (6-MP)
  - Risk
    - Little uncertainty when used as monotherapy < 1%
      - Moderate uncertainty risk of reactivation < 0.1%

Drug	Little Uncertainty	Moderate Uncertainty
Azathioprine, 6-mercaptopurine	1%	0.1%
Methotrexate	< 1%	
Corticosteroids high dose	10%	(lower in persons who are HBsAg-, anti-HBc+)
Biologicals	1% to 10%	(Lower in persons who are HBsAg-. Anti-HBc+, than in HBsAg+ persons)
– Anti-TNF inhibitors	Lower risk in HBsAg-, anti-HBC+, than in HBsAg+ persons	
▪ Rituximab in HBc+ persons	> 10%	

Prophylaxis Alert

- Persons taking high-risk immunosuppressants, and who are HBsAg+ and anti-HBc+
  - Reactivation rate of HBV (HBV_R) > 10% → recommended to use HBV prophylaxis (prophylaxis may also be of benefit when HBV_R rate is ≤ 2%.

Abbreviations: 6-MP, 6-mercaptopurine; AZA, azathioprine; HBVR, hepatitis B viral resistance; HBV, hepatitis B virus

- Screening for HBV_R
  - For patients taking high (>10%) or medium (1-10%) risk drugs
  - The need for screening should be determined according to the recommendations outlined by the US Preventive Services Task Force (USPSTF), which reflects the anticipated population prevalence.

- Prophylaxis
  - Entecavir, tenofovir
    - Remember "renal dosing" in persons with renal insufficiency

- Phases of CHB Infection

Phase	ALT	Liver histology
Immune tolerance phase	Normal or minimally elevated	Minimal activity; absent or scant fibrosis
Immune clearance phase (HBeAg-positive CHB)	Elevated, usually persistently or with intermittent elevations	Active; liver biopsy showing chronic hepatitis (necroinflammatory score ≥4)
Low viral replication	Persistently normal	Inactive; liver biopsy showing variable, usually minimal fibrosis (necroinflammatory score <4)
Reactivation phase (HBeAg-negative CHB)	Elevated, often fluctuating levels	Active; liver biopsy showing variable amounts of fibrosis (necroinflammatory score ≥4)
Resolution	Normal	Inactive; scant fibrosis

Serum HBV DNA, IU/mL	HBeAg	Anti-HBe
○ High levels: serum HBV DNA >20,000 IU/mL	+	-
○ High levels: serum HBV DNA >20,000 IU/mL	+	-
○ Low or undetectable levels: serum HBV DNA negative or <2000 IU/mL	-	+
○ Moderate, often fluctuating levels: serum HBV DNA >2000 IU/mL	-	+
○ No detectable serum HBV DNA (low levels may be detectable in the liver)	-	+

- ○ Note
  - − For all the above, HBsAg is positive after 6 mon, except for when there is no elevated serum HBV DNA, when HBsAg is negative.

➢ Follow-up of untreated patients

- ○ HBeAg-positive or -negative CHB with HBV DNA ≥2000 IU/mL and normal ALT
  - − Assess ALT levels every 3–6 mon
  - − Consider liver biopsy or transient elastography to assess fibrosis
  - − Consider initiating treatment when ALT levels increase or fibrosis is present
- ○ HBV DNA <2000 IU/mL and normal ALT
  - − Assess ALT levels every 6–12 mon
  - − If ALT levels become increased, check serum HBV DNA and exclude other causes of disease

➢ Anti-viral resistance

- Relating to Antiviral Resistance to Nucleoside and Nucleotide Analogue Treatment for CHB
  - ○ Biochemical breakthrough − ↑ in ALT level above ULN after achieving normalization during continued therapy
  - ○ Cross-resistance − ↓ susceptibility to more than 1 antiviral drug conferred by same amino acid substitution or combination of amino acid substitutions
  - ○ Genotypic resistance − Detection of viral populations bearing amino acid substitutions in reverse transcriptase region of HBV genome that have been shown to confer resistance to an antiviral in phenotypic assays during antiviral therapy.
    - ▪ These mutations are usually detected in patients with virologic breakthrough but can also be present in patients with persistent viremia and no virologic breakthrough.

- Viral rebound
  - ↑ in serum HBV DNA to >20,000 IU/mL or above pretreatment level after achieving virologic response during continued therapy
- Virologic breakthrough
  - ↑ in serum HBV DNA level by >1 log10 IU/mL above nadir after achieving virologic response during continued therapy

Adapted from: Martin P, et al. Clin Gastroenterol Hepatol 2015; 13: 2071-87.

- Laboratory methods to detect antiviral resistance
  - Standard population-based sequencing
  - INNO-LIPA
  - Restriction fragment length polymorphism analysis
  - Allele-specific PCR
  - DNA chip
  - Ultradeep pyrosequencing

- Causes/associations
  - The clinical conditions and examples of drugs associated with ↑ risk of reactivation of HBV in persons who are HBsAg+.
    - Rituximab, ofatumumab (↑↑↑ anti-CD20 B cell-depleting agents)
    - Hematopoietic stem cell transplantation
    - Doxorubicin, epirubicin (anthracycline)
    - High-dose prednisone (> 20 mg daily) for > 4 wk
    - Alemtuzumab (anti-CD 52)
    - Infliximab, Adalimumab (↑↑ anti-TNF)
    - Abatacept, natalizumab, ustekinumab, vedolizumab (cytokine integrin inhibitors)
    - Cytotoxic chemotherapy, Imatinib, nilotinib, sorafenib (tyrosine kinase inhibitor), prednisone
    - Antirejection regimens for solid organ transplant
    - Azathioprine, methotrexate, 6-mercaptopurine (immunosuppressive therapy)
    - Any dose of glucocorticoids for 1 wk
    - Antra-articular glucocorticoids

Adapted from Janssen HLA and Fung S. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 79, Table 79.4, page 1226.

➢ Treatment

- General management strategy
  - Pre-treatment baseline evaluation of the patient with HBV infection.
    - Revised normal ALT levels (30 IU/L for men, and 19 IU/L for women) should be used as criteria for treatment
    - Baseline evaluation should include HBV genotype, particularly if peginterferon therapy is considered
    - Preferred first line treatment options: adefovir, entecavir, peginterferon alfa-2a, and possibly telbivudine
      - Lamivudine is not first-line choice because of the high rate of resistance to Interferon alfa-2b

- Recommendations for treatment of HBV

	HBV DNA	ALT	Histopathology	Treatment*	Monitoring	Long-term Treatment
○ HBeAg+	< 2000 IU/mL	N	N	-	q6-12 mon	
			ABN	+		
	≥ 2000 IU/mL	N	N	-	q12mon	
			ABN	+		
		↑	N	+		
			ABN	+		+
○ HBeAg-	< 2000 IU/mL	N	N	-	q6-12 mon	
			ABN	+		
	≥ 2000 IU/mL	N	N	-	+	
			ABN	+		
		↑	N	+		+
			ABN	+		

*treatment with entecavir (ENT), tenofovir (TEN), PEG-IFNγ

- ULNs for serum ALT concentrations are 30 IU/L for men and 19 IU/L for women
- On initial diagnosis, monitor every 3 mon for 1 yr to ensure stability

- The potential management strategies for HBV by on-treatment virologic response categories.
  - Virological response - HBV DNA < 2000 IU/mL at 0, 6 and 12 mon after the end of therapy
  - Sustained virological response - HBV DNA < 2000 IU/mL at 12 mon after the end of therapy
  - Virological break through
    - ↑ HBV DNA 1 $\log_{10}$ IU/mL compared to lowest previous level of HBV DNA on Rx
    - Characterized by ↑ ALT
    - Due to
      - Poor adherence to therapy, or
      - HBV resistance (due to therapy-associated selection of HBV resistant variants)

- Terminology

Category	Strategy
Primary treatment failure at wk 12	– If noncompliant, counsel patient on importance of adherence toprescribed drug regimen – If compliant, change therapy to more potent drug / possibly a drug combination
Complete virologic response at wk 24	– Continue therapy with same drug; monitoring may be extended to 6-mon intervals
Partial virologic response at wk 24	– If drug has a low genetic barrier to resistance, add a second drug that is not cross-resistant – If drug has a high genetic barrier to resistance, repeat monitoring at 3-mon intervals and continue beyond 48 wk – If drug has a delayed antiviral effect e.g., adefovir, repeat monitoring at 3-mon intervals, and – If response becomes complete at 48 wk, continue therapy; but – If response remains partial or becomes inadequate at 48 wk, add a more potent drug
Inadequate virologic response at wk 24	– Add another drug (preferably one that is more efficacious, or if such a drug is not available, then add one that is not cross-resistant) – Repeat monitoring at 3-mon intervals – Monitoring after 48 wk may be extended from 3 to 6 mon if response becomes complete

*Patients with advanced disease should be monitored at 3-mon intervals while on treatment, regardless of virologic response

- Factors predictive of a viral response (VR) to treatment of HBV infection.
  - Patient
    - Immunocompetent
  - HBV
    - Adult-acquired infection
    - Low HBV-DNA level
      - ↑ response to interferon
      - HBV recurrence with liver transplantation
    - Absence of HDV or HIV co-infection
    - HBeAg +ve
  - Biopsy
    - Active liver disease—ALT > 5x upper limit of normal (ULN), active hepatitis on biopsy
    - Should be considered for HBV-infected patients with normal ALT levels, especially if age >35 yr
  - Specific treatment algorithms
    - HBeAg+
    - HBeAg-
  - PEG-IFN or NA monotherapy used for finite duration
    - PEG-IFN (in the absence of contraindications) for HBeAg- positive and -negative patients for 48 wk
  - Treatment strategies
    - NA monotherapy for long-term duration (suppresses but does not eradicate HBV)
  - Do **not** combine PEG-IFN with lamivudine or telbivudine (↑ risk development of severe neuropathy)
  - Entecavir or tenofovir for 12 mon after seroconversion in about 2/3 of those initially HBeAg-positive HBV patients
  - Entecavir or tenofovir monotherapy for
    - HBeAg-positive patients who failed to seroconvert
    - HBeAg-negative patients
    - All HBV cirrhosis
  - NA for long term maintenance (continuously duration)
  - Monitoring and applying stopping rules

- Direct-acting anti-viral agents (DAAs)
  - Genotype of HCV and Recommended

DAAs	Protease Inhibitor 1,4 NS3/4A	NS5A	Non-nucleos(t)ide Polymerase Inhibitor 1-6 NS5B
− Daclatasvir	+		
− Dasabuvir		+	+
− Elbasvir	+		
− Grazoprevir	+		
− Glecaprevir	+		
− Ledipasvir		+	
− Ombitasvir		+	+
− Paritaprevir	+		
− Pibrentasvir	+		
− Simeprevir	+		
− Sofosbuvir	+		
− Velpatasvir	+		
− Voxilaprevir	+		

Adapted from: Papdakis MA and McPhee SL. Current Medical Diagnosis and Treatment. Chapter 16, Freedman LS. 2020. Table 16-6, page 707

- Classification of mechanism of action of DAAs for HCV infection and dosage*
  - NS3 4A Protease Inhibitors
    - − Glecaprevir 300 mg
    - − Grazoprevir 100 mg
    - − Paritaprevir 150 mg
    - − Simeprevir 150 mg
    - − Voxilaprevir 100 mg
  - NS 5A Inhibitors (Favirs)
    - − Daclatasvir 60 mg
    - − Elbasvir 50 mg
    - − Ledipasvir 90 mg
    - − Ombitasvir 25 mg
    - − Pibrentasvir 120 mg
    - − Velpatasvir 100 mg
  - NS5B Nucles(t)ide Polymerase Inhibitor**
    - − Sofosbuvir 400 mg
  - NS5B Non-nucleos(t)ide Protease Inhibitors**
    - − Dasabuvir 250 mg

* all medications given po od, except Dasabuvir, given as 250 mg po b.i.d.

** “the favirs”

- DAA Treatment Combinations by Genotype

1,4	1-6	1,4
○ Sofosbuvir (NS5B) plus Ledipasvir (NS5A) ○ Grazoprevir (NS3/4A) plus Elbasvir (NS5A)	− Sofosbuvir (NS5B), plus Velpatasvir (NS5A) − Glecaprevir (N33/4A) plus Pibrentasvir (NS5A) − DAA-experienced ▪ Sofosbuvir (NS5B), plus ▪ Velpatasvir (NS5A) plus ▪ Voxilaprevir (NS3/4A) also for DAA-experienced genotype 1	▪ Sofosbuvir (NS5B) plus Daclatasvir (NS5A)

Adapted from: Papdakis MA and McPhee SL. Current Medical Diagnosis and Treatment. Chapter 16, Freedman LS. 2020. Table 16-7, page 708

- First-line therapies for treatment-naïve patients with chronic hepatitis B after 1-yr of treatment

Outcome (%)	PEG-IFN-α	ETN	TDF	TAF
• HBeAg-positive chronic hepatitis B (immune active phase)				
○ Viral suppression	32 (< 4 log IU/mL)	67 (< 60 IU/mL	66 (< 60 IU/mL	64 (< 29 IU/mL
○ HBeAg loss	34	22	21	14
○ HBsAg loss	3	2	3	1
○ ALT normalization	41	68	68	72
○ Histologic response	49	72	74	N/A
• HBeAg-negative chronic hepatitis B (reactivation phase)				
○ Viral suppression	43 (< 3 log IU/mL)	90 (< 60 log IU/mL)	71 (< 60 log IU/mL)	94 (< 29 log IU/mL)
○ HBsAg loss	4	< 1	0	0
○ ALT normalization	59	78	76	83
○ Histologic response	55	70	72	N/A

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- First- and second-line therapies for different clinical situations of HBV infection requiring treatment with DAAs

	Therapy	
	First-line	Second-line
○ Treatment		
− Naïve		
▪ GFR > 60 mL/min	ENT, TAF, or TDF	TEL
▪ GFR < 60 mL/min	ENT, or TAF	TEL
− TAF, TDF, or ENT, but continued low-level viremia while on treatment	TAF, TDF or ENT continued, or switch to one of the other of those DAAs with high magnetic barrier	-
○ Prior exposure		
− LAM, or TEL	TAF, TDF	ENT
− LAM and ADS	TAF, TDF, or ENT	TEL
○ Proven resistance		
− ADE	ENT	TAF, or TDF
− ENT	TAF, or TDF	Ade/ADE
− LAM	TAF, or TDF	Ade/ADE
− TEL	TAF, or TDF	Ade/ADE

Abbreviations: ADE, adefovir; ENT, entecavir; LAM, lamivudine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TEL, telbivudine

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❖ **DRUG CHOICES**

- ○ IFN (interferon)
  - − PEG-IFN (pegylated IFN)
- ○ Nucleosides
  - − Emtricitabine (EMT)
  - − Entecavir (ENT)
  - − Lamivudine (LAM)
  - − Telbivudine (TEL)
- ○ Nucleotides
  - − Adefovir (ADE)
  - − Tenofovir (TEN)

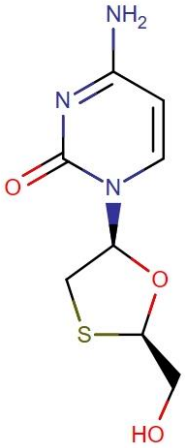
- **Nucleoside** (NS) **/ Nucleotide** (NT) **Analogs** (NA)
  - "Competitive inhibitors of reverse transcriptase and DNA polymerase".
  - "Replace natural nucleoside during the synthesis of the first or second strand (or both) of HBV DNA".

- Advantages and disadvantages of nucleosides and nucleotide analogs for the treatment of chronic HBV infection.

Agent	Advantages	Disadvantages
○ Lamivudine (LAM)	− Oral administration − Excellent tolerance − Use in ESLD and adefovir failures	▪ Drug resistance: common (~20%/yr, and up to 70% with 4-5 yr of therapy)
○ Adefovir (ADE)	− Oral administration − Excellent tolerance − Use in ESLD − Use in lamivudine failures	▪ Less potent, with suboptimal responses not uncommon ▪ Drug resistance: delayed and less common (0% at year 1, 2% at year 2, 7% at year 3, 15% at year 4, and 29% at year 5 of therapy)
○ Entecavir (ENT)	− Oral administration − Excellent tolerance − High potency in lowering HBV DNA levels − Use in adefovir failures	▪ Drug resistance: rare in nucleoside naïve patients (0.1% at year 1, 0.4% at year 2 and 1.1% at year 3), but common in patients with LAM resistance (6% at year 1, 14% at year 2, and 32% at year 3)
○ Telbivudine (TEL)	− Oral administration − Excellent tolerance − High potency in loweringHBV DNA levels	▪ Drug resistance: intermediate rates (5% at year 1, and 21.6% at year 2 in HBeAg-positive patients, and 8.6% in HBeAg-negative patients)
○ Tenofovir (Ten)	− Resistance doses not seen	

Abbreviation: ESLD, end-stage liver disease

- **Lamivudine** (LAM)



➢ Indication
- High rate of viral mutation and viral resistance
- ~40% at 2 yr, 65% at 5 yr
- Higher rate of resistance with treatment of co-infection with treatment of co-infection with HIV.
- HBV viral suppression
  - Lam < adefovir (Ade) < entecavir < telbivudine (Tel) < tenofovir (Ten)
- HBV resistance
  - Ten > Tel > Ent >Ade

➢ Mechanism of action
- Synthetic nucleoside analogue which is phosphorylated intracellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP).
- This nucleoside analogue is incorporated into viral DNA by HIV reverse transcriptase and HBV polymerase, resulting in DNA chain termination.

➢ Pharmacokinetics
- Absorption
  - Rapidly absorbed after po administration
  - Absolute bioavailability in adult 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution
  - Cmax was 1.5 ± 0.5 µg/mL when an oral dose of 2 mg/kg b.i.d.
  - When given with food, absorption is slower, compared to the fasted state
- Volume of distribution
  - Apparent volume of distribution, IV administration = 1.3 ± 0.4 L/kg
  - Volume of distribution was independent of dose and did not correlate with body weight

- Metabolism
  - Metabolism of lamivudine is a minor route of elimination
  - The biotransformation is catalyzed by sulfotransferases.
- Route of elimination
  - Majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine.
  - Lamivudine is excreted in breast milk
- Half-life
  - 5-7 h
- Clearance
  - Renal clearance = 199.7 ± 56.9 mL/min [300 mg po]
  - Renal clearance = 280.4 ± 75.2 mL/min [single IV]

➢ Pros and cons of Lamivudine versus interferon (IFN) for the treatment of HBV.

Favoring Lamivudine	Favoring IFN
○ Needle phobia	– Young Asian person
○ HIV co-infection	– Genotype A
○ Other immunosuppression (e.g., transplantation)	– Recent infection
○ Patients with depression	– AST > 100
○ ↓ WBC count	– ↓ serum HBV-DNA
○ ↓ platelet count	– Active liver biopsy
○ Autoimmune disease	– HBeAg+
○ Decompensated cirrhosis	– Possibility of seroconversion (eAg+→eAb+)
○ Vertical transmission	– Marginal benefit to baby
○ Cost concerns	– Contraindicated with depression, renal failure
○ Pregnancy, may be used	– Do **not** use in pregnancy
○ Has 70% resistance rate at 5 yr. – Acts as an immunomodulatory agent resulting in ▪ Loss of circulating HBeAg and HBV DNA in 30-40% of cases, and to a lesser extent ▪ An antiviral agent resulting in loss of HBsAg in less than 5% of cases.	
○ Cross resistance with tenofovir	

- **Interferon** (IFN)
- Advantages and disadvantages of interferon for the treatment of chronic HBV infection.

Agent	Advantages	Disadvantages
○ Interferon	– HBsAg loss – Short treatment duration – No drug resistance	▪ Parenteral administration ▪ Frequent side effects
○ Peg-IFN	– HBsAg loss – Fixed duration of treatment – No drug resistance	▪ Parenteral administration ▪ Frequent side effects but less than interferon

➢ Mechanism of action

○ Act on specific cell receptors → activate well-defined transduction pathways → enhance expression of hundreds of different Interferon-Stimulated Genes (ISGs) leading to antiviral state.

➢ Adverse effects of interferon.

○ Early
- Flu-like illness; headaches, nausea
- Tenderness at site of infection

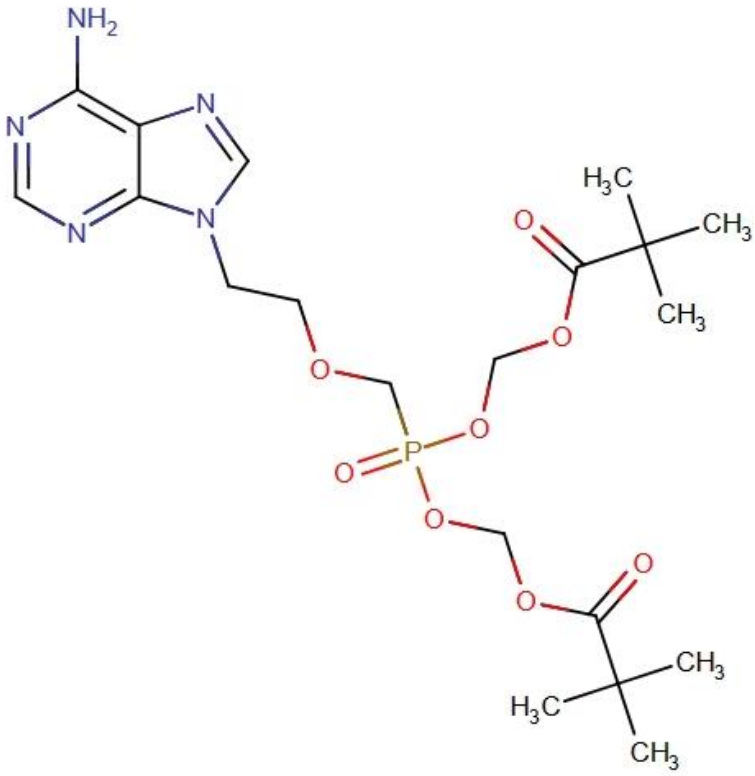
○ Late

– General	▪ Fatigue ▪ Irritability Anxiety and depression
– Eyes	▪ ↑ retinopathy DM ▪ Optic tract neuropathy
– CNS	▪ Neuropsychiatric issues
– MSK	▪ Muscle aches
– Skin	▪ Alopecia ▪ Lichen planus worsens
– GI	▪ Weight loss ▪ Diarrhea ▪ Anorexia ▪ IBD worsens
– Endocrine	▪ Autoimmune autoantibodies ▪ Worsening thyroid disease ▪ Autoimmune diseases worsen
– Pregnancy class C	
– Bone marrow suppression	▪ Bacterial Infections

Abbreviations: CNS, central nervous system; DM, diabetes mellitus; GI, gastroenterology; IBD, inflammatory bowel disease; MSK, musculoskeletal

- Contraindications to the use of IFN/PEG-IFN.
  - Uncontrolled/severe depression/psychosis, Autoimmune disease
  - Decompensated HBV cirrhosis (↑ risk of bacteremia and ↑ decompensation)
  - Pregnancy
  - Renal transplant patients (↑ risk of rejection)

- **Adefovir dipivoxil**

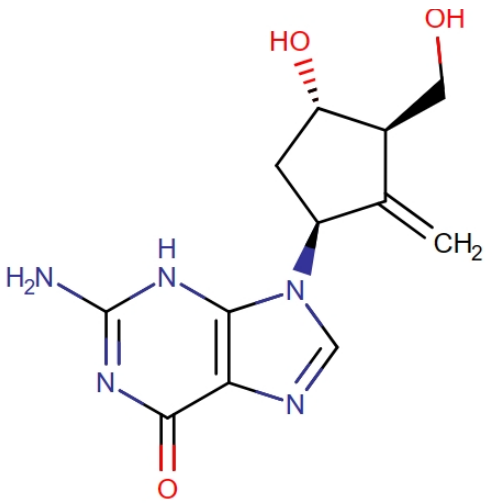


- Indication
  - Chronic HBV in adult patients with evidence of
    - Active viral replication
    - Persistent elevations in serum aminotransferases (ALT or AST)
    - Histological, virological, biochemical, and serological responses in adult patients with HBeAg+ and HBeAg- chronic hepatitis B with compensated liver function
    - Adult patients with clinical evidence of lamivudine-resistant HBV with either compensated or decompensated liver function.

- Mechanism of action
  - Prodrug of adefovir
  - Acyclic phosphate nucleotide analog of adenosine monophosphate
  - ↓ HBV polymerase and reverse transcriptase
  - HBV resistance
    - Ten > Tel > Ent >Ade

- Pharmacokinetics
  - Absorption
    - Oral bioavailability of adefovir from HEPSERA is 59%
    - When a single 10 mg po is given to chronic hepatitis B patients, the Cmax) was 18.4 ± 6.26 ng/mL with Tmax 0.58 - 4 h post dose
    - Adefovir area under the plasma concentration-time curve (AUC) was 220 ± 70.0 ng·h/mL.
    - Food does not affect the exposure of adefovir.
  - Volume of distribution
    - 392 ± 75 mL/kg [Vd at steady state, 1.0 mg/kg/d IV]352 ± 9 mL/kg [Vd at steady state, 3.0 mg/kg/day IV]
  - Metabolism
    - Following oral administration, rapidly converted to adefovir.
    - 45% of the dose is recovered as adefovir in the urine over 24 h at steady state following 10 mg po doses
    - Adefovir is not a substrate of the cytochrome P450 enzymes
  - Route of elimination
    - Renally excreted by a combination of glomerular filtration and active tubular secretion.
  - Half-life
    - Plasma adefovir concentrations declined in a biexponential manner with a terminal elimination T1/2 of 7.48 ± 1.65 h
  - Clearance
    - 469 ± 99.0 mL/min [normal renal function patients receiving a 10 mg single dose]
    - 356 ± 85.6 mL/min [mild renal impairment patients receiving a 10 mg single dose]
    - 237 ± 118 mL/min [moderate renal impairment patients receiving a 10 mg single dose]
    - 91.7 ± 51.3 mL/min [severe renal impairment patients receiving a 10 mg single dose]

- **Entecavir**



➢ Indication

- Chronic HBV infection in adults with evidence of active viral replication and evidence of
  - Persistent ↑ serum aminotransferases (ALT or AST) or
  - Histologically active disease

➢ Mechanism of action

- Deoxyguanine nucleotide analog which selectively inhibits replication of HBV
- ↓ priming of HBV DNA polymerase
- ↓ synthesis of positive strand of HBV DNA
- Low rates of resistance (1.2% after 5 yr), and
- 20% rate of eAg seroconversion after 48 wk
- Development of resistance is associated with flares.

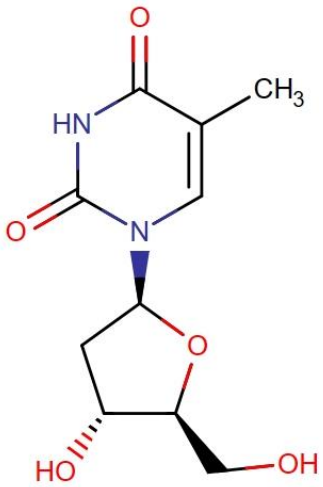
➢ Pharmacokinetics

- Absorption
  - Absorption following po administration in healthy subjects, with Tmax 0.5-1.5 h.
  - In healthy subjects, the bioavailability of the tablet is 100% relative to the oral solution
- Metabolism
  - Not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system
  - Efficiently phosphorylated to the active triphosphate form
- Half-life
  - After reaching Cmax, plasma concentrations ↓ in a bi-exponential manner with a terminal elimination T1/2 ~128-149 h
  - The phosphorylated metabolite has T1/2 of 15 h

- Clearance

	Renal Clearance (mL/min)	Apparent Oral Clearance (mL/min)
− Unimpaired renal function	383.2 ± 101.8	588.1 ± 153.7
− Mild impaired renal function	197.9 ± 78.1	309.2 ± 62.6
− Moderate impaired renal function	135.6 ± 31.6	226.3 ± 60.1
− Severe impaired renal function	40.3 ± 10.1	100.6 ± 29.1
− Severe impaired renal function managed with hemodialysis		50.6 ± 16.5
− Severe impaired renal function managed with CAPD		35.7 ± 19.6

- **Telbivudine**



➢ Indication

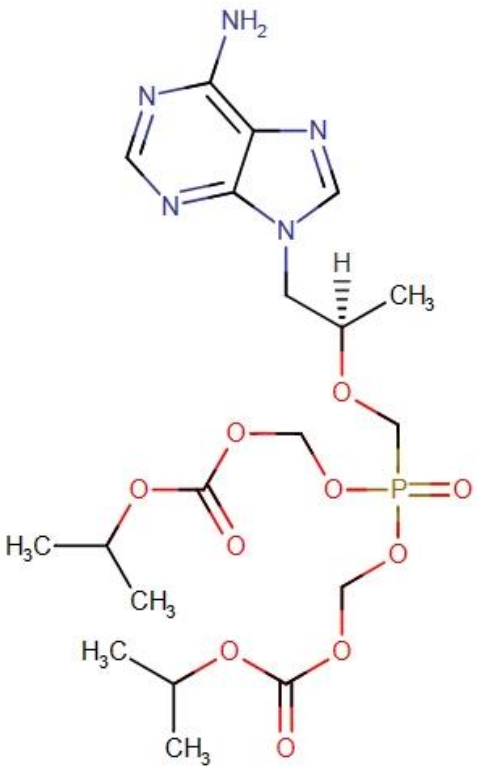
- Treatment of chronic HBV in adult and adolescent patients ≥16 yr with evidence of viral replication and either evidence of persistent ↑ serum aminotransferases (ALT or AST) or histologically active disease.

➢ Mechanism of action

- Nucleoside analog of thymidine
- Inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'–triphosphate → chain termination of DNA synthesis → inhibiting viral replication.
- Incorporation of telbivudine 5'–triphosphate into viral DNA → DNA chain termination → inhibition of HBV replication.
- Because telbivudine develops resistance mutations at the same site as for lamivudine, telbivudine is not effective in persons who have lamivudine resistance

- Pharmacokinetics
  - Absorption
    - Absorbed following oral administration
    - Absorption and exposure were unaffected when a single 600 mg dose was administered with a high–fat (~55 g), high–calorie (~950 kcal) meal.
  - Metabolism
    - No metabolites detected following administration of [14C]–telbivudine in humans.
    - Telbivudine is not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system
  - Route of elimination
    - Eliminated primarily by urinary excretion of unchanged drug
  - Half-life
    - 15 h
  - Clearance
    - 7.6 +/- 2.9 L/h [normal renal function (CrCl>80 mL/min)]
    - 5.0 +/- 1.2 L/h [mild renal function impairment (CrCl=50-80 mL/min)]
    - 2.6 +/- 1.2 L/h [moderate renal function impairment (CrCl=30-49 mL/min)]
    - 0.7 +/- 0.4 L/h [severe renal function impairment (CrCl<30 mL/min)]

- **Tenofovir disoproxil fumarate**



- Indication
  - The diagnosis of chronic HBV infection in an HIV patient is an indication to start tenofovir-based therapy
- Mechanism of action
  - Chemically similar to adefovir mechanism of action similar to adefovir (a cyclic nucleotide inhibitor of HBV polymerase and reverse transcriptase
  - Resistance does not occur
- Pharmacokinetics
  - Absorption
    - After po administration to patients with HIV infection, quickly absorbed and metabolized to tenofovir
    - Administration of tenofovir disoproxil 300 mg tablets after a high-fat meal ↑ oral bioavailability of this drug
      - ↑ AUC0 of ~40% as well as an ↑ Cmax of 14%~
    - Administration with a light meal did not exert a relevant effect on the pharmacokinetics of tenofovir when compared to administration under fasting conditions
    - The presence of ingested food slows the time to tenofovir Cmax by ~ 1 h.
  - Volume of distribution
    - Volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following IV administration of tenofovir 1.0 mg/kg and 3.0 mg/kg
  - Oral tenofovir is distributed to the majority tissues with the highest concentrations measured in the kidney, liver and the intestinal contents (based on data from preclinical studies)
  - Metabolism
    - Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil.
    - Tenofovir disoproxil is absorbed and converted to its active form, tenofovir, a nucleoside monophosphate (nucleotide) analog → converted to the active metabolite, tenofovir diphosphate, a chain terminator, by constitutively expressed enzymes in the cell
    - Two phosphorylation steps are required to convert tenofovir disoproxil to the active drug form
    - The cytochrome P450 enzyme system is not involved with the metabolism of tenofovir disoproxil or tenofovir
  - Route of elimination
    - Following IV administration of tenofovir, ~ 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 h of dosing.
    - Eliminated by a combination of glomerular filtration and active tubular secretion.
    - There may be competition for elimination with other compounds that are also eliminated by the kidneys.
  - Half-life
    - When a single po dose is given, the terminal elimination T1/2 is ~ 17 h

- Clearance
  - Clearance of tenofovir is highly dependent on renal function and may vary greatly.
  - Total clearance has been estimated to be ~ 230 mL/h/kg (~300 mL/min)
  - On average, renal clearance has been estimated to be ~ 160 mL/h/kg (~ 210 mL/min), which is in excess of the glomerular filtration rate.
  - This shows that active tubular secretion is an essential part of the elimination of tenofovir
  - It is important to consult product labeling before administering tenofovir to individuals with renal dysfunction, as the clearance of this drug may vary greatly among these patients

➢ Recommendations for monitoring and stopping HBV treatment.

- PEG-IFN
  - HBeAg-positive
    - On treatment
      - Every 6 and 12 mon: anti-HBe antibodies, serum HBV DNA, ALT, HBsAg
    - Off treatment
      - Every 12 mon: HBeAg, anti-HBe antibodies, serum HBV DNA, ALT, HBsAg
    - HBeAg seroconversion (HBeAg-positive → negative)
      - Test HBsAg every 12 mon (seroreversion)
    - No HBeAg seroconversion (serum HBsAg > 20,000 IU/mL, or no ↓ HBsAg at 3 mon)
      - Stop PEG-IFN
  - HBeAg-negative
    - On treatment, at mon 3 if ↓ HBV DNA ≥ 2 $\log_{10}$ IU/mL, and no ↓ HBsAg
      - Stop PEG-IFN (especially genotype D)

- NA (nuceos[t]ide)
  - On treatment
    - Every 6 mon HBeAg, anti-HBe, HBV DNA, serum creatinine
    - Measure HBsAg every 12 mon after HBe seroconversion
    - Stop NA 12 mon after anti-HBe seroconversion, or
    - Stop NA until loss of HBsAg (with or without antibodies to HBsAg), especially if there is severe fibrosis or cirrhosis.

➢ Reassessing/stopping HBV therapy should be reassessed or stopped.
  - HBeAg+: HBeAg seroconversion and – HBV DNA
  - HBeAg-: Long term therapy
  - Inadequate viral response (VR) (<2,000 IU/mL) at week 24
  - Development of antiviral drug resistance

- If HBV DNA reappears during treatment of HBV, then resistance to the drug has likely occurred.
- In fulminant HBV, the HBsAg may have disappeared, but the diagnosis can be made by finding HBV DNA in serum.

➢ Treatment strategy

- HBeAg-positive compensated patients (based on their HBV DNA and ALT)

HBV DNA	ALT	Treatment Strategy
<20,000 IU/mL (inactive)	Normal	− No treatment − Monitor every 6-12 mon − Consider therapy in patients with known significant histological disease even if low-level replication
≥20,000 IU/mL (active)	Normal	− Low rate of HBeAg seroconversion for all treatments − Monitor every 3-12 mon − Younger patients often immune tolerant − Consider liver biopsy; particularly if age > 35-40 yr − In the absence of a liver biopsy, observe for rise in ALT levels.
≥20,000 IU/mL	Elevated	− If “high” HBV DNA: adefovir, entecavir or telbivudine preferred over peginterferon alfa-2a.

- HBeAg-negative compensated patients (based on their HBV DNA and ALT)

HBV DNA	ALT	Treatment strategy
<2,000 IU/mL	Normal	− No treatment: usually are inactive HBsAg carriers − Monitor every 6-12 mon
≥2,000 IU/mL	Normal	− Consider liver biopsy; treat long term if disease present. − In the absence of biopsy, observe for rise in serum ALT − levels (ALT often fluctuates). − If treated, adefovir, entecavir, peginterferon alfa-2a, or − possibly telbivudine preferred.
≥2,000 IU/mL	Elevated	− Adefovir, entecavir, peginterferon alfa-2a, or possibly telbivudine are preferred − Long-term treatment required for oral agents

➢ Comparisons

- Treatment of chronic hepatitis B at 6 mon following 48-52 wk of pegylated interferon alpha (PEG-IFNα), and at 48-52 wk of nucleos(t)ide analog (NA) therapy.

	PEG-IFN		Nucleotide Analog			Nucleoside Analogs	
	PEG IFN-2a	PEG IFN-2b	LAM	TEL	ENT	ADE	TEN
• HBeAg Positive							
○ Dose	180 µg	180 µg	100 µg	600 mg	0.5 mg	10 mg	245 mg
○ Anti-HBe seroconversion (%)	32	29	16-18	22	21	12-18	21
○ HBV DNA < 60-80 IU/mL (%)	14	7	36-44	60	67	13-21	76
○ ALT normalization (%)	41	32	41-72	77	68	48-54	68
○ HBsAg loss (%)	3	7	0-1	0.5	2	0	3
• HBeAg Negative							
○ Dose	180 µg		100 µg	600 mg	0.5 mg	10 mg	245 mg
○ HBV DNA < 60-80 IU/mL (%)	19		72-73	88	90	51-63	93
○ ALT normalization (%)	59		71-79	74	78	72-77	76
○ HBsAg loss (%)	4		0	0	0	0	0
○ Drug resistance1/5 yr	0/0		24/70	41	0.2/1.2	0/29	0/0

Abbreviations: ADE, adefovir; ENT, entecavir; LAM, lamivudine; TEL, telbivudine; TEN, tenofovir

Adapted from: European Association for the Study of the Liver J Hepatol. 2012;57(1):167-85 (Table 1 and Table 2)

➢ Comparisons between current nucleos(t)ide analogues in treatment-naïve patients with chronic hepatitis B, in terms of (by reduction and undetectable) HBV-DNA (PCR) and HBeAg seroconversion and drug resistance

	LAM		ADE		ENT		TEL		TEN	
HBV-DNA (PCR)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)	e(+)	e (-)
Log reduction:										
Year 1	5.4	4.5	3.6	3.7	6.9	5.0	5.7	4.4	6.5	4.5
Undetectable										
Year 1	40%	7.3%	21%	61%	6.7%	9%	60%	88%	76%	93%
Year 2	39%	52%	-	71%	74%	-	5.6%	82%	78%	99%
Year 3	20%	40%	-	77%	-	-	-	-	-	-
Year 4	-	34%	-	73%	-	-	-	-	-	-
HBeAg Seroconversion										
Year 1	20%	NP	13%	NP	21%	NP	23%	NP	23%	NP
Year 2	26%	NP	29%	NP	31%	NP	30%	NP	26%	NP
Year 3	40%	NP	37%	NP	-	NP	-	NP	-	NP
Year 4	47%	NP	35%	NP	47%	NP	-	NP	-	NP
Drug resistance										
Year 1	11%	6-27%	0%	0%	0%	0%	5%	2%	0%	0%
Year 2	14%	26%	-	3%	0%	NP	25%	11%	0%	0%
Year 3	40%	54%	-	11%	1.2%	NP	-	-	-	-
Year 4	56%		20%	29%	1.2%	NP	-	-	-	-

Abbreviations: ADE, adefovir; EN, tenofovir; ENT, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LAM, lamivudine; NP, not applicable; PCR, polymerase chain reaction; TEL, telbivudine

Printed with permission: Chien RN and Liaw YF. *Best Practise Res Clin Gastroenterol* 2008; 22:1081-1092 (Table 1).

- Note:
  - Reduce the dose of NAs (NTs and NSs) if creatinine clearance < 50 mL/min.
  - Screen all HBV positive patients for HIV before starting HBV treatment with lamivudine, entecavir or tenofovir (since these drugs have activity against HIV andshould not be used as more therapy for HBV for fear of causing HIV resistance).
    - PEG-IFN, adefovir and telbivudine are not active against HIV.
  - PEG-IFN has advantages over nucleos(t)ide (NA) because of
    - The absence of resistance
    - The possibility of seroconversion (HBsAg-positive → negative) in about 25% patients
    - The ~4% change of loss of HBsAg in persons who achieve and maintain undetectable HBV DNA (by sensitive testing).
    - IFN therapy responders enjoy a ~ 50% reduction in cirrhotic complications and 80% reduction in liver- related mortality.

- Overview of response rates in HBeAg+ and HBeAg- patients with currently available antiviral drugs

Antiviral Therapy	HBeAg Positive HBeAg Seroconversion		HBeAg Negative Undetectable HBV DNA	
	End of Therapy	Post Treatment	End of Therapy	Post Treatment
○ Alpha interferon	35%	30%	60%	35%
○ Peginterferon	40%	35%	63%	19%
○ Lamivudine (LAM)	19%	12%	65%	10%
○ Adefovir (AFE)	12%	NA	51%	NA
○ ADE in LAM resistance	20%	NA	19%	NA
○ Entecavir (ENT)	21%	NA	90%	NA
○ ENT in LAM resistance	8%	NA	26%	NA
○ TEL	22%	NA	88%	NA
○ TEN	21%	NA	92%	NA

Abbreviation: NA, not applicable

Printed with permission: Buster EHCJ, et al. *Best Practise Res Clin Gastroenterol* 2008; 22: 1093-1108 (Table 1).

➢ **Mutants and Mutations**

- HBsAg mutants
  - Vaccine escape
    - In persons for whom HBIG does not present HBV, ~50% of these "escapes" are due to alterations in the "a" determinants of the HBsAg, leading to immune escape.
  - May influence HBV recurrence after liver transplantation.
- Mutations in the Precore, Basal Core Promoter and Core Genes
  - More common in HBe-Ag-negative persons
  - Stop the synthesis of HBeAg
  - ↑ development of fulminant HBV
  - ↑ risk of HCC
  - ↓ response to interferon
- Mutations in HBV DNA polymerase
  - "HBV reverse transcriptase function of the polymerase gene is highly preserved…." (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 1291).

- Viral resistance may occur weeks to months before a virologic breakthrough
  - Virologic breakthrough
    - "> 1 $\log_{10}$ (10-fold) increase in serum HBV DNA levels above the previous nadir" (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, Table 78.3, page 1304).
  - Virologic rebound may follow virologic breakthrough; define "virologic rebound".
    - Virologic rebound HBV DNA > 10^5 (20,000 IU/mL)

- **Before starting immunosuppressive therapy or chemotherapy**
  - HBeAg-positive
    - NA before, during and for 12 mon after immunosuppressive therapy or (preferably entecavir or tenofovir) chemotherapy, regardless of serum HBV DNA level
  - HBeAg-negative patients with detectable HBV DNA –treat as above
  - HBeAg-negative, anti-HBe antibody positive, detectable serum HBV DNA – treat asper above,
  - HBeAg-negative, anti-HBe antibody positive, undetectable serum, HBV DNA – monthly monitoring of ALT and HBV DNA.
  - Anti-HBe positive patients receiving bone marrow or stem cell transplantation – NA prophylaxis
  - HBsAg negative recipient of liver graft from anti-HBe-positive donor – indefinitelamivudine prophylaxis
  - Polyarteritis nodosa (PAN) – consider possible of HBV/HCV infection

- **Corticosteroid withdrawal / Immune Rebound**
  - The reason why acute liver failure (ALF) may occur during steroid withdrawal for treatment of polyarthritis nodosa (PAN) in HBV, but not in HCV.
    - Hepatic damage in HBV (but not in HCV) is immune-mediated, and would cause aggressive necrosis upon immune reconstitution resulting from withdrawal of steroids fortreatment of PAN.
    - When steroids are stopped, there is ↑ activation of T lymphocytes that promote the Th1 cytokine responses.
    - The ↑ Th1 cytokine response occurs at the time when there is ↑ expression of HBV.
    - The combination of ↑ HBV antigen plus ↑ Th1 cytokine response causes hepatic decompensation.

Please see: Peltekian KM, Hirsch G. Chapter 59. In: Therapeutic Choices. Grey J, Ed. 6thEdition, Canadian Pharmacists Association: Ottawa, ON, 2011, page 789.

- Precore mutant HBV (aka HBeAg-negative HBV) flares due to a change in the ratio of precure HBV / wild-type HBV.
- Mutations in basal core promoter region (with or without precore mutants)
  - ↑ HBeAg
  - ↑ HBV replication
  - ↑ necroinflammation
- HBeAg-negative HBV plus both precore and core mutations
  - ↑ risk of flare with chemotherapy

❖ Treatment Flare

- Idiopathic
- Iatrogenic
  - Interferon
    - 30% of interferon-treated patients experienced a flare usually within the first 3 mon may occur before HBeAg seroconversion
  - Nucleoside/nucleotide analogs
    - Development of antiviral drug-resistance
    - Non-adherence
    - Previously treated effective, drug stopped → flare clinically, ↑ ALT, ↑ HBV DNA
- Infection/co-infection
  - HCV
    - Treated HCV in HBV plus HCV infection → HBV flare (HCV may ↓ HBV)
  - HDV
    - Usually suppressed HDV
  - HIV
    - Antiviral / anti-HIV drugs
      → Direct toxicity to liver (HBV → ↑ toxicity of ART)
      → Immune reconstitution
  - HBV
    - HBeAg-
      - Development of core/precure promoter mutants may ↑ALT
    - Immunosuppressants
      - Most immunosuppressants may cause of flare during/after use of immunosuppressants

- HBV Reactivation During Immunosuppressive Therapy

Estimated Risk	
> 10%	Treat
1-10%	Treat - If prophylaxis declined, monitor q1-3mon
< 1%	Monitor q1-3mon

- Post-exposure prophylactic treatment for HBV
  - No previous vaccination
    - HBIG, 0.06 ml/kg, plus HBV vaccination
  - Previous vaccination
    - Known responder
      - Hepatitis B immunoglobulin (HBIG), as above, given in two doses a mon apart, or
      - HBIG, 1 dose plus HBV revaccination
    - Unknown antibody response
      - Anti-HBs < 10 mIU/L, HBIG 1 dose plus HBV booster revaccination

HBV Infection Related Extrahepatic Manifestations

- Polyarteritis Nodosa (PAN)

➢ Clinical

- As compared to primary PAN, patients with HBV-related have ↑ risk of
  - CNS
    - Neuropathy (82% vs. 64%)
    - Microaneurysms (71% vs. 49%)
  - CVS
    - Hypertension
      - Recent (49% vs. 27%)
      - Severe (11% vs. 5%)
    - Cardiac involvement (13% vs. 4%)
  - GI
    - Gut involvement (50% vs. 30%)
    - Weight loss (8% vs. 5%)
  - GU
    - Orchitis (24% vs. 13%)
  - Activity/severity
    - Birmingham Vasculitis Activity Score (BVAS)
    - Five-factor score (FFS)

➢ Treatment

- Corticosteroids
- Anti-HBV drugs
- Plasma exchange
- The only clinical feature of HBV-related PAN vs. primary involvement of the skin (35% vs. 58%)

- Mixed Cryoglobulinemia Vasculitis

➢ Definition

  - Systemic vasculitis of small and medium-sized immune complement-mediated inflammation of blood vessels associated with
    - IgG, polyclonal
    - IgM, polyclonal or monoclonal

➢ Clinical

  - Skin, purpura, 100%
  - Joints, arthralgia, ~70%
  - Nerves, peripheral, ~30%
  - Kidney, glomerulonephritis, ~20%

➢ Treatment

- Glomerular Nephritis (GN)
  - Membranes (MGN)
    - HBV DNA in epithelial cells nucleus/cytoplasm mesangial cells
    - Does not correlate with severity of HBV infection
    - Associated with
      - Acquired missense nucleotide mutations of the HBX-X gene
  - Membranoproliferative (MPEN)
    - Association with nephrotic syndrome
  - Mesangial proliferative
  - IgA nephropathy

- Hematological Malignancies
  - Infection associated with
    - Non-Hodgkin B cell lymphoma (B-NHL)
      - ↑ RR 2-5X
      - HBsAg- / anti-HBc+ / HBs+ (naturally acquired immunity)
      - aOR for B-NHL, 2.3
      - HBsAg+ / HBeAg+ (current HBV infection), aOR for B-NHL, 6.2
      - NHL treated with rituximab (B cell depleting) → ↑ HBV reactivation in HBeAg+ patients
    - ↓ risk of HBV
      - Reactivation when using rituximab for HNL by using ETV prophylaxis (7% vs. 30%)
      - HBV hepatitis (0% to 13%)
    - Diffuse large B-cell lymphoma (DLBCL)
      - ↑ HR 2.2 vs. non-HBV infected cohort
      - ↓ 2- / ↓ 5 yr overall survival
      - ↓ 2- / ↓ 5 yr progression free survival

Hepatitis C Virus (HCV) **Infection**

- Demography
  - Perinatal exposure
    - Transmission rate
      - HCV ~ 5%
      - HCV + HIV ~ 15%
    - Breast feeding dangerous when HCV > 10^8 copies/mL
  - Percutaneous
    - Blood products ($1/2x10^6$)
    - IV drug use (60% to 90% HCV infected)
    - Nucleotide accidents
    - Hemodialysis
  - Non-percutaneous
    - Sexual contact
    - Intercourse
      - Per rectum
      - During menstruation
- Pathogenesis

- Life Cycle of HCV
  - Receptor binding of HCV
    ↓
  - Endocytosis into hepatocyte
    ↓
  - Cytosolic fusion/uncoating
  - Translation into polyprotein precursor
    ↓
  - Structural proteins C (core), as well as envelop proteins E1/E2 cleaved by endoplasmic reticulum (ER)
    - A host signal dipeptidase
    - A viroporin protein
      ↓
  - Ion channel assembles / releases infections virions
  - NS cysteine protease itself (autocatalytically) from the polyprotein
  - Formation replication complex
    ↓
  - NS3 unwinds double-stranded RNA
    ↓
  - Generation of (-) strand RNA template
    ↓
  - Disproportionate synthesis of (+) strand viral genomic RNA from (-) template
    ↓
  - Assembly/packaging
    ↓
  - Virion transport and glycoprotein maturation
    ↓

↓

- Fusion of vesicles and release of mature virion (infections)

- NS3 protease cleaves the non-structural proteins
  - NS3
    - Serine protease
    - RNA helicase
  - NS4A
    - NS3 protease factor
  - NS4B
    - Unknown
  - NS5A
    - RNA binding site
  - NS5B
    - RNA dependent RNA polymerase (RdRp)
- About 75% of persons with acute HBV develop chronic HCV because the HBV escapes the immune response to clear the infection.
- 75% of persons with acute HCV progress to chronic HCV infection because of ineffective immune against the HCV
- HCV-enters hepatocytes by attachment and transport, using proteins
  - E1 and E2
    - Envelop proteins
  - CD81
    - Tetraspanin superfamily
  - SR-B1
    - Scavenger receptor class B type 1
  - LDL-R
    - LDL receptor

➢ Risk factors (and estimated prevalence in persons being in "developed" countries)

Groups at Risk	Estimated prevalence (range %)
A blood transfusion received before 1990/91	- 5-10
Children born from HCV positive mothers	- 3-10
Health care workers	- Related to country of origin
Hemodialysis patients	
Hemophiliac treated before 1990/91	- 50-90
HIV infected persons	- 25-35
Incarcerated persons	- 30-80
Injection drug users	- 35-90
Migrants coming from endemic regions	- Related to country of origin
Persons with unexplained persistently elevated ALT	- 15
Thalassemic	- 42-83

Abbreviation: ALT, alanine aminotransferase

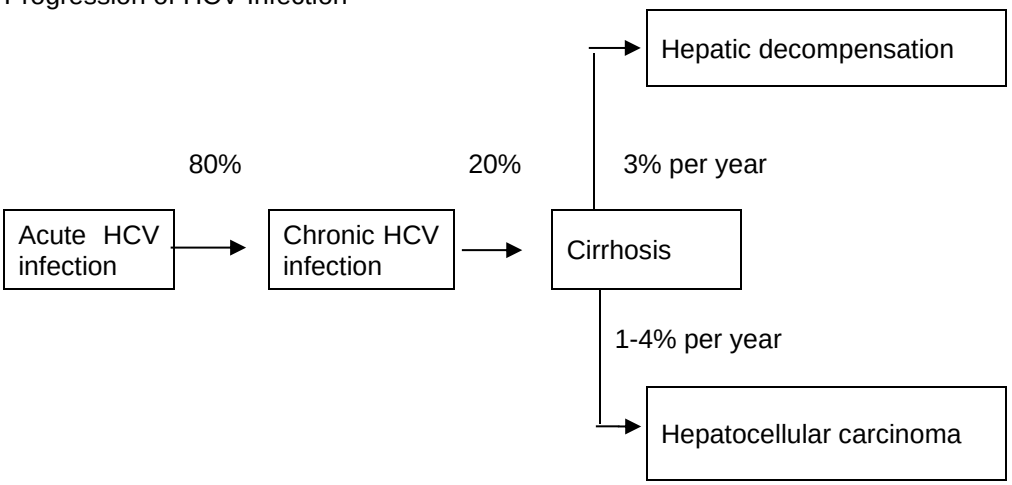
➢ Screening

- Groups/types of persons who should be screened for HCV.
  - Concurrent disease
    - Blood transfusion before approximately 1990 (depends on country)
    - Hemophilia
    - Hemodialysis
    - Immunosuppressed patients
    - Transplantation

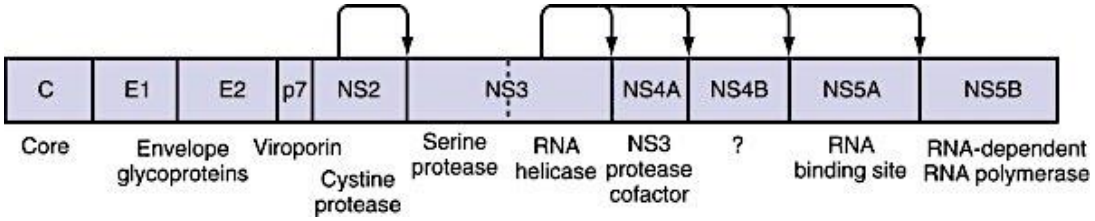
- At risk occupations
  - Needle stick injury
    - The person pricked with an HCV-contaminated needle should be tested for HCV RNA within 4 wk, then tested for anti-HCV and ALT at 12 and 24 wk.
  - Inmates
- At risk behavior
  - IV drug users
  - HIV-positive patients
  - Men who have sex with men (MSM)
  - Sex trade workers (STWs)
  - Those with > 50 lifetime sexual partners
  - Sexually transmitted disease (STD) / history of STD
- Regular folks
  - Those with unexplained elevated ALT
  - New Canadians (recent immigrants)
- Family members and sexual contents of HCV-infected persons need to be tested for anti-HCV.
- Test the children of HCV-infected mothers for HCV RNA when 1 mon old.

➢ Clinical

Progression of HCV Infection



Schematic Representation of the HCV Polyprotein



- The structural proteins C (core), E1, and E2 (envelope proteins are cleaved from the polyprotein by the host signal peptidase
- P7, a viroporin protein is cleaved by the endoplasmic reticulum signal peptidase and forms an ion channel that is essential for assembly and release of infectious virions.
- The NS2 cysteine protease autocatalytically cleaves itself from the polyprotein (first arrow).
- The NS3 protease cleaves the remainder of the non-structural proteins; NS3 (serine protease and RNA helicase)
- NS4A (NS3 protease cofactor), NS4B, NS5A (RNA binding site), and NS5B (RNA-dependent RNA polymerase (second, third, fourth and fifth arrows))

Printed with permission: Holmes JA and Chung RT. Hepatitis C. Chapter 80. Sleisenger and Fordtran's Gastrointestinal and Liver Disease-Pathophysiology, Diagnosis, Management, 11th Edition, 2020. Figure 80.2.

- Extrahepatic manifestations
  - Skin
    - Vitiligo
    - Lichen planus
    - PCT (porphyria cutanea tarda)
      - Sporadic or autosomal dominant heredity
      - Sun exposed areas, especially dorsal aspect of hands
    - Mixed cryoglobulinemia
    - Palpable purpura in legs (leukocytoclastic vasculitis)
    - Reactions
      - At sites of injection of IFN (interferon)
      - Localize cellulitis/necrosis
      - Erythema multiforme major (Steven Johnson Syndrome [SJS])
      - Exfoliative dermatitis
      - Vesiculobullous reaction
      - Ribavirin (histamine-like reaction)
        - Localized/confluent lesions
        - Vesicular lesions
  - Lung
    - Idiopathic pulmonary fibrosis

- Endocrine
  - Diabetes mellitus
  - Autoimmune thyroiditis
  - Thyroid cancer

- Likely diagnosis in a patient who presents with abdominal pain, leukocytoclastic vasculitis, palpable purpura, and ↓ complement.
  - Hematology
    - B cell non-Hodgkin lymphoma
    - Mixed cryoglobulinemia
    - Monoclonal gammopathies
    - Henoch-Schönlein purpura; usually in young adults
    - Mixed cryoglobulinemia (e.g., associated with HCV)
  - Musculoskeletal disorders (MSK)
    - Chronic polyarthritis
    - Sicca syndrome
  - Kidney
    - Cryoglobulinemic nephropathy
    - Non-cryoglobulinemic nephropathies
    - Renal cell carcinoma
    - Membranous nephropathy
    - MPEN (membranoproliferative) nephropathy
    - Glomerulonephritis

- The clinical findings in the patient with HCV which suggests associated cryoglobulinemia.
  - Skin
    - Purpuric leukocytoclastic vasculitis
  - CNS/PNS
    - Peripheral neuropathy
  - GI
    - Vasculitis → abdominal pain
  - Kidney
    - Acute/chronic renal failure
    - Nephrotic syndrome
    - Glomerulonephritis (membranoproliferative)
  - Laboratory
    - RF (rheumatoid factor) positive
    - ↓ complement

➢ Laboratory
  - In acute HCV infection, HCV RNA appears before anti-HCV antibodies.
  - The presence of HCV RNA plus anti-HCV antibiotics may arise from acute HCV infection or a flare (exacerbation) of chronic hepatitis C.
  - If hepatitis in the immunosuppressed patient, HCV RNA must be measured to make the diagnosis of anti-HCV antibiotics.

- Recommended laboratory assessment prior to therapy of HCV.
  - Anti-HCV
  - HCV RNA (qualitative +/- quantitative)
  - HCV genotyping
  - ALT, ALP, bilirubin, albumin, PT INR, HBsAg, HIV
  - CBC, glucose, TSH, ANA, smooth muscle antibody (SMA), quantitative immunoglobulins, creatinine, B-HCG
  - Abdominal Ultrasound, ECG (if age >50, cardiac disease history)
  - Liver biopsy recommended, but **not** mandatory

- Interpretation of anti HCV results.

Anti HCV by ELISA	Anti HCV by RIBA	Interpretation
Positive	Negative	False positive ELISA; patient does not have true antibody
Positive	Positive	Patient has antibody (anti- HCV does not necessarily indicate current hepatitis C infection)
Positive	Indeterminate	Uncertain antibody status

Abbreviations: ELISA, enzyme linked immunosorbent assay; HCV, hepatitis C virus; RIBA, recombinant immunoblot assay

- Reasons why the ALT or AST are not useful markers for the progress of HCV.
  - The transaminases
    - Fluctuate widely in HCV
    - A normal level may occur even though chronic HCV infection is present
    - Women with low levels of HCV RNA may more commonly have low ALT, less inflammation and less fibrosis.

- Non-biopsy tests to predict the presence of fibrosis in HCV.
  - Blood tests
    - ↑ AST and ↑ ALT, ALT > AST, AST-to-platelet index
    - A2-macroglobulin
      - Haptoglobin
      - Apolipoproteins A-1
      - GGT
      - Bilirubin
    - FibroSure®
      - Composite score of blood tests

- Transient elastography (FibroScan®; MRI elastography)
  - AUC (area-under-the-curve) for predicting cirrhosis, 0.94
  - Note
    - These tests do **not** accurately categorize
      - Lower grades of cirrhosis
      - Amount of inflammation

➢ Histopathology

- Liver biopsy grading of HCV is made by a scoring system (e.g., Knodell, Ishak or METAVIR)

SO YOU WANT TO BE A HEPATOLOGIST!

Scoring systems have been used in patients with HCV for the estimation of the extent of fibrosis and the presence of cirrhosis.

- Give reasons relating to the performance characteristics of one grading system (such as the METAVIR scoring system), which would shed light on possible limitations of liver biopsy as the test for standard of care.
  - Concordance (intra- and interobserver variation in reporting degree of fibrosis), 85% to 90%
  - Sampling error
  - False negative rate (for correct staging of cirrhosis), 15% difference in reported extent of fibrosis
    - 1 stage, 33%
    - 2 stage, 2%

- **METAVIR** system for staging/grading chronic hepatitis C infection on liver biopsy.
  - Inflammation
    - None, mild, moderate, severe
  - Fibrosis
    - None (0)
    - Portal (1)
    - Portal fibrosis with septa (2)
    - Bridging fibrosis (3)
      - Focal
      - Diffuse
      - Marked
      - Cirrhosis

	Piecemeal and Lobular Necrosis *(A)	Fibrosis (F)
0	None	None
1	Mild activity	Portal fibrosis without septa
2	Moderate activity	Portal fibrosis with septa
3	Severe activity	Numerous septa (bridging fibrosis), without cirrhosis
4		Cirrhosis

- HCV genotype, no obvious cirrhosis
  - Perform liver biopsy
  - There is no correlation between ALT or viral load, and stage of fibrosis.
  - Surrogates for the presence of advanced fibrosis such as reversal of ALT/AST ratio, platelet count, pro time-INR are not sensitive.
  - Markers of fibrosis such as hydroxyl proline are not sufficiently specific.
  - Given the variable natural history and the complexity and cost of treatment, informed decision can only be made based on histology.
  - Over half of persons with acute HCV progress to chronic HCV, and about 1% of persons per year after infection will progress to have compensated cirrhosis.

    Acute $\xrightarrow{50\%}$ Chronic $\xrightarrow{1\% / year}$ Cirrhosis

  - Patients who do **not** respond need further advice on what is next, and
    - Histology may be essential in these persons.
  - Liver biopsy may be safer than treatment when you consider alternatives such as treating everyone.
  - Post-liver transplantation

SO YOU WANT TO BE A HEPATOLOGIST!

- Circumstances when liver biopsy needs to be considered in patients with HCV.
  - Genotype 1, 4 – perform liver biopsy when results will change treatment of HCV
  - Genotype 2,3 – perform liver biopsy when treatment of HCV may be postponed
  - Liver biopsy not necessary if clinical, laboratory or diagnostic imaging suggests that cirrhosis is already present

- Pros and cons of performing a percutaneous liver biopsy in a patient with HCV and with acceptable risk for performing the biopsy.

Issues	Argument in Favour of Biopsy	Against Biopsy
○ Prognosis	– Extent of fibrosis and inflammation are best predictors of disease progression	▪ Non-invasive markers may accurately stage and grade disease
○ Decision to treat	– Genotype 1: Identify those most in need of therapy (therapy longer in duration and less likely to succeed)	▪ Genotypes 2 and 3: Patients motivated for therapy may forgo biopsy (therapy shorter in duration and more likely to succeed)
○ Treatment-related side effects	– Severity of liver disease helps in deciding of whether to endure or stop therapy	▪ Commitment to therapy should be independent of disease severity
○ Previously treated	– Lower success with retreatment. Identify those most in need of therapy (advanced fibrosis)	▪ Motivated patients who are genotype 2 or 3, were previously treated with interferon monotherapy, are candidates for re-treatment regardless of disease severity

Source: Reddy KR. *2006 AGA Institute Postgraduate Course Syllabus:* pg. 81.

Clinical Alert!

- HCV and autoimmune conditions
  - Because autoantibodies are common in HCV, and may not be associated with disease, be **cautious** making the diagnosis of an autoimmune condition in a person with HCV based just on seropositivity for autoantibodies.
- False-negative HCV serology
  - Even though the EIAs (enzyme immunoassays) for HCV have excellent performance characteristics (sensitivity and specificity of ~ 99%), anti-HCV may be negative in some persons who have HCV replication in the liver.
    - This false-negative HCV serology is seen with
      - Hemodialysis
      - Immune suppression
    - If the person is not at high risk for a false negative HCV (e.g., hemodialysis, immune suppression), a negative anti-HCV on an EIA excludes HCV infection.
    - Anti-HCV positive is diagnostic of HCV infection if there is ↑ serum ALT
  - Early diagnosis of HCV depends on the time after exposure when the test becomes positive:
    - HCV RNA 1 to 3 wks
    - Anti-HCV 7 to 8 wks

- Modifiable and non-modifiable risk factors **histological progression** of HCV infection:
  - Patient*
    - Age (> 40 yr)
    - Caucasian
    - Men
  - Lifestyle
    - Alcohol (> 50 g/day)
    - Cannabis use (marijuana)
    - Obesity
    - Smoking
  - Co-morbidities
    - Co-infection
    - HBV
    - HIV
    - Diabetes (genotypes 1 and 4)
    - Immunosuppression
    - Insulin resistance
    - Iron overload
    - Schistosomiasis
    - Steatosis
  - Virus
    - Progression of HCV is not associated with HCV load or genotype
  - Laboratory/ pathology
    - Elevated serum ALT levels (elevated)
    - Histology - Moderate to marked necroinflammation

- The clinical feature of acute HCV infection which suggests that the patient will be in the lucky group and clear their HCV without treatment.
  - Persons with acute HCV associated with jaundice have an ↑ chance of clearing in HCV.

- High mortality-associated subtype variant of HCV infection (> 3 x 10^6 copies/mL, seen in HCV infected persons who are immune suppressed for organ transplantation)
  - Fibrosing cholestatic variant of HCV-associated hepatitis with high mortality.

➢ Natural history

Acute	→ Chronic HCV	55% to 89%
Chronic HCV after infection	→ Compensated cirrhosis	~1% per yr
Compensated cirrhosis	→ HCC	~2% per yr
	→ Decompensation	~3% per yr

➢ Treatment

- **Management principles**
  - Prevention, screening, vaccination (none), prophylaxis on exposure
  - General management strategy
  - Assessment of factors predictive of viral response
  - Specific treatments
  - Select optimal agent
  - Reassess therapy
  - Screen for HCC
  - Patients with chronic hepatitis C should be
    - Vaccinated against HAV and HBV
    - Tested for HIV
    - Consider to have possible (treat appropriately)
      - Alcohol abuse and /or
      - Fatty liver

- Objectives of therapy.
  - Eradicate HCV
    - SVR (sustained viral response)
  - Absent serum HCV RNA 6 mon after treatment

➢ Terminology

- The amazing success of newly introduced protease inhibitors and the possibility of interferon- and ribavirin-free treatment regimens being standard of care in the very near future, some of the following terms may become used much less.
- In the patient with HCV, define the terms RVR, EVR, pEVR, cEVR, PVR, NR, ETR and SVR, as well as the definition and clinical implication of each of the 4 types of responses.
- RVR
  - Rapid virologic response
  - Undetectable HCV on a serum after 4 wks of anti-HCV therapy
  - Higher chance of SVR; may respond as well with only 24 wks of treatment
- EVR
  - Early virologic response
  - 2-log (100-fold) drop in HCV RNA load after 12 wks of anti-HCV therapy
  - Failure to achieve EVR associated with almost no chance of SVR and treatment can usually be stopped

- pEVR
  - Partial EVR
  - > 2-log (100-fold) decrease in HBV DNA after 12 wks of anti-HBV therapy (residual HBV RNA still present)
- cEVR
  - Complete EVR
  - No HCV RNA in serum after 12 wks of anti-HCV therapy
  - On treatment response. Observe for SVR
- PVR
  - Partial viral response
  - HCV RNA present in serum at 12 wks, but not at 24 wks
- NR
  - No response, aka will response
  - Failure to achieve EVR
- ETR
  - HCV RNA undetectable at end of treatment wk 48 – 1 genotype, wk 24 – 2,3
- SVR
  - Sustained viral response
  - Surrogate marker for eradication of SVR
  - No detectable HCV RNA in serum after 24 wks of anti-HCV therapy

Printed with permission: Janssen HLA and Fung S. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Volume 2, 2020; Chapter 79; Figure 79.7, page 1329.

- HCV-RNA levels at week 4,12 and 24 in persons with rapid virologic response (RVR), early virologic response (EVR), slow virologic response (SVR) and no virologic response (NVR)

	HCV-RNA Week 4	Week 12	Week 24
○ Rapid virologic response (RVR)	Undetectable (<50 IU/ml) [a]	Undetectable	Undetectable
○ Early virologic response (EVR)	>50 IU/ml	Undetectable	Undetectable
○ Slow virologic response (SVR)	>50 IU/ml	>50 IU/ml, but >log 2 drop	Undetectable
○ No virologic response (NVR)	>50 IU/ml	>50 IU/ml, but < log 2 drop	Detectable

[a] Level of detection (LOD) changes with more sensitive test. The currently available new tests have a LOD <15 IU/ml , no prospective studies using these tests have been performed.

Abbreviations: EVR, early virologic response; NVR, no virologic response; RVR, rapid virologic response; SVR, slow virologic response

Printed with permission: Ferenci P. Best Pract Res Clin Gastroenterol 2008; 22:1109-1122. (Table 1).

- Lifestyle recommendations
  - Persons with HCV infection should be counselled
    - To avoid sharing toothbrushes and dental or shaving equipment, and be cautioned
    - To cover any bleeding wound to prevent the possibility of others coming into contact with their blood
  - Persons should be counselled to stop using illicit drugs and enter substance abuse treatment.
  - Those who continue to inject drugs should be counselled
    - To avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment
    - To use new sterile syringes and filters and disinfected cookers
    - To clean the injection site with a new alcohol swab; and dispose of syringe and needles after one use in a safe, puncture-proof container
  - Persons with HCV infection should be advised
  - Not to donate blood
  - To discuss HCV serostatus prior to donation of body organs, other tissue, or semen

- Pharmaceutical therapy
- Factors which **predict a poor treatment response** in HCV.
  - Patient
    - Older (age (> 40)
    - Male
    - Alcoholism
    - African racial origin
    - Latino ethnicity
    - Weight: lighter patients (<75kg) more likely to respond (odds ratio 1.91) (fixed dose)
  - Liver
    - Anemia/thrombocytopenia adverse effects
    - Coinfection with HBV
    - Decompensated cirrhosis
    - Drug dose inadequate
    - Fibrosis score
  - Lifestyle
    - Poor adherence to anti-HCV treatment
    - HIV coinfection

- The virus itself
  - Genotypes1, 4
    - Viral genotype: Genotype 1&4 (42-46%), Genotype 2, 3 (76-82%)
  - When all other factors are taken into account, being in prison improves the clinical outcomes, because all treatment is given (forced high compliance rate)
  - High HCV load
  - No IL-28 B CT, TT genotype
  - Non-I
  - Lower viral levels: >2 x 10^6 (42-53%), <2 x 10^6 (62-78%)
  - Early virologic response: negative EVR (defined as 2-log decrease in HCV RNA in first 12 wks of treatment) is predictive negative SVR (97%)
  - Overall sustained virologic response (SVR) (undetectable HCV RNA 24 wks after cessation of therapy) to interferon monotherapy: 5-15%, to combined interferon and ribavirin: 30-40%, to combined pegylated interferon and ribavirin: 54-56%.
- Co-morbidities
  - Insulin resistance / Diabetes
  - ↓ social support
  - Renal disease
    - Ribavirin contraindicated with ↑ GFR
  - Poor psychiatric comorbidity
  - Advanced hepatic fibrosis (high fibrosis score)
  - Steatosis
  - Decompensated cirrhosis
- Types of response to anti-HCV therapy
  - NR > pEVR > cEVR > RVR
- Absolute or relative contraindications
  - Pregnancy or attempting conception
  - Active autoimmune diseases
  - Significant cardiopulmonary disease
  - Uncontrolled psychiatric disease
  - Uncontrolled seizures
  - Severe cytopenia, including transfusion-dependent anemia

Abbreviations: EVR, early virologic response; NVR, no virologic response; RVR, rapid virologic response; SVR, slow virologic response

MCQ Trick

- Give the effect of incarceration on the response to HCV treatment.
  - You might think response rate might be lower, but
    - Treatment-associated SVR depends on HCV genotype and therapy used, for example
      - I/R (interferon plus ribavirin)
        - Genotype I, 40% to 50%
        - Genotype II, 70% to 80%

- When are mothers with chronic hepatitis C infection allowed to breast-feed their children.
  - As long as they are negative for HIV
  - Do **not** use intravenous drugs
  - Nipples are not cracked

➢ Options

Therapeutic Agents used to Treat Hepatitis C (HCV)

Holmes JA and Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease-Pathophysiology, Diagnosis, Management. 11th Edition, 2020, Chapter 80, pages 1258-1265

- **Interferon** (IFN) "… naturally occurring glycoproteins that exert a wide area of
  - Antiviral
  - Anti-proliferate
  - Immunomodulatory

  } − Effects
  - Combining interferon to polyethylene glycol prolongs its duration of action
  - Please see section on interferon in chapter on hepatitis B viral (HBV) infection

- Interferon (IFN) eligibility

❖ Genotype 1

Eligible to Receive IFN	**Not** Eligible for IFN
○ *Recommended regimen for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN.* – Daily SOF 400 mg od and weight-based RBV (1000 mg [75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 wks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.	○ *Recommended regimen for treatment-naïve patients with HCV genotype 1 who are not eligible to receive IFN.* – Daily SOF 400 mg plus SIM 150 mg, with or without weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg] for 12 wks is recommended for IFN-ineligible patients with HCV genotype 1 infection, regardless of subtype
○ *Alternative regimen for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN.* – Daily SIM 150 mg for 12 wks and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 24 wks is an acceptable regimen for IFN-eligible persons with either ▪ HCV genotype 1b or ▪ HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment. For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.	○ *Alternative regimens for treatment-naïve patients with HCV genotype 1 who are eligible to receive IFN.* – Daily SOF 400 mg and weight-based RBV (1000 mg [75 kg] to 1200 mg [≥ 75 kg]) for 24 wks ○ This regimen may be less effective than daily SOF 400 mg plus SIM 150 mg, particularly among patients with cirrhosis.

Printed with permission: Holmes JA and Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease- Pathophysiology, Diagnosis, Management. 11th Edition, 2020, Chapter 80, Figure 80.3, page 1249.

- **Ribavirin** (RBV)
  - "…an oral guanosine analog with activity against DNA and RNA viruses"
  - Mechanism of synergistic effect of RBV with IFN
    - Cytokine changes, which change usual T-helper cells types to type 1
    - ↓ IMD (inosine monophosphate dehydrogenase) → ↓ intracellular GTP (guanosine triphosphate)
    - HCV RdRp (RNA-dependent RNA polymerase)
    - ↑ "lethal mutagenesis" drug HCV RNA replication
    - ↑ sensitivity / ↑ responsiveness to IFN type 1

Safety alert

- RBV is teratogenic
  - **No** pregnancy while on RBV for 6 mon
- RBV renal dosing required when creatinine clearance < 50 mL/min

- The following regimens are **not** recommended for treatment-naïve patients with HCV genotype 1.
  - PEG/RBV with or without telaprevir (TEL) or boceprevir (BOC) for 24 to 48 wks
  - Monotherapy with PEG, RBV, or a DAA

❖ **Genotype 2** – Regardless of interferon eligibility

- Recommended regimen for treatment-naïve patients with HCV genotype 2, regardless of eligibility of IFN therapy:
  - Daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 wks.

- Regimens **not** recommended for treatment-naïve patients with HCV genotype 2.
  - PEG/RBV for 24 wks
  - Monotherapy with PEG, RBV, or a DAA
  - TEL, BOC, or SIM-based regimen

❖ **Genotype 3**– Regardless of interferon eligibility

- *Recommended regimen for treatment-naïve patients with HCV genotype 3, regardless of eligibility for IFN therapy:*
  - Daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 wks is recommended for treatment-naïve patients with HCV genotype 3 infection.
  - *Alternative regimen for treatment-naïve patients with genotype 3 who are eligible to receive IFN.*
    - Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 wks is an acceptable regimen for IFN-eligible persons with HCV genotype 3.
- Regimens **not** recommended for treatment-naïve patients with HCV genotype 3.
  - PEG/RBV for 24 to 48 wks
  - Monotherapy with PEG, RBV, or a DAA
  - TEL, BOC, or SIM-based regimen should not be used for patients with genotype 3 HCV infection.

❖ **Genotype 4**– Interferon eligibility

Eligible	Not Eligible
○ *Recommended regimen for treatment-naïve patients with HCV genotype 4 who are eligible to receive IFN.* – Daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 wks. ○ Alternative regimens for treatment-naïve patients with HCV genotype 4 who are eligible to receive IFN. – Daily SIM 10 mg for 12 wks and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 24 to 48 wks.	○ *Recommended regimen for treatment-naïve patients with genotype 4 who are not eligible to receive IFN.* – Daily SOF 400 mg weight-based RBV (1000 mg [75 kg] to 1200 mg [≥ 75 kg]) for 24 wks. -

- Regimens **not** recommended for treatment-naïve patients with HCV genotype 4.
  - ○ PEG/RBV for 48 wks
  - ○ Monotherapy with PEG, RBV, or a DAA
  - ○ Telaprevir-, boceprevir-based regimen

❖ **Genotype 5, 6**– Regardless of interferon eligibility

- ○ *Recommended regimen for treatment-naïve patients with HCV genotype 5 or 6.*
  - – Daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 weeks.
  - – *Alternative regimen for treatment-naïve patients with genotype 5 or 6*
    - ▪ Daily weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 48 wks is an acceptable regimen for persons infected with HCV genotype 5 or 6.

- Regimens **not** recommended for treatment-naïve patients with genotype 5 or 6 HCV.
  - ○ Monotherapy with PEG, RBV, or a DAA
  - ○ TEL, BOC-based regimen

Abbreviations: BOC, boceprevir; DAA, direct activity agent; PEG, pegylated interferon; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; TEL, Telaprevir

Adapted from: Holmes JA and Chung RT. Sleisenger and Fordtran's Gastrointestinal and Liver Disease- Pathophysiology, Diagnosis, Management. 11th Edition, 2020, Chapter 80.

- Possible contraindications to the use of Ribavirin.
  - Pregnancy
  - Inadequate contraception (contraception to prevent conception for 6 mon after RBV stopped
  - Known allergy to ribavirin
  - End-stage renal disease (ESRD)
  - Anemia (cannot give adequate dose, since ribavirin may cause anemia, and thus require dose reduction)
  - Angina pectoris (possible)
  - Old age (possible)

❖ **Direct Acting Antivirals** (DAAs)

Types	Targets HCV Inhibitors
○ PREVIRS	− NS3/N64A protease
○ ASVIRS	− NS5A protein
○ BUVIRS	− NS5B polymerase

▪ Inhibitors

➢ Mechanisms of Action

❖ DAA

- PREVIRS: NS3 / N64A Inhibitors
  - NS3
    - Complexes with N62 → autocatalytic cleavage/destroys of NS2-NS3 site
      - ↑ serine proteases activity when associated NS4A, with cleavage of

	Site
NS3	NS4A
NS4A	NS4B
NS4B	NS5A
NS5A	NS5B

    - Cleaves/destroys Cardiff and TRIP (Toll/interleukin receptor domain-containing adapter-inducing IFN-B
    - RNA helicase unwinds
      - Viral RNA
      - Viral DNA
  - NS4A
    - Complexes with NS3
    - ↑ formation of membrane wall on which there is transportation of HCV

- ASVIRS: NS5A Inhibitors
  - NS5A
    - Binds to zinc (Zn) → forms j=homodimer → bind to membrane of ER
    - In ER, NS5A is an RNS binding site in the complex for viral replication → ↓ HCV replication
    - ↓ apoptosis of cells infected with HBV
    - ↑ sensitivity of IFN

- UVIRS: NS5B inhibitors (nucleoside and non-nucleoside polymerase inhibitors)
  - Barrier for resistance to DAA therapy for HDV
    - Genetic
    - Residence-associated substitution (RAS)
  - Genomic RNA
    - Positive strand template to produce RNA negative strand
    - Negative strands used for polyprotein translation synthesis of intermediates of replication inserted into new HCV particles)
  - NS5B RNA-dependent polymerase (RdRp) → catalyzes replication of HCV)

➢ Complications

- Use combinations of DAAs with different mechanism of action to

	Use another combination of DAAs	Extend treatment with this combination
Patients with HCV genotype 1a		
− Elbasvir / grazoprevir	+	+
− Sofosbuvir / ledipasvir	+	-
Patient with HCV genotype 3		
− Daclatasvir / sofosbuvir treatment experienced, or cirrhosis ▪ Add ribavirin if Y93H NS5A RAS+	+	-
− Sofosbuvir / velpatasvir, treatment experienced or cirrhosis ▪ Add ribavirin of Y93H NS5A RAS+	+	-

➢ Individual DAAs / DAA Combinations

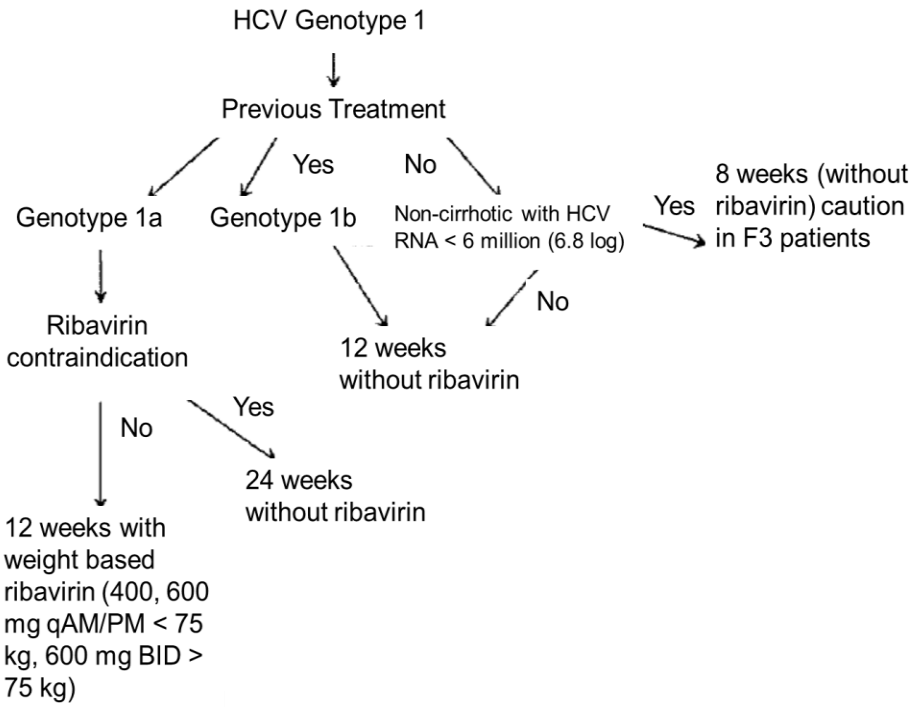
- Alert
  - All DAAs have varying drug-drug interactions, and before starting DAAs consult a pharmacologist, or refer to reference material

- **Sofosbuvir** (SOF)
  - Effective against all genotypes of HCV
  - Because of 80% renal excretion, renal dosing is required when estimated glomerular filtration rate < 30 mL/min per 1.73 m^2
  - No dosing reduction required for patients with cirrhosis (not metabolized in liver)
    - Lactic acidosis and decompensation when used with ribavirin
  - Do **not** use with inducers of p glycoprotein (p glycoprotein)
  - Alert!
    - SOF plus the anti-arrhythmic drug amiodarone may cause dangerous bradycardia.
      - "…if a sofosbuvir-containing DAA regimen is planned for a patient on amiodarone and the amiodarone can be safely discontinued, the DNA should be delayed for at least 3 mon after cessation of the amiodarone.

- **Sofosbuvir / Ledipasvir** (SOF-LED)
  - Marketed as a 2-day combination tablet
  - LED metabolism in liver
    - Secreted unchanged in bile
  - Excretion
    - SOF → renal

    *Caution: renal dosing required
    - LED → Bile
  - Caution
    - Drug-interaction with other drugs which induce P-glycoprotein / BRCP (breast cancer resistance protein)
  - Alert
    - Do **not** use SOF-LED with
      - Rosuvastatin
      - Other statins: use cautiously
    - Less effective LED if intragastric pH becomes less acidic (antacids, H2RA, PPIs
      - Dose SOF-LED 12 h from when pH raising indications taken
    - Higher concentrations (↑ AEs) when SOF-LED given with
      - Ritonavir
      - Tenofovir

Harvoni (Sofosbuvir/Ledipasvir) – from ION-1,2,3 and 4 trials



***If reliable NS5A resistance testing is performed

- Treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis who have NS5A Ras that confer high-level resistance to ledipasvir (M28A/G/T, Q30E/G/H/K/R, L31MV, P32L/S, H58D, and/or Y93C/H/N/S) detected at baseline should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 wk with ribavirin
- Those without ledipasvir RASs at baseline can be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 wk without ribavirin (B1)

- IFN-free combinations to treat all genotypes (1 to 6) of HCV
  - Sofosbuvir +/- ribavirin
  - Sofosbuvir + daclatasvir +/- ribavirin

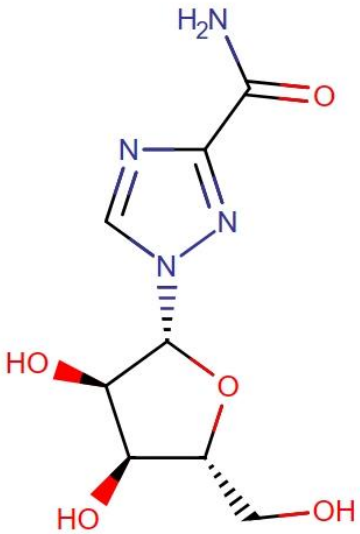
- **Elbasvir / grazoprevir** (ELB-GRAZ combination)
  - Marketed as a combination tablet
  - Metabolism
    - Bile/feces
    - ↑ AEs with cirrhosis / Child-Pugh B/C
    - Hepatic CYP3A4
  - Excretion
    - Safe in patients with renal failure

- **Sofosbuvir / velpatasvir** (SOF-VEL)
  - Marketed as a combination tablet
  - VEL metabolism
    - Hepatic CYP2B6, CYP2C8, CYP3A4, but
      - Safe to use in patients with cirrhosis
      - Inhibited P-gp / BCRP – do **not** use SOF-VEL with inducers of P-gp
  - Less effective LED if intragastric pH becomes less acidic (e.g., antacids, H2RA, PPIs)
    - Dose SOF-VEL 12 h from when pH medications taken.

- **Sofosbuvir / velpatasvir / voxilaprevir** (SOF-VEL-VOX)
  - Marked as a 3-day combinations, taken with food
  - Effective against all HCV genotypes
  - VOX metabolism
    - Liver CYP 3A4
    - Do **not** use with cirrhosis, CP class B/C
  - Renal excretion of VOX
  - Inhibition of P-gp, ECRP, OATP1B1 / OATP1B3
  - Do **not** use SOF-VOL-VOX with
    - Birth control pill (BCP) containing ethynyl estradiol (hepatotoxicity: ↑ ALT)
    - Other statins use cautiously
    - Rosuvastatin

Characteristic	SOF	SOF-LED	SOF-VEL	SOF-VBL-VOX	CLB-GRAZ	GLG-PIB
○ Contraindication: organ failure						
− Kidney	+	+	+	+		
− Liver				+	+	+
○ Use with caution						
− Antacids, H2RA, PPIs		+	+		+	+/-
○ Drug-drug interactions						
− Statins		+(LGD)	+	+		
− Estrogens			+	+		
− Amiodarone	+	+	+	+		
− Tenofovir, ritonavir, cobicistat		+				
− Inducers of						
▪ P-gp	+	+	+	+	+	+
▪ BRAC		+	+	+		+
▪ CYP3A, CYP 2B6, 2C8, 3A4			+	+	+	
▪ OATP1B1, OATP1B2,			+	+		
▪ OATP1B3				+		+
○ Take with food				+		
○ Effective against all genotypes of HCV						

- **Ribavirin** (RBV)



- Indication
  - Chronic HCV infection in combination with other antiviral agents with the intent to cure or achieve a sustained virologic response (SVR)
  - Typically added to improve SVR and reduce relapse rates
  - The addition of ribavirin in Technivie therapy indicated for treating HCV genotype 1a and 4 infections is recommended in patients with or without cirrhosis.
  - Resistance: viral genetic determinants resulting in variable response to ribavirin therapy has not been yet determined.

- Mechanism of action
  - Inhibition of viral RNA and protein synthesis.

- Pharmacokinetics
  - Absorption
    - Rapidly and extensively absorbed following oral administration.
    - The average time to reach Cmax was 2 hours after po administration of 1200 mg ribavirin
    - Oral bioavailability is 64% following a single 600 mg po
  - Volume of distribution
    - Displays a large volume of distribution
  - Metabolism
    - Ribavirin is phosphorylated intracellularly by adenosine kinase to ribavirin mono-, di-, and triphosphate metabolites → undergoes two metabolic pathways where it is reversibly phosphorylated or degraded via deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite.
    - In vitro studies indicate that ribavirin is not a substrate of CYP450 enzymes 10.
  - Route of elimination
    - Metabolites of ribavirin are renally excreted.
    - After 600 mg radiolabeled ribavirin po
      - ~ 61% detected in the urine
      - 12% detected feces
  - Half-life
    - Terminal T1/2 following administration of a single 1200 mg po is ~ 120-170 h
  - Clearance
    - Total apparent clearance rate after a single 1200 mg po ribavirin is 26L/h

- Clinical
  - “flu-like symptoms”, fatigue, anorexia, nausea, nasal congestion, irritability, cognitive impairment, insomnia

➢ Laboratory

Test	Level		Other clinical considerations
○ Hemoglobin	10 gm/dL	- ↓ ribavirin by 200 mg/day	▪ Consider starting erythropoietin; if Hgb responds poorly to dose reduction, check iron studies and consider reducing peginterferon
	8.5 gm/dL	- Stop ribavirin	▪ Hold ribavirin and consider stopping; transfuse as necessary
○ WBC	1500/μL	- ↓ pegIFN by 50%	▪ Monitor more closely
	1000/μL	- Stop treatment	▪ Monitor more closely; consider G-CSF
○ Absolute neutrophils	750/μL	- ↓ pegIFN by 50%	▪ Monitor more closely
	500/μL	- Stop pegIFN	▪ Monitor more closely
○ Platelets	50,000/μL	- ↓ pegIFN by 50%	▪ Individualize dose adjustment
	25,000/μL	- Stop IFN	▪ Consider platelet transfusion or platelet stimulating factor

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- Dose reduction of ribavirin required in19% of Ribavirin-treated persons, with discontinuation of Ribavirin in 10%

➢ Standard therapy for chronic HCV according to viral genotype.

Genotype	Interferon Dose (per week)	Ribavirin Dose (mg/day)	Duration (weeks)	SVR
1	180 μg PEG alfa-2a, or 1.5 μg/kg PEG alfa-2b	800-1400 mg/day weight-based	48	41-42%
2	180 μg PEG alfa-2a, or 1.5 μg/kg PEG alfa-2b	800 mg/day	24	66-75%
3	180 μg PEG alfa-2a, or 1.5 μg/kg PEG alfa-2b	800 mg/day	24	66-75%
4	180 μg PEG alfa-2a, or 1.5 μg/kg PEG alfa-2b	1000-1200 mg/day	48	55%
5	180 μg PEG alfa-2a, or 1.5 μg/kg PEG alfa-2b	1000-1200 mg/day	48	64%
6	180 μg PEG alfa-2a, or 1.5 μg/kg PEG alfa-2b	1000-1200 mg/day	48	63%

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- Clinical significance in HCV infection of CC, CT and TT genotypes of the IL-28 gene on chromosome 19.
    - CC genotypes
        - Codes for IFN-λ-3 ("lambda"), with ↑ production of intrinsic IFN
        - ↑ efficacy of PEG-IFN + ribavirin (@x > rate of RVR, complete EVR, and SVR
        - More common in European and Asian ancestry
    - CT and TT genotypes
        - No ↑ lambda IFN1, so lower rates of RVR, EVR, SVR
        - More common in Latino and African ancestry
        - DADs (direct acting anti-viral agents), aka STAT-C (specifically targeted anti-viral therapy) for HCV
        - Telaprevir and boceprevir are linear PIs (protease inhibitors) against the NS 3/4a proteases.
        - PEG-IFN-alpha + RBV (ribavirin) + PI for genotype 1 HCV

- **Protease Inhibitors**
    - In the past 35 years, three Nobel prizes have been won in the area of gastroenterology/ hepatology: the H2-receptor and its antagonists, the LDL receptor, and the rediscovery of Helicobacter pylori and the establishment of its importance in peptic ulcer disease.
    - With the identification of the hepatitis C virus (HCV) by Heyden and the recent "game changing" development of protease inhibitors, the hope for the sustained eradication of HCV has gone from dismal to greater than 95%.
    - This will have a major impact on liver transplantation rates for HCV, and more importantly to the quality of life of sufferers.
    - Unfortunately, with the very high cost of these new anti-HCV medications, this revolutionary therapy may not be available to all persons with HCV infection.
    - The rates of regional governmental approval will vary widely in making the drugs available even for the persons of wealth.
    - Most national professional groups have not yet formulated guidelines.
    - Nonetheless, the candidate coming forward for examination will be required to be aware of these existing new developments.
    - Therefore, included here are the summarized 2014 AASLD (American Association for Study of Liver Disease) and IDSA (infectious Diseases Society of America) Recommendations.

These AASLD/IDSA recommendations are available online at
http://www.aasld.org/PRACTICEGUIDELINES/Pages/default.aspx
http://www.idsociety.org/IDSA_Practice_Guidelines/

❖ ***Retreatment***

Genotype	Recommended	Alternative	Not Recommended
• Patients in whom previous PEG/RBV has failed (Failure [non response] is defined as partial or null response to treatment with PEG/RBV. ○ Relapse to prior therapy should be treated the same as treatment-naïve)			
1	○ SOF + SMV ± RBV x 12 wk	- SOF x 12 wks + PEG/RBV x 12 – 24 wk - SOF + RBV x 24 wk - SMV x 12 wks + PEG/RBV x 48 wk*	- PEG/RBV ± telaprevir or boceprevir - Monotherapy with PEG, RBV, or a DAA - Do **not** treat decompensated cirrhosis with PEG or SMV
* For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present			
2	○ SOF + RBV x 12 wk	- SOF + PEG/RBV x 12 wk	- PEG/RBV ± telaprevir or boceprevir - Monotherapy with PEG, or direct-acting anti-viral agent - Do **not** treat decompensated cirrhosis with PEG
3	○ SOF + RBV x 24 wk	- SOF + PEG/RBV x 12 wk	- PEG/RBV ± any current protease inhibitor - Monotherapy with PEG, RBV, or a DAA - Do **not** treat decompensated cirrhosis with PEG
4	○ SOF + PEG/RBV x 12 wk	- SOF + RBV x 24 wk	- PEG/RBV ± any current HCV protease inhibitor - Monotherapy with PEG, RBV, or a DAA - Do **not** treat decompensated cirrhosis with PEG
5-6	○ SOF x 12 wks + PEG/RBV 12 wk		- PEG/RBV + any current HCV protease inhibitor - Monotherapy with PEG, RBV, or a DAA - Do **not** treat decompensated cirrhosis with PEG

- Patients with previous PEG/RBV plus telaprevir/boceprevir** failed†† †††

Genotype	Recommended	Alternative	Not Recommended
1	○ SOF x 12 wks + PEG/RBV x 12-24 wks	- SOF + RBV x 24 wks‡ - SOF† - PEG/RBV x 24 wks ‡‡	- PEG/RBV ± telaprevir or boceprevir or SMV - Monotherapy with PEG, RBV, or a DAA - Do **not** treat decompensated cirrhosis with PEG or SMV

○ Note: stop anti HVC therapy
- pEVR in genotype 1, 4 (the use of serum HBV RNA level at week 12) to indicate an EVR, does not apply to genotype 2 or 3 infection
- HBV RNA still present at 24 wks for each of interferon and ribavirin, 30% of HCV patients have to stop therapy because of AEs (adverse effects)

***Failure (non-response) is defined as partial or null response to treatment with PEG/RBV plus telaprevir or boceprevir. Relapse to prior therapy should be treated the same as treatment naïve

† Consideration should be given to postponing treatment, pending release of new drugs for patients with limited (F 0-2) hepatic fibrosis

†† A recommendation for simeprevir use for patient with previous telaprevir or boceprevir exposure not provided due to potential risk of pre-existent resistance to protease inhibitor treatment.

††† Given the lack of prior approval of protease inhibitor therapy for genotypes 2, 3, 4, 5, 6 and the lack of sufficient data, no recommendations are given for these genotypes at this time

‡ IFN ineligible

‡‡ IFN eligible

❖ Genotype 1

Eligible for IFX	Not Eligible for IFX
○ *Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) non-responder patients:* – Daily SOF 400 mg plus SIM 150 mg, with or without weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 wks.	○ *Recommended regimen for HCV genotype 1 PEG/RBV (with an HCV protease inhibitor) non-responder patients:* – Daily SOF 400 m) for 12 wks plus weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) and weekly.
○ *Alternative regimen for PEG/RBV (with or without an HCV protease inhibitor) non-responder patients with HCV genotype 1.* – Daily SOF 400 mg for 12 wks and weight-based RBV (1000 mg [75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 to 24 wks.	○ Daily SOF 400 mg for 24 wks and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 wks.

- *Alternative regimen for PEG/RBV (without an HCV protease inhibitor) non-responder patients with HCV genotype 1 who are eligible to receive IFN.*
  - Daily SIM 150 mg for 12 wks plus weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) and weekly PEG for 48 wks.
  - *The following regimens are NOT recommended for PEG/RBV (with or without an HCV protease inhibitor) non-responder patients with HCV genotype 1:*
    - PEG/RBV with or without telaprevir or boceprevir
    - Monotherapy with PEG, RBV, or a DAA
    - History of decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), treatment is not indicated because of the risks of PEG, BOC and TEL in this population.

❖ Genotype 2– Non-responder; regardless of interferon eligibility

- *Recommended regimen for genotype 2 PEG/RBV non-responders.*
  - Daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 12 wks
    - Patient with cirrhosis may benefit by extension of treatment to 16 wks.)
- *Alternative regimen for PEG/RBV non-responder patients with HCV genotype 2 infection who are eligible to receive IFN.*
  - Retreatment with daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 wks.
- *Regimens are NOT recommended for non-responder patients with HCV genotype 2:*
  - PEG/RBV with or without telaprevir, boceprevir or simeprevir
  - Monotherapy with PEG, RBV, or a DAA

❖ Genotype 3

- *Recommended regimen for HCV genotype 3 PEG/RBV non-responders.*
  - Daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 wks.
- *Alternative regimen for HCV genotype 3 PEG/RBV non-responder patients who are eligible to receive IFN.*
  - Retreatment with daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 wks.
- *Regimens are NOT recommended for non-responder patients with HCV genotype 3 infection:*
  - PEG/RBV with or without telaprevir, boceprevir or simeprevir
  - Monotherapy with PEG, RBV, or a DAA

- Genotype 4
  - *Recommended regimen for HCV genotype 4, PEG/RBV non-responder patients.*
    - Daily sofosbuvir (400 mg) for 12 wks and daily weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 wks.
  - *Alternative regimen for HCV genotype 4, PEG/RBV non-responder patients.*
    - Daily SOF 400 mg and weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) for 24 wks.
  - *Regimens are NOT recommended for non-responder patients with genotype 4 HCV infection:*
    - PEG/RBV with or without telaprevir or boceprevir
    - Monotherapy with PEG, RBV, or a DAA
- Genotype 5, 6
  - *Recommended regimen for HCV genotype 5 or 6, PEG/RBV non-responder patients.*
    - Daily SOF 400 mg for 12 wks and daily weight-based RBV (1000 mg [< 75 kg] to 1200 mg [≥ 75 kg]) plus weekly PEG for 12 wks.
  - Alternate regimen for PEG/RBV non-responder patients with HCV genotype 5 or 6.
    - None
  - Regimens are **not** recommended for non-responder patients with HCV genotype 5 or 6.
    - PEG/RBV with or without TEL or BOC
    - Monotherapy with PEG, RBV, or a DAA

Adapted from: Holmes JA and Chung RT. Hepatitis C. Chapter 80. Sleisenger and Fordtran's Gastrointestinal and Liver Disease-Pathophysiology, Diagnosis, Management, 11th Edition, 2020.

❖ **Special Considerations**

- **Renal Impairment**
  - Dose adjustments are needed for patients with renal impairment

Renal Impairment	eGFR/CrCl Level (mL/min/ 1.73 m^2)	Interferon (IFX)	Ribavirin (RIB)	Sofosbuvir (SOF)	Simeprevir (SIM)
– Mild	50-80	180 µg PEG (2a) PEG (2b) 1.5 µg/kg	Standard	Standard	Standard
– Moderate	30-50	180 µg PEG (2a) PEG alfa-2b 1 µg/kg or 25% reduction	Alternating doses 200 and 400 mg every other day	Standard	Standard
– Severe	< 30	135 µg PEG (2a) PEG alfa-2b 1 µg/kg or 50% reduction	200 mg/d	Data not available	Standard
– ESRD / HD		PEG (2a) 135 µg/wk. or PEG 2b) 1 µg/kg/wk or standard FN 3 mU 3x/wk	200 mg/d	Data not available	Data not available

Abbreviations: ESRD, end stage renal disease; HD, hemodialysis

❖ HCV/HIV coinfection

Genotype	Recommended	Alternative	NOT Recommended	Allowable anti-retroviral Therapy
1	○ Treatment-naïve and prior PEG / RBV relapsers – IFN eligible: ▪ SOF + PEG / RBV x 12 wk – IFN ineligible: ▪ SOF + RBV x 24 wk ▪ SOF + SMV ± RBV x 12 wk ○ Treatment experienced (prior PEG/RBV non-responders) regardless of – IFN eligibility ▪ SOF + SMV ± RBV x 12 wk	Treatment naïve and prior PEG / RBV relapsers – IFN eligible: SMV x 12 wk + PEG/RBV x 24 wk* Treatment experienced (prior PEG/RBV non-responders) – IFN eligibility: SOF + PEG / RBV x 12 wk – IFN ineligibility: SOF + RBV x 24 wk	TVR + PEG / RBV x 24 or 48 wk (RGT) BOC + PEG / RBV x 28 or 48 wk (RGT) PEG/RBV x 48 wk	For SOF use: ALL except didanosine, zidovudine, or tipranavir For SMV use: LIMITED to abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, rilpivirine, tenofovir
2	○ SOF + RBV x 12 wks regardless of treatment history	– Treatment naïve and prior PEG / RBV relapsers: None – Treatment experienced (prior PEG/RBV non-responders) – IFN ineligibility ▪ SOF + PEG / RBV x 12 wk – IFN ineligibility: None	PEG/RBV x 24 48 wk Any regimen with TVR, BOC, or SMV	All except didanosine, zidovudine, or tipranavir

Genotype	Recommended	Alternative	NOT Recommended	Allowable anti-retroviral Therapy
3	○ SOF + RBV x 24 wks regardless of treatment history	– Treatment naïve and PEG/RBV relapsers: None – Treatment experienced (prior PEG RBV non-responders) – IFN eligible: ▪ SOF + PEG / RBV x 12 wks – IFN ineligible: None	PEG/RBV x 24-48 wks Any regimen with TVR, BOC, or SMV	All except didanosine, zidovudine, or tipranavir
4	○ Regardless of treatment history: – IFN eligible: ▪ SOF + PEG / RBV x 12 wks – IFN ineligible: ▪ SOF + RBV x 24 wks	– None	PEG/RBV x 48 wks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine, or tipranavir

- Effects of HIV co-infection on the clinical course of HCV.
  - ↓ HCV clearance rate
  - ↑ risk of chronic HCV
  - ↑ risk of progression to fibrosis
  - Do **not** use interferon-based regimen
    - C**ontraindicated**, since
      - Interferon **accelerates** HIV infection
  - In the setting of HIV plus HCV in the transplantation setting, there is ↑ graft rejection and loss

- Factors which enhance the risk of accelerated fibrosis in the setting of HCV co-infection with HIV.

○ Patient	– Older (> 33 yrs) – Women
○ HIV	– CD4+ < 100 mm3 while on HAART – HIV viral load still detectable while on HAART therapy
○ HCV	– Untreated

- Mechanisms for the acceleration of hepatic fibrosis in the patient with HCV and co-infection with HIV.

○ TGF-B1	– HIV → ↑ TGF-B1 – ↑ TGFB1 → ↑ HCV replication
○ TJ permeability	– HIV → ↓ CD4+ – ↓ CD41 → ↑ TJ permeability – ↑ TJ permeability → ↑ bacterial translocation
○ Stellate cells	– HIV → activate hepatic stellate cells – ↑ activated stellate cells → ↑ production of collagen

Abbreviation: TJ, tight junctions

❖ **HCV after Liver Transplantation**

➢ Risk factors

- Virus
  - HBV
    - No HBV infection with HCV before LT (HBV coinfection → ↓ severity of HCV
  - HCV
    - Genotype 1 b
    - ↑↑ HCV RNA before and 2 wk after LT
    - ↓ CD4+ T-cell responses to HCV
  - CMV
    - Coinfection with HCV
- Medications
  - Multiple treatments of LT rejection treated with prednisone (cumulative dose of prednisone is large)
  - OKT3 used to treat rejection
- Liver
  - Graft liver
    - Ischemic presentation on imaging
    - Given to non-white recipient

Clinical Pearls

- Monitor the HCC patient treated with TACE for the development of leukopenia
- Gastric acid inhibition with PPIs ↓ solubility of anti-HCV drugs, to the point that the dose may need to be changed (or the PPI stopped).

➢ Hepatic complications following liver transplantation (LT) for HCV.

- Recurrence of HCV (~100%) post-LT
- ↑ risk of cirrhosis
  - 20% to 40% in 5 yrs
- Rapid progression to cirrhosis
- High risk of cirrhosis becoming decompensated
  - In 1 yr, about half of decompensated HCV cirrhotics will die
- Fibrosing cholestatic hepatitis

SO YOU WANT TO BE A HEPATOLOGIST!

- Give scientific reasons why the development of a **vaccine** for HCV has been challenging.
  - Requires the production of both
    - Cellular immune response
    - Neutralizing antibodies
  - Anti-HCV does not lead to protective immunity (escape from antibody recognition)
  - High mutational rate of HCV
  - Heterogeneity of HCV envelop proteins

➢ Histologic features of recurrent HCV infection after liver transplantation (and comparison with acute cellular rejection).

Histological Features	HCV Recurrence	Rejection
○ Portal inflammation	– Bland, uniform	▪ Activated
○ Lymphocytes, lymphoid aggregates, or follicles	– Common (~50%)	▪ Uncommon
○ Eosinophils	– Uncommon	▪ Common
○ Steatosis	– Common	▪ Never
○ Acidophilic bodies	– Common	▪ Uncommon
○ Atypical features	– Cholestasis, ballooning degeneration without significant inflammation	▪ Prominent periportal and lobular necroinflammatory activity w/o sub-endothelial venular inflammation

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/ Management*. Ninth edition, 2010, page 1609.

- **HCV and HBV Coinfection**

- The risk of cirrhosis, hepatocellular carcinoma (HCC) and mortality in hepatitis B and hepatitis C virus (HBV/HCV) monoinfected and coinfected patients.

Feature	Cirrhosis	HCC	Mortality (SMR)
○ HBV monoinfection	22%	OR 16-23	1.4-5.3
○ HCV monoinfection	30%	OR 8-17	2.4-3.1
○ HBV/HCV coinfection	50%	OR 36-165	5.6-49

Abbreviations: HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; OR, odds ratio; SMR, standard mortality ratio

Printed with permission: Wursthorn K, et al. Best Pract Res Clin Gastroenterol 2008; 22: 1063-79. (Table 2).

- HCV core surrogate marker for HCV-RNA
  - Anti-HCV+ → RNA- → repeat in 3 mon
    ↑
    window period

- Ribavirin boosting effect
  - Rash, cough, teratogenic
  - Drug/drug interactions

- Amiodarone / cyclosporin contraindicated in HCC → D/C for 3 mon (↑ risk arrhythmia)

HEREDITARY HEMOCHROMATOSIS (HH)

- Definition
  - Hereditary hemochromatosis (HH) is an inherited disorder of the control of iron absorption.

- Physiology
  - An understanding of physiology of iron absorption and iron balance is helpful to understand the role of phlebotomy to remove excessive iron from the body by removing the iron-containing
    - Red blood cells
      - Thereby overcome the toxic effects of the excessive body iron stores created by the defective feedback on intestinal absorption of iron which fails to prevent the body's accumulation of toxic levels of iron.

- Iron Body Stores
  - Daily
    - Iron in: Absorption 1-2 mg
    - Iron out: Desquamation of GI epithelial cells
      - Menstruation
  - Approximately 3500 mg of iron is stored by the human body.

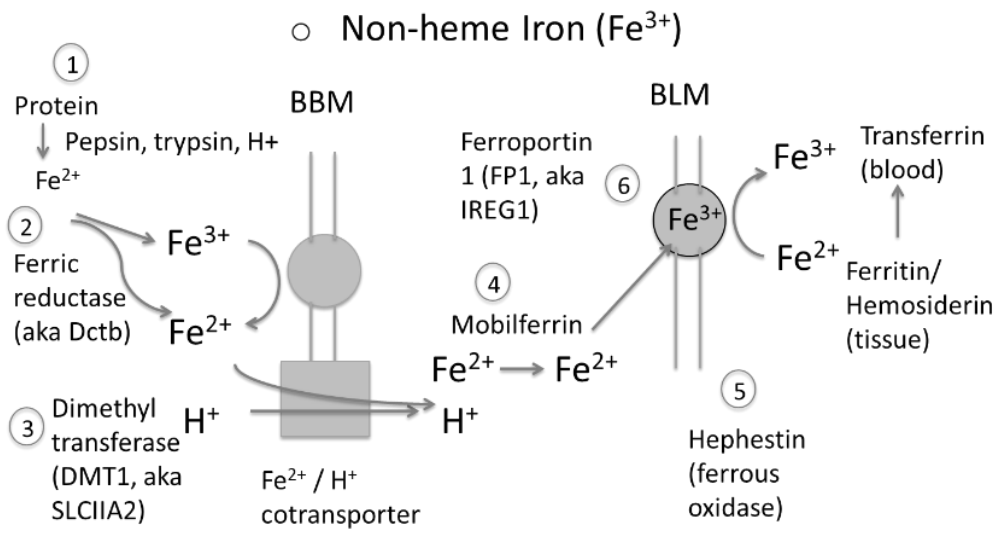
Tissue	RBC hemoglobin muscle	2300 mg
	Muscle (myoglobin)	350 mg
	Bone marrow	150 mg
Storage	Macrophages	500 mg
	Liver (RE system)	200 mg
	Bone marrow	150 mg

- Iron Homeostasis
  - Diet
    - Heme-bound Fe^{3+} (meat, myoglobin)
    - Non-heme Fe^{3+}
  - Out
    - About 1-2 mg of iron is lost daily from the body by way of the desquamation of epithelial cells of the skin, gastrointestinal tract, bile ducts and urinary tract, and via blood loss during menstruation.
    - The loss of iron from the body is not controlled
    - Body iron balance (homeostasis) is controlled only by the controlled modification of iron absorption (IA) by the duodenal enterocytes.

- Luminal Factors and Iron Absorption (IA)

↑ IA	↓ IA
○ Reducing agents – HCl – Ascorbic acid ○ Chelating agents – Organic acids – Amino acids	○ Intraluminal binders – Dietary fiber – Phosphate – Phthalates – Oxalates

- Dietary Iron Absorption in Duodenocytes



❖ Non-Heme Iron

- Stomach
  - H^+ / pepsin begin digestion and release of Fe^{3+}
    - This is continued by pancreatic secretion of trypsinogen → trypsin
  - (1) HCl reduces dietary Fe^{3+} to Fe^{2+}
  - (2) Fe^{3+} is also reduced to Fe^{2+} by duodenocytes BBM ferric reductase [Dcytb].
  - Fe^{2+} is solubilized by HCl and chelating agents such as ascorbic acid, amino acids and organic acids.

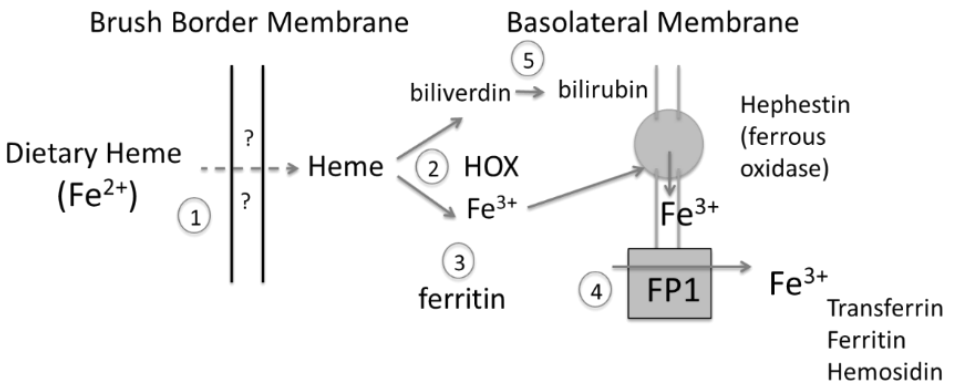
- Duodenum: BBM (Brush Border Membrane) DMTI
  - (3) Fe^{2+} from non heme Fe^{3+} crosses the duodenal BBM by the Fe^{2+} -H^{+} transporter DMT1 (divalent metal transporter aka SLCIIA2), which cotransports Fe^{2+} with H^{+}.

- Cytosol: Mobilferrin and Hephaestin
  - (4) In the cytosol, Fe^{2+} binds to mobilferrin, which diffuses to the BLM.
  - Fe^{2+} dissociates from mobilferrin at the basolateral membrane (BLM)
  - (5) At the BLM, Fe^{2+} is oxidized to Fe^{3+} by hephaestin (ferrous oxidase).

- Basolateral Membrane (BLM): FP1
  - (6) The Fe^{3+} binds to BLM FP1 (ferroportin transporter, aka IREE1), and is transported into the portal blood, where it is bound to
    - Transferrin (7)
    - Insoluble hemosiderin
    - Apoferritin plus Fe^{3+} form soluble protein “ferritin”
  - Ferritin is the major storage form of iron, ferritin may also be detected in the blood (8).
  - Mobilferrin traffics back to the BBM to bind to more non-heme Fe^{2+} delivering into the cytosol by DMT.

Heme Iron Absorption in Duodenum

- Heme Iron (Fe^{2+})



- Heme Iron: Hox1, Ferroportin, Biliverdin
  - (1) Heme-Fe^{2+} crosses the BBM by an unknown mechanism.
  - (2) In the cytosol of the enterocyte, heme oxygenase (Hox1) oxidizes the heme to release Fe^{3+}.
  - In the cytoplasm of the duodenal enterocyte, Fe^{3+} either binds to ferritin (3), or is transported across the BLM by ferroportin (4).
  - (c) The remaining biliverdin in heme is reduced to bilirubin, which is excreted in bile (please see Liver Chapter for detail on bilirubin metabolism)

- Infection / Inflammation
  - Infection / inflammation → ↑IL6 → ↑HFE (involving JAK dependent activation of STAT3)
  - ↑HFE leads to
    - ↓ iron absorption
    - ↑ macrophage Fe (↓ release)

➢ Iron Hemostasis in Patients with Iron Deficiency or Low Body Iron Stores (↓BIS)
  - HFE binds to TFR1 and TFR2
  - The HFE-TFR1 complex on the surface of the hepatocyte senses TS (transferrin saturation)
  - When TS↑, diferric transferrin displaces HFE from the HFE-TFR1 complex → HFE now binds to TFR2
    ↑ TS → Fe moves from TFR1 to TFR2
    ↑ TRF2 → ↓FP
    → ↓ IA → correction of ↑TS
    → ↓ release of Fe from macrophages / Kupffer cells
    → ↓ferroportin on BLM → ↓IA → corrects ↑BIS/ ↑TS

➢ Role of Hepcidin in Iron Homeostasis
  - Binds to ferroportin on basolateral membrane (BLM) of duodenocytes and on macrophages, and causes the ferroportin to be internalized and inactive, with ↓ exit of iron from
    - Enterocyte
    - Macrophage
  - ↑ ferroportin in BLM causes ↑ Fe transfer out of enterocyte, and overall ↑ iron absorption
  - ↑ HJV - ↓ hepcidin - ↑ iron absorption
  - ↑ hepcidin - ↑ ferroportin internalization - ↓ Fe transport across enterocyte BM

❖ Sensing Body Iron Stores (BIS)

- Hepatic iron sensing
  - Hepcidin (HFE protein, ↑hepcidin → ↓FP1 in BLM → ↓IA)
  - Hemojuvelin (↑HJV → ↓hepcidin → ↑IA
  - Transferrin receptor 2 (TFR2)
- Enterocyte Iron Sensing
  - BMP6 (bone morphogenetic protein) binds to its receptors on the hepatocyte → SMAD protein-dependent activation of hepatocyte expression
    - BMPR1/2, and
    - HJV (cofactor)

- Hepcidin Controls Body Iron Stores by Modifying Absorption

↑ HFE	○ ↑ Fe intake ↑BIS / ↑TS,	→ ↑TS → hepcidin binding on TFR1 → ↑hepcidin binding on TFRs → ↓ ferroportin (FP) in BLM → ↓IA corrects ↑BIS
	○ ↑IL6 (inflammation) Hypoxia	→ ↑hepcidin → ↓FP in BLM → ↓transfer of Fe^{2+} into body (↓IA/↓FP) → ↓iron exit from macrophages/ ↑macrophage Fe → corrects ↑ BIS
↓ HFE	○ ↓ Fe intake (diet) ○ ↓ IL-6 ○ ↑ hypoxia	→ ↓hepcidin → ↑ferroportin in BLM → ↑ Fe^{2+} transfer of Fe^{2+} into body → ↑iron exit from macrophages /↓ macrophage iron → ↓ BIS

↑BIS → ↑hepcidin (HFE) bound to TFR2 → ↓FP / ↓DMT1 → ↓IA → corrects the ↑BIS → ↓Fe exit from macrophage (↑macrophage Fe)

❖ Hepcidin

- Iron regulatory protein which
  - Displaces ferroprotein from enterocyte basolateral membrane → ↓ iron absorption (IA)
  - Restores iron in macrophages
- Secreted by hepatocytes in proportion to body iron stores (BIS)
  - ↓ BIS → ↓ hepcidin → ↑ IA
- Determination of hepcidin concentration
  - ↑
    - ↑ BIS (body iron stores)
      - Iron binds
        - BMP6 (bone morphogenetic protein 6) on hepatocyte receptors → ↑ activity of SMAD protein-dependent activation of hepcidin
        - ↓ BMP6 → ↓ hepcidin
        - Signaling between hepcidin and BMPs modified by BMP type / receptor Alk3

        - Inflammation
            - ↓Proinflammatory IL-6 → ↑ STAT3 → ↑ hepcidin
            - Reactive oxygen species (ROS) → CODAT/enhancer-binding protein α-mediated mechanism
        - Gene
            - Encodes 343 amino acid protein
            - Signal peptide
            - Extracellular domain
            - Cytoplasmic (intracellular) trial
    - ↓
        - Iron deficiency
        - Hypoxia
        - ↑ erythropoiesis
        - Iron regulatory proteins (HFE, HJV, TFR2)
- Regulation of secretion of hepcidin
    - HFG (gene on chromosome 6)
    - HJV (hemojuvelin)
    - TFR2 (transferrin receptor 2)

    } Part of iron sensing process

➢ Changes in Iron Binding, Sensing and Transport Proteins

- Hepcidin
    - ↓ iron "release" from enterocytes (↓ transport of Fe across the enterocyte BLM; ↓IA),
    - ↓ iron release from macrophages (↑ macrophage iron)
- The ↓ functional hepcidin in HH causes ↑ iron release from macrophages
    - ↑FP in BLM → ↑IA → ↑BIS
    - ↑/↓ Fe in macrophages release of iron from macrophages

- Iron Deficiency, Low Body Iron Stores (BIS)
    - ↓ BIS → ↓HFE → ↑FP / ↑DMT1 → ↑IA until the ↓ BIS have been restored to normal.

- Hereditary Hemochromatosis
    - Genetic defect in HFE (abnormal HFE, C282Y, or H63D) → loss of appropriate sensing of ↑ body iron stores (BIS)
        - The mutation in HFE provides abnormal "sensing" of the body iron stores the intestinal crypts "sense" that the body iron stores (BIS) are low, despite these BIS being high in HH.
    - Loss of control of hepcidin, ferroportin, and loss of control of body iron stores (BIS)
    - Normally, ↑BIS → ↑HFE → ↓IA
    - The sensing of "↓ BIS" leads to ↓ (normal) hepcidin, ↑FP / ↑DM1 → ↑IA

❖ HFE protein

- Extracellular domain
  - Loops α1, α2, α3
- Associates with a B2-microglobulin
- HFG gene mutations in HH
  - α3 loop cysteine replaced by tyrosine at AA 282 (mutant protein → loss if α3-disulphide bond
    ↓
  - Abnormal interaction of HFE protein to B2-microglubulin
    ↓
  - ↓ mutant HFE at surface of cell
  - ↑ retention in endoplasmic reticulum
  - ↑ degradation

Simple Concept

- The loss of normal HFE in HH results in "…inappropriately low hepcidin expression relative to body iron stores".

Baron BR and Fleming RE. Sleisenger and Fordtran's Gastrointestinal and Liver Disease-Pathophysiology, Diagnosis, Management. 11th Edition, 2020, Chapter 75, pages 1172-88.

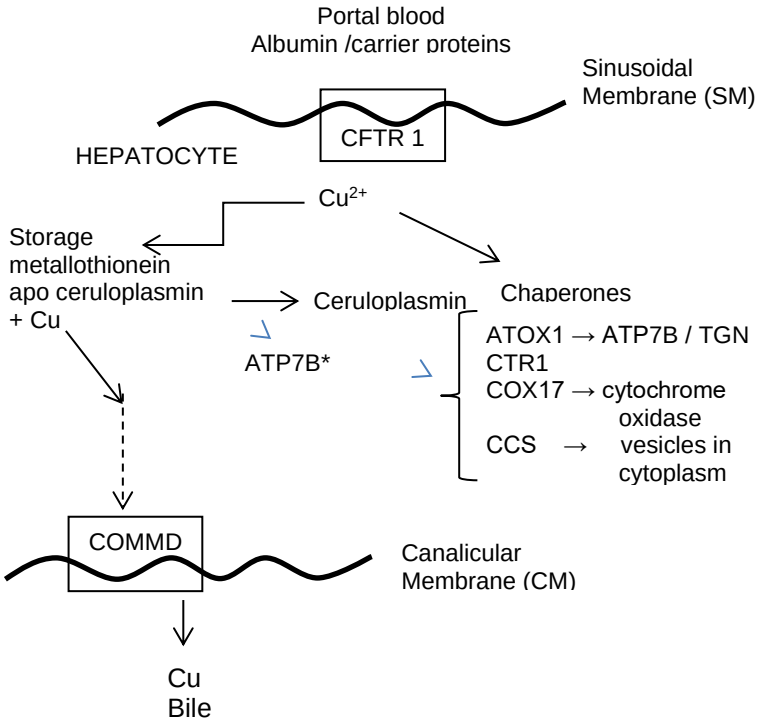
➢ Changes in Iron Binding, Sensing and Transport Proteins

- As BIS increase → ↑ BMP binding to hepatocyte receptors → ↑ SMAD protein-dependent increased expression of hepcidin → ↑ inactive ferroportin → ↓ iron absorption
- Mutations of HFE (HH), HJV, hepcidin, TFR2, ↑ ROS, ↑ IL-6, HFE – TFR2 complex → ↓ expression of functionally normal hepcidin → body behaves as if there is ↓hepcidin → ↑ active ferroportin (and ↑ DMT1) → ↑ Fe absorption → ↑ BIS (body iron stores).
- In HH, the mutation in HFE provides abnormal "sensing" of the body iron stores the intestinal crypts "sense" that the body iron stores (BIS) are low, despite these BIS actually being high in HH.
- The sensing of ↓ BIS leads to ↓ hepcidin, ↑ active ferroportin, and ↑ iron absorption
- The ↑ iron absorption continues, unresponsive to the ↑ BIS because of the mutation of HFE

WILSON DISEASE (WD)

- Definition
  - WD is an autosomal recessive condition caused by a mutation in the ATP1B WD gene on chromosome 13.
    - This results in reduced secretion of copper from the liver into the bile, and accumulation of excessive copper in numerous tissues such as CNS, eye, liver, red blood cells, kidney.

- Pathophysiology



  - Copper (Cu) from albumin and other carriers in blood is taken up into the hepatocyte by the copper transporter CTR1 in the hepatocyte sinusoidal membrane.
  - Copper (Cu) enters the liver and binds to Cu chaperones CTR1, COX17, CCS, and ATOX1.
  - These 3 chaperones target the Cu to 3 different proteins
    - ATOX1 → ATP7B → trans-Golgi network (TGN) → vesicles → COMMD transporter in canalicular membrane (CM)
    - COX17 → SCO1
    - CCS → mitochondrial membrane
    - Cu / Zn superoxide dismutase (SOD)
    - Cytochrome oxidase
  - Copper in the liver binds to apoceruloplasmin, forming ceruloplasmin (α2-glycoprotein).

- Sinusoidal membrane copper (Cu) transport receptor (CTR)
- Cytoplasmic Cu binding "metallochaperone" transport other Cu binding protein targets
- Copper chaperone for superoxide dismutase (CCS)
- Cytochrome C oxidase 17 (COX17) and synthesis of cytochrome C oxidase (SCD1) → Cu transported to mitochondrial membrane.
- Antioxidant 1 copper chaperone (ATOX1) delivers Cu to ATP in the trans-Golgi network (TGN).
  - Cu-OTP continuing vesicles traffic to hepatocyte canalicular membrane → hepatic canalicular space / bile
  - Other Cu binding proteins are in the cytoplasm, such as COMMD1
- In WD, the ATP is matched to AT7B (Wilson ATPase) with 6 metal binding domain
  - ↓ exit of Cu binding protein, ceruloplasmin
  - The intracytoplasmic Cu-binding protein COMMD1 is included in the trafficking of ATPB-Cu vesicles, and may be dysfunctional in WD and modify the trafficking/movement of ATP7B vesicles across the CM of the hepatocyte → further ↑ Cu retention

Adapted from: Roberts EA, Sleisenger and Fordtran's Gastrointestinal and Liver Disease – Pathophysiology, Diagnosis, Management, 11th Edition, 2020, Chapter 76, pages 1180-8.

- ATP7B is the Wilson ATPase which is mutated in Wilson disease, leading to
  - ↓ incorporation of copper (Cu) into apoceruloplasmin (apoceruloplasmin + Cu → ceruloplasmin), and
  - ↑ copper tissues such as the liver because of
  - ↓ trafficking of Cu-ATP7B from TGN to COMMD, and across CM
- Under basal conditions, the Wilson ATPase is located in the trans-Golgi network (TGN), where it receives Cu from the Cu chaperone ATOX1.
- At low Cu concentrations, the Wilson ATPase participates in the mechanism for incorporating Cu into apo-ceruloplasmin to generate holo-ceruloplasmin (blue collar plus Cu).
- High copper concentrations in the Wilson ATPase lead to reduced biliary excretion of Cu.
- Cu transfer to the transmembrane domain is accompanied by ATP hydrolysis and formation of transiently phosphorylated intermediates of the Wilson ATPase ('phosphorylation').

- Structural phenotypic defects include
  - Absence of any intact Wilson ATPase
  - Misfolding of Wilson ATPase leading to its retention in the endoplasmic reticulum
  - Failure to bind to ATOX1 (not shown)
  - Ineffective interaction with other proteins, which directs the intracellular movement of the Wilson ATPase.

- Functional phenotypic defects include
  - Abnormal phosphorylation or copper transfer
  - Disruption of intracellular copper trafficking.
- Either type of phenotypic defect can result in copper accumulation and toxicity in hepatocytes.

Abbreviations: BC, bile canaliculus; Mt, metallothionein; RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum; TGN, trans-Golgi network.

➢ Routine tests for diagnosis of Wilson disease.

Test	Typical finding	False negative*	False positive*
○ Serum ceruloplasmin	↓ by 50% of lower normal value	− Normal levels in patients with marked hepatic inflammation − Overestimation by immunologic assay − Pregnancy, estrogen therapy	− ↓ levels in: ▪ Malabsorption ▪ Aceruloplasminemia ▪ Heterozygotes
○ 24-hour urinary copper	> 1.6 µmol / 24 h > 0.64 µmol / 24 h in children	− Normal ▪ Incorrect collection ▪ Children without liver disease	▪ ↑ hepatocellular necrosis ▪ ↑ cholestasis ▪ ↑ contamination
○ Serum “free” copper	> 1.6 µmol / L	▪ Normal if ceruloplasmin overestimated by immunologic assay	
○ Hepatic copper	> 4 µmol/g dry weight	− Due to regional variation ▪ In patients with active liver disease ▪ In patients with regenerative nodules	− Cholestatic syndromes
○ Kayser-Fleischer rings by slit lamp examination	Present	− Absent ▪ In up to 50% of patients with hepatic Wilson ▪ In most asymptomatic siblings	− Primary biliary cholangitis (PBC)

Printed with permission: European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-85 (Table 4).

➢ Treatment

➢ Clinical Alert in Treatment of WD: Stopping Rules – "the don'ts"

- Do **not** suddenly stop chelating treatment in patients with WD
- Suddenly stopping chelating therapy may
  - ↑ neurological defects
  - ↑ risk of fulminant hepatic failure
  - ↑ risk of being refractory to treatment when Cu-chelating therapy is reintroduced
- Important to appreciate that it takes ~ 6 mon for D-penicillamine and trientine to improve neurological symptoms and liver enzymes in WD.
  - Implication: Therapy is may be considered to be unsuccessful therapy incorrectly and prematurely stopped.

- Choices
  - Mobilization of excess body Cu
    - D-penicillamine
    - Trientine
    - Ammonium tetrathiomolybdate
  - Maintenance of normal body Cu

➢ Adverse effects of therapy of Wilson disease (WD).

- **D-penicillamine**
  - CNS
    - ↑ neurological symptoms
  - Hypersensitivity reaction
    - Fever
    - Rash
    - Lymphadenopathy
    - Neutropenia
    - Thrombocytopenia
  - Endocrine
    - Hypothyroid
  - Skin lesions
    - Pemphigoid lesions
    - Lichen planus
  - Hematology
    - ↓ RBC
    - ↓ WBC
    - ↓ platelets
    - Lymphadenopathy
  - MSK
    - Lupus-like syndrome
    - Arthralgias
  - Lung
    - Goodpasture syndrome
  - Kidney
    - Proteinuria

- Pregnancy
  - − Teratogenic
  - − Iron deficiency
  - − Suppression of bone marrow

- **Trientine**
  - Gastritis
  - Iron deficiency
  - Bone marrow suppression

- **Ammonium tetrathiomolybdate**
  - Suppression of bone marrow
  - Hepatotoxicity

ALPHA-1 ANTITRYPSIN DEFICIENCY

➢ Molecular physiology/pathophysiology

- Alpha 1 antitrypsin (α1-AT) → ↑ serum protease degradation
- Neutrophil elastase is a protease in the lung which is normally inhibited by α1-AT, to prevent extracellular matric degradation by neutrophil elastase in the lungs.
- Long loss of function which α1-AT is reduced in the serum, there is less inhibition of neutrophil elastase, and ↑ degradation of matric of lung → emphysema / intestinal lung disease / pulmonary inflammation.
- Gain function
  - In health, α1-AT is produced in the hepatocyte endoplasmic reticulum (ER) and is secreted by the Golgi apparatus.
  - With α1-AT deficiency, and ↑ mutant of α1-AT-Z, protein becomes dysfunctional with
    - Misfolding
    - Polymerization

    } Retention of α1-AT-Z protein in Golgi → gain in function
  - Misfolding of the protein-cases breakdown by the endoplasmic reticulum (ER), a process called ER (ER-associated degradation), using
    - Ubiquitin-proteosome
    - Calnexin
  - Abnormal protein incorporated into autophagosomes → lysosomal breakdown
  - ↑ apoptosis

SO YOU WANT TO BE A GASTROENTEROLOGIST!

- Give factors which may increase the liver damage in the patient with α1-AT deficiency.
  - Inflammation → IL-1 / IL-18
  - HFE variant H63A

VASCULAR DISEASES

- **Portal Hypertension** (PHT)

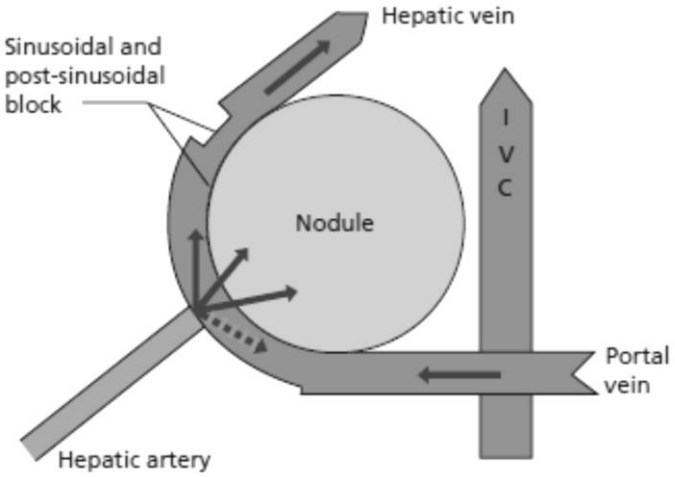
➢ Definition:

- Hepatic sinusoidal pressure ≥ 6 mm Hg

➢ Background

- Blood supply to the liver is dual
  - 70% portal vein (PV) blood (from mesenteric circulation)
  - 30% hepatic artery (HA) from celiac artery (systemic circulation)
- With the dual blood supply to the liver, when blood flow increases in the PV, it decreases in the HA, and vice versa, through an autoregulatory mechanism
  - Thus, we are dealing with three distinct vascular beds
    - Intrahepatic
    - Splanchnic
    - Systemic
- After a meal, portal blood flow increases, with no ↑ portal pressure, because the hepatic sinusoids have
  - High compliance/accommodation
  - Low resistance

THE CIRCULATION OF HEPATIC CIRRHOSIS



The dotted line (- - -) in the figure above represents possible retrograde flow in the PV

- A nodule obstructs the sinusoids and HV, causing ↑ HV pressure
- The nodule is suppled mainly by the HA

Abbreviation: HA, hepatic artery; HV, hepatic vein; PBC, primary biliary cirrhosis; PV, portal vein; S, sinusoids

Adapted from: Sherlock and Dooley, 11th Edition, 2020, pages 168-70.

➢ Pathophysiology

- Systemic and splanchnic / hyperdynamic circulation
  - Ohm's law

    $\Delta P = FxR$

  F, flow; ΔP, change in pressure; R, resistance

- ↑ portal flow (F)
  - ↑ flow hyperdynamic circulatory state
  - ↑ collaterals (↑ angiogenesis)
  - ↓ fenestration
  - ↑ intrahepatic vasoconstriction, and ↓ response to vasodilation
  - ↑ systemic sympathetic activity
  - Splanchnic endothelial cells from ↑ sheer stress, ↑ → cytokines, and ↑ phosphorylation of eNOS → vasodilation in splanchnic and systemic vascular beds (note below that there is ↓ intrahepatic NO, ↓ intrahepatic vasodilation, ↑ intrahepatic vasoconstriction)
- ↑ portal resistance (R)
  - Mechanical factors
  - Regenerative nodules
  - Fibrotic bands
  - Defenestration and capillarization of sinusoids
  - Swelling of hepatocytes and Kupffer cells

- Hepatic vasoconstriction and ↑ increased intrahepatic resistance
  - Law of Poiseuille $R = 8 \eta L / \P r^4$
  - Resistance (R) is affected by the length and radius (r) of the vessel, and by the viscosity of the blood
  - ↑ sheer stress on sinusoids
    - ↑ eNOS → ↑ NO (nitric oxide) → ↑ intrahepatic vasodilation
    - ↑ ET-1 (endothelin-1) → binds to
      - ET-A receptors on HSC → ↑ HSC contraction → intrahepatic vasoconstriction
      - ET-1 also binds to ET-B receptors on endothelial cells → activates eNOS → vasodilation
  - Sympathetic overactivity (norepinephrine) in cirrhosis will also act as an intrahepatic vasoconstrictor, as also will
    - Angiotensin
    - Leukotrienes
    - Thromboxane
  - In cirrhosis, there is ↓ production of NO
    - ↓ activation of eNOS protein in endothelial cells
    - ↑ caveolin-1 (an eNOS inhibiting protein)
    - ↓ AKT (protein kinase B)
    - Phosphorylation of eNOS
    - ↑ GRK (G protein-coupled receptor kinase, which inhibits eNOS)
    - ↑ VEGF (vascular endothelial growth factor) from shear stress may ↑ eNOS (VEGF is a NO stimulatory growth factor)

- The vasodilation in splanchnic and systemic (peripheral) vascular beds leads to
  - ↑ cardiac output
  - ↓ mean arterial pressure
  - ↑ systemic blood flowing into splanchnic circulation
- The overall effect is ↓ intrahepatic NO and ↓ intrahepatic vasodilation (effect on endothelial cells as well as possibly on HSCs)
- ↓ intrahepatic vasodilation results in ↑ intrahepatic vasoconstriction
- ↑ intrahepatic vasoconstriction leads to ↑↑ intrahepatic resistance (law of Poiseuille)
- Giving NO in cirrhosis will restore the intrahepatic vasodilation arising from the endothelial cells, but
  - The HSC in cirrhosis contribute to the vasoconstriction and are less responsive to NO.
- In cirrhosis, benefit of restoring ↓ NO levels do not fully restore the vessel diameter to normal
- In cirrhosis, there is ↑ intestinal endotoxin (LPS) → ↑ TGF-β, ↑ ET-1, with binding to ET-A receptors on HSC, and intrahepatic vasoconstriction

➢ Classification

- The different sites of increased resistance to portal flow (posthepatic, intrahepatic, and prehepatic) and associated diseases are shown.
- Many diseases have a mixed pattern.

- Prehepatic
  - Portal vein (PV) thrombosis
  - Splenic vein (SV) thrombosis
  - Wedge hepatic vein pressure (WHVP) may be high in patients with “presinusoidal” causes, especially as the disease progresses, indicating sinusoidal and/or collateral involvement
  - Some “post sinusoidal” conditions may also have sinusoidal component

- Intrahepatic
  - Pre-sinusoidal (non-cirrhotic)
    - Idiopathic
      - Idiopathic portal hypertension
    - Inherited
      - Congenital hepatic fibrosis
    - Infection
      - Schistosomiasis

        - Immune
            - Primary biliary cholangitis (PBC)
            - Sarcoidosis
            - Chronic active hepatitis
        - Iatrogenic / drugs
            - Toxins: vinyl chloride arsenic
    - Sinusoidal
        - Alcoholic hepatitis/cirrhosis
        - Cryptogenic cirrhosis
        - Post-necrotic cirrhosis
    - Post-sinusoidal
        - Central hyaline sclerosis (alcoholic liver disease)
        - Sinusoidal obstruction syndrome (SOS)
        - Veno-occlusive disease

- Post hepatic
    - Budd-Chiari syndrome
    - Constrictive pericarditis
    - Inferior vena cava (IVC) obstruction
    - Right-sided heart failure
        - Webs
        - Tumour
        - Invasion
        - Thrombosis
    - Severe tricuspid regurgitation

➢ Treatment

- Mechanism(s) of action of drugs used to treat portal hypertension (PHT).
    - Drugs used for treatment of PHT generally are selected to act to
        - ↓ portal blood flow, or
        - ↓ intrahepatic resistance

- ↓ Portal Blood Flow → ↓ PP (Portal Pressure)
  - Octreotide
    - ↓ glucagon
      - ↑ splanchnic vasoconstriction
      - ↓ portal and azygous blood flow
      - ↓ postprandial splanchnic blood blow
    - ↓ GT-1-dependent contraction of HSC (hepatic stellate cells)
  - β-adrenergic blocking agents (non-selective)
    - ↓ cardiac output (CO)
    - Vasodilation of mesenteric circulation
    - ↑ "unopposed action of α1-adrenergic receptors
      - ↓ portal flow
      - ↓ intrahepatic resistance
  - Vasopressin
    - Splanchnic vasoconstriction
    - ↓ PV (portal vein) inflow
    - ↓ CO (inotropic)
    - ↓ HR (chronotropic)

- ↓ Intrahepatic Resistance
  - Nitrates
    - Venodilation from ↓ Ca_i^{2+} in smooth muscle in venous wall
  - α1-adrenergic antagonists
  - ARBs (angiotensin II receptor type I blockers)

Therapeutic Gem

- Give what must be excluded in the patient with Budd-Chiari Syndrome (BCS) before considering liver transplantation.
  - Exclude associated malignancy, causing a procoagulative state → HV thrombosis → BCS

Budd-Chiari Syndrome (BCS)

- Treatment options and indications for the use different modalities in the patient withBudd-Chiari Syndrome (BCS), and also their advantages and disadvantages

Treatment	Indication	Advantages	Disadvantages
○ Thrombolytic therapy	– Acute thrombosis	▪ Reverses hepatic necrosis	Risk of bleedingLimited success
○ Angioplasty +/- stenting	– IVC webs IVC stenosis – Focal hepatic vein stenosis	▪ No long-term sequelae ▪ Averts need for surgery	↑ rate of restenosis / shunt occlusion
○ TIPS	– Possible bridge totrans-plantation infulminant BCS – Acute BCS (HE)	▪ Low mortality ▪ Useful even with compression of IVC bycaudate lobe	↑ rate of shunt stenosis Extended stents may interfere with liver transplantation
○ Surgical shunt	– Subacute BCS if portacaval pressure gradient <10 mm Hg or occluded IVC	▪ Definitive procedure for many patients ▪ Low rate of shunt dysfunction with portacaval shunt	Risk of procedure-related death Limited applicability
○ Liver transplantation	– Subacute BCS – Portacaval pressure gradient >10 mmHg – Fulminant BCS Presence of cirrhosis – Failure of portosystemic shunt	▪ Reverses liver disease ▪ May reverse underlying thrombophilia	Risk of procedure related death Need for long-term immunosuppression

Abbreviations: HE, hepatic encephalopathy; IVC, inferior vena cava; TIPS, transjugular intrahepatic portosystemic shunt

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HEPATIC ENCEPHALOPATHY (HE)

➢ Pathophysiology

- Small and large intestine
  - Dietary amino acids and urease-positive bacteria → glutamine → glutamate + NH_3
  - Uptake of glutamine

glutaminase (deamination) Glutamine → glutamate + NH_3 ← glutamine synthetase (amination)

  - In patients with liver disease
    - Lumen ↑ urease-producing bacteria in GI tract
    - BBM ↑ intestinal glutaminase

    } ↑ NH_3, ↑ glutamate
  - ↑ production of ammonia by urease-producing bacteria in GI tract
  - ↑ production of ammonia and glutamate from increased action of intestinal glutaminase

- Liver
  - Portosystemic shunting, by-passing portovenous system with less hepatic detoxification of ammonia via the urea cycle
  - NH_3 → urea, periportal hepatocytes → glutamine, perivenous hepatocytes
  - In presence of hyponatremia (↓Na^+_s), myoinositol falls, with less compensation for ↑ intracellular glutamine

- Skeletal muscle
  - Normally responsible for uptake of 50% of NH_3 and metabolism by urea cycle containing enzyme in hepatocytes
  - Atrophy of skeletal muscles → ↓ muscle glutamine synthetase → ↓ synthesis/utilization of NH_3 → ↑ NH_3

- Kidney
  - ↓ NH_4 excretion ↑↑ NH_3 accumulation in blood
  - ↑ NH_3 production in presence of hypokalemia (↓ K^+_s) especially n presence of hypokalemia and metabolic alkalosis,

    NH_4 → NH_3, which crosses blood brain barrier (BBB)
  - Plasma NH_3 > 150 µmol is associated with brain herniation from brain edema.

- Brain
  - In health,

    NH_3 + glutamate $\xrightarrow{\text{glutamine synthase in astrocytes}}$ glutamine
  - In patients with cirrhosis
    - ↓ glutamine synthase / ↓ brain glutamine / ↑ glutamate + NH_3 → ↑ BBB permeability plus ↑ brain blood flow → brain / astrocyte mitochondrial damage / edema → ↑ NH_3 uptake into cerebellum and basal ganglia
    - ↑ brain edema → ↑ swelling of astrocytes → ↑ activity of GABA-benzodiazepine system, including peripheral type benzodiazepine receptors (PTBR)
  - ↓ glutamate uptake by synaptic excitatory amino acid transporters → ↑extracellular brain levels of glutamate, ↓ glutamatergic neurotransmitter system.
  - ↑ N-methyl-D-aspartate-nitric oxide-C-guanylate cyclase (NMDA-NO-C6MP) signal transduction pathway → ↓ memory, learning and sleep.

➢ Treatment

❖ Precipitants

- ↑ ammonia production - ↑ protein intake, constipation, GI bleed (20%), azotemia (30%), hypokalemia (↓ K^+_s) →
- ↑ protein catabolism - surgery, diuretics, arterial hypotension/hypovolemia,
- Malnutrition - skeletal muscle wasting, → ↓ muscle metabolism of NH_3
- ↑ diffusion across BBB – alkalosis
- Synergistic effects of cytokines – infection (SBP) (10%)
- Altered brain function
  - Analgesics/alcohol
  - Astrocyte swelling
  - Benzodiazepines;
  - Hyponatremia
  - Psychotropics
  - Sedative drugs
- Dehydration – fluid restriction, diuretics, excessive paracentesis, vomiting, diarrhea (mechanism unknown)
- Hypoxia, anemia, fever, sepsis
- Metabolic – K^+↓ (50%), ↑ blood sugar (BS), alkalosis; ↓ hypoxemia, dehydration
- Drugs (30%) - benzodiazepines, analgesics, interferon, alcohol, NSAIDs, acetaminophen
- Surgical shunting, anesthetic, TIPS
- Liver decompensation, HCC, PVT
- Surgery, including liver transplant (LT)

❖ Pharmacology

- Lactulose
  - Lactulose (beta-galactosidofructose)
    - Enters colon, broken down by colonic bacteria to lactic acid and short chain fatty acids, withacidification of stool pH < 5
      - At acidic pH short chain fatty acids provide the H+ convert NH_3 to NH_4
      - NH_4 is trapped and is lost in the stool

$$NH_3 \xrightarrow{pH < 5} NH_4^+ \text{ (non-absorbable)}$$

    - Use lactulose 30 mL po every 1-2 h until bowel evacuation, then adjust to a dosage that will result in 2-3 formed bowel movements per day (usually 15-30 mL po b.i.d.)
    - Lactulose can be discontinued
      - Once the precipitating factor has resolved, and
      - Once the HE resolves
    - Give lactulose enemas (300 mL in 1L of water) in patients who are unable to take lactulose po

- Hyperosmolar purgation (including lactulose)
  - ↑ stool volume
  - ↑ loss of nitrogen compounds

- Acarbose
  - α-glucosidase inhibitor → ↓ proteolytic urea-producing luminal microbiotica → ↓ NH_3

- Antibiotics (pre-, pro- and synbiotics)
  - ↑ lactobacillus spp., ↓ urease-containing bacteria → ↓ NH_3 production
  - ↑ bacterial NH_3 utilization
  - ↓ pro-inflammatory response
  - ↓ gut permeability
  - ↓ bacterial translocation of proinflammatory antigens

SO YOU WANT TO BE A HEPATOLOGIST!

A patient with cirrhosis develops HE (hepatic encephalopathy), is treated with antibiotics, and their MELD score rises.

- Give the explanation for this deterioration in HE with antibiotics.
  - The antibiotic given for HE reduces the intestinal microbiotica
  - This ↓ microbiotica → ↓ bacterial synthesis of vitamin K
  - With ↓ bacterial vitamin K available for absorption and ↓ production of coagulation factors (II, VII, IX, X, protein C), the INR rises
  - ↑ INR contributes points to ↑ MELD score (which does not reflect worsening liver dysfunction and ↑ induction for LTx

  - Note: osmotic agents (e.g., lactulose) and antibiotics (metronidazole, neomycin, rifaximin) improve symptoms, but do **not** change mortality rate in HE

- L-ornithine-L-aspartate (LOLA)
  - Activates the urea cycle → ↑ NH_3 clearance
    - Improves grade 3 or 4 HE in ~ 25% of patients

- Neurotransmitters
  - Bromocriptine
  - Flumazenil (a competitive GABA-benzodiazepine receptor antagonist)

❖ Nutrition
  - Treat malnutrition, including using enteral nutrition (EN), or total parental nutrition (TPN), as indicated
  - Treat associated zinc deficiency
  - Give branched chain amino acids (BCAA)
  - Short term (< 72 h) protein restriction may be considered in severe HE, but is not used for long-term, nor for mild to moderate HE
  - No long-term protein restriction (to maintain muscle mass to provide source of tissue containing enzymes for the urea cycle, and utilization of NH_3 to form urea)

- Intracranial pressure (ICP) monitoring
  - 45˚ elevation of head of bed
  - Jugular venous oximetry
  - Transcranial Doppler measurement
  - Moderate hypothermia to
    - ↓ cerebral blood flow (CBF) / ↓ intracerebral pressure (ICP)
    - ↓ arterial NH_3
    - ↓ cerebral NH_3 uptake
  - IV mannitol
  - Hyperventilation
    - Vasoconstriction → ↓ CBF
  - Manage circulatory effects
  - Fluid management, consider central venous pressure (CVP) monitoring
  - Manage lactic acidosis and sepsis
  - Perform short synacthen test, and give glucocorticosteroids if adrenal insufficient
  - Inotropes: terlipressin (a vasopressin analog) or norepinephrine
  - Albumin infusion

- Extracorporeal liver assist devices (ELADs)
  - Molecular absorbent recirculating system (MARS)
    - Provides counter-current hemodialysis against albumin and bicarbonate circuits
  - SPAD (single-pass albumin dialysis)
    - Counter-current albumin dialysis against high blood flow in a fiber hemodiafilter, and
    - Continuous veno-venous hemofiltration
  - Prometheus R system
    - Direct albumin adsorption through a specific polysulfone filter
  - Enteral feeding / Total parenteral nutrition (TPN)

- Orthoptic liver transplantation (LTx)
  - Removes shunted (non-detoxified) blood
  - ↓ production of potentially toxic SCFA (propionate, butyrate, valerate)

- Sedation (e.g., for EGD and EVL)
  - Propofol safe in patients with cirrhosis who have no change in pre-endoscopy cognition
  - Midazolam or fentanyl worsens HE
    - ↑ NCT (number connecting time), i.e., ↑ severity of HE score
    - ↑ agitation
      - Titrate sedation only to point where patient's speech is slurred.

ASCITES

- Demography
  - ~20% of persons with cirrhosis develop ascites (ascites is often first feature of decompensation)
  - 42 randomized clinical trials of 2870 persons with treated ascites were analysed to compare the outcomes with different therapeutic modalities.
  - The difference of paracentesis plus fluid replacement (PFR) in persons with decompensated cirrhosis (but without other features of decompensation) was enhanced with addition of
    - Transjugular intrahepatic portosystemic shunt (TIPS): RR 9.44; 95%CI: 1.93 to 62.68
    - Aldosterone RR 30.63; 95%CI: 5.06 to 692.98
    - These additions to PFR are likely not of benefit on mortality rate (MR), need for liver transplantation (LT) or frequency of adverse event s (AEs), 1/3 of patients given PFR for their ascites died with 11 mon
  - Adding aldosterone plus loop diuretics to PFR resulted in ↑ complications (RR 2.07; 95%CI: 1.37 to 3.10; very low certainty evidence)
    - Hepatic encephalopathy (HE)
    - Hepatorenal syndrome (HRS)
    - Variceal bleeding (VB) (esophageal variceal hemorrhage [EVH])
  - There is uncertainty about whether interventions for ascites in people with decompensated liver cirrhosis decrease
    - Mortality
    - Adverse events
    - Liver transplantation compared to paracentesis plus fluid replacement in people with decompensated liver cirrhosis and ascites.
  - Transjugular intrahepatic portosystemic shunt (TIPS) and adding aldosterone antagonists to paracentesis plus fluid replacement may ↑ resolution of ascites compared to paracentesis plus fluid replacement alone.
    - Aldosterone antagonists plus loop diuretics may ↑ decompensation rate compared to paracentesis plus fluid replacement.

- Causes/association
  - Usually, first decompensation event in patients with cirrhosis
  - Development of ascites associated with reduction in 5-yr survival from 80% to 50%.
  - The ↑ mortality is due to

	Treatment
− Renal sodium retention	▪ Diuretics
− Arterial underfilling	▪ Albumin infusion
− Portal hypertension	▪ Portal decompressive procedures

- Diagnostic paracentesis (DP) should be performed in all patients with new-onset ascites that is accessible for sampling
  - Some authorities also suggest DP on every hospitalization, or clinical visit where new decompensation is suspected.
- The initial laboratory investigation of ascitic fluid should include ascitic fluid neutrophil count, ascitic fluid total protein, ascitic fluid albumin, and serum albumin to calculate the serum albumin ascites gradient (SAAG).
  - Exclude malignancy, heart failure, TB, and pancreatic disease (please see table below)

Medical History	Physical Exam	Investigations
○ Risk factors for chronic liver disease − Alcohol − Autoimmune disorder − Family history of liver − Heart disease − Hematologic disorder (thrombosis, excessive bleeding) − Malignancy − Metabolic − Pancreatitis − TB risk factors − Thyroid disease − Travel history − Viral hepatitis,	− Shifting dullness* − Abdominal masses/tenderness/ guarding − Hernias − Hepatic hydrothorax − Stigmata − Heart failure signs (JVD) − Malnutrition − Thyroid disease signs − Malignancy or infection signs	▪ U/S with doppler ▪ CBC, LFTs, Cr_s, Lytes ▪ Ascitic fluid analysis ▪ SAAG >11 g/L = portal HTN ▪ Total protein >25 g/L, cardiac source of ascites

* Even using the “JAMA recommendations for physical examination for ascites, and with no experienced clinician doing a focused examination, at least 1 L of fluid must be present to detect by physical examination.

- Grading severity (see table below)

According to amount	According to Tx response
− Grade 1 mild = only detected by US No treatment recommended	▪ Responsive: becomes grade 1 ascites with diuretics +/- sodium restriction
− Grade 2 moderate = moderate symmetric distension of abdomen	▪ Recurrent: recurs 3 times in 12 mon despite diuretics + sodium restriction
− Grade 3 large = marked distension	▪ Refractory: cannot be prevented by medical therapy or treatment limited by side effects

➢ Treatment

Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis (Benmassaoud A, et al. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD013123. DOI: 10.1002/14651858.CD013123.pub2)

- Diet
  - Moderate sodium restriction (2 g or 90 mmol/day) and diuretics (spironolactone with or without furosemide) are the first-line treatment in patients with cirrhosis and grade 2 ascites.
    - Education on food sodium content, avoiding adding salt and guarding against nutritional deficiency (dietician consultation)
  - Fluid restriction is not necessary for ascites management unless there is concomitant moderate or severe hyponatremia (serum sodium 125 mmol/L).

- Diuretics
  - Spironolactone with an initial dose of 100 mg/day up to 400 mg/day
    - Long half-life, and effects may not be seen up to 3 days
    - Eplerenone 50 mg, or Amiloride 10 mg are equivalent
  - Furosemide with an initial dose of 40 mg/day titrated up to max 160 mg/day
    - Initially use spironolactone alone, then combined with furosemide
    - Patients with CKD need more loop diuretic

- Monitoring
  - Daily weight monitoring at the same time of day
  - Safe limits of weight loss= 0.5 kg/day without edema, 1 kg/day with edema
    - More diuresis may cause renal injury due to the peritoneal membrane's inability to re-absorb more than 500 mL ascites per day
  - Urine sodium excretion < 80 mmol/day indicates insufficient diuretic dose
  - Spot urine sodium/potassium ratio > 1 indicates that the patient should lose weight
    - If no weight loss, then suspect dietary non-compliance
  - After ascites is adequately mobilized, attempts should be made to taper the diuretics to the lowest dose necessary to maintain minimal or no ascites to prevent the development of adverse effects.
  - In patients receiving diuretics, body weight and serum creatinine and sodium should be regularly monitored to assess response and to detect the development of adverse effects (see table below).
    - Daily weight monitoring with the same scale and at the same time of day

- Muscle cramps
  - Human albumin solution (20-40 g/week) or baclofen administration (10 mg/day, with a weekly increase of 10 mg/day, up to 30 mg/day) can be considered in cases of severe muscle cramps.

Loop diuretic adverse effects	Aldosterone antagonist adverse effects
− Acute kidney injury (AKI) − Hyponatremia − Hypokalemia − Hepatic encephalopathy − Muscle cramps	− Hyperkalemia − Gynecomastia: may respond to drug switching − Muscle cramps

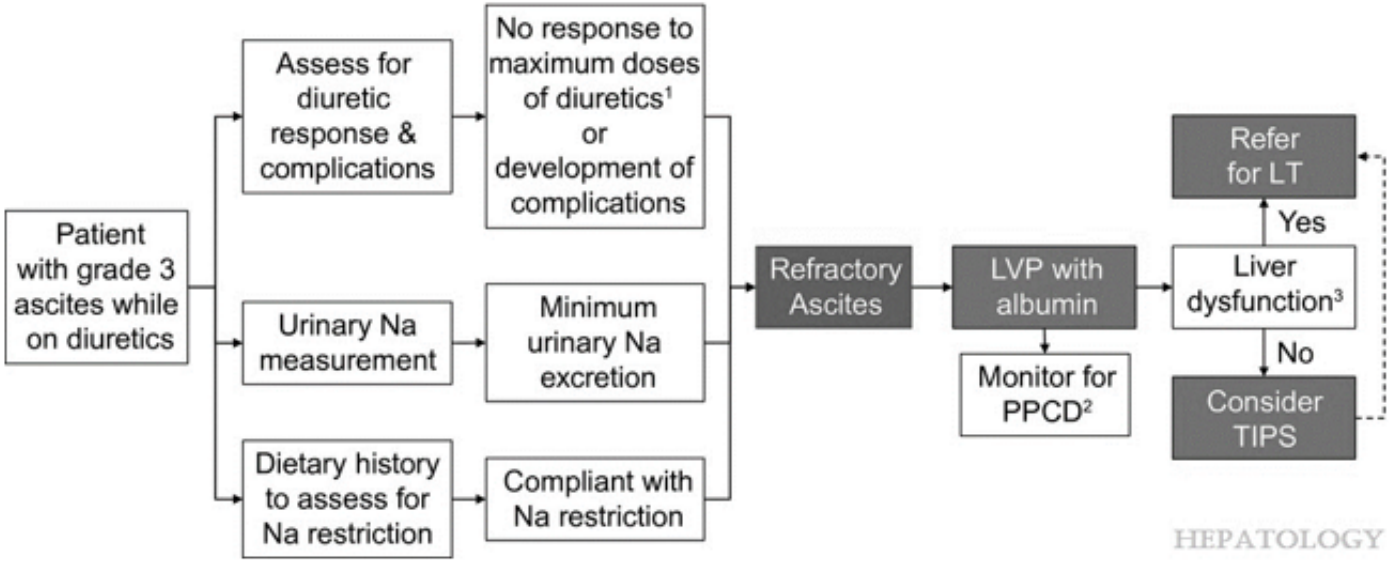
- Large volume paracentesis (LVP)
  - Large volume paracentesis (LVP) is the first-line treatment of grade 3 ascites.
    - After paracentesis, sodium restriction and diuretics should be started.
      - INR > 1.5 and platelet count <50,000 are **not** contraindications
      - Disseminated intravascular coagulopathy (DIC) and thrombocytopenia with uremia are relative contraindications
  - Referral for LT evaluation should be considered in patients with grade 2 or 3 ascites.
  - Nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) should be avoided in patients with cirrhosis and ascites
    - Will further ↓ effective arterial volume (EAV) / ↓ renal perfusion
  - Do **not** use aminoglycosides should be avoided whenever possible in the treatment of bacterial infections.
    - Nephrotoxic
  - For patients with cirrhosis and diuretic-responsive ascites, controversial data suggest potential benefits of long-term infusion of human albumin solution.
    - Two trials showing conflicting effects on survival with chronic albumin
      - At present, **no** recommendation can be made for its use in routine clinical practice

- **Refractory Ascites** (RA)
  - Continued dietary sodium restriction (<2 g/day) is required in patients with RA to reduce the rate of ascites accumulation.
    - Review patient's food diary
    - Discontinue diuretics for refractory ascites to minimize adverse events
  - Fluid restriction is ineffective for the management of RA, but restricting fluid intake to less than 1000 mL/day is recommended for treatment of hyponatremia (e.g., <125 mEq/L).
  - In the management of RA, there are insufficient data to recommend the long-term use of albumin infusions outside the setting of large-volume paracenteses
  - LVP is the first-line treatment for RA.
    - Lower incidence of electrolyte abnormalities, renal dysfunction, and hemodynamic disturbances than diuretics when done repeatedly

- Albumin infusion at the time of LVP of >5 L is recommended to mitigate the risk of post-paracentesis circulatory dysfunction (PPCD).
  - The risk of PPCD may increase with >8 L of fluid evacuated in one single session.
    - PPCD may results in renal impairment (HRS), dilutional hyponatremia, hepatic encephalopathy, and death
    - Consider giving albumin for smaller volume paracentesis in patients with SBP < 90 mmHg, sodium <130 mmol/L, and/or presence of AKI
- The recommended dose of albumin replacement, based on expert opinion, is 6-8 g for every liter of ascites removed.

- **Ascites - Transjugular Intrahepatic Portosystemic Shunt** (TIPS)
  - Careful patient selection is the key to the success of TIPS in the management of RA
    - High MELD score (>18) suggests that the patient is a poor candidate for TIPS
    - Best: younger patients with low MELD scores, receiving smaller diameter covered stent, complete response to TIPS with total elimination of ascites
    - Worst: advanced age, cardiopulmonary insufficiency pulmonary hypertension (PHT) and sarcopenia
  - With correction of PHT: there is gradual suppression of activated neurohormonal vasoconstrictive systems over 4-6 mon
    - Discontinue diuretics after TIPS as they ↓ intravascular volume, and may delay ascites clearance
    - Continue sodium-restricted diet after TIPS
  - A small diameter coated stent of less than 10 mm is preferred to ↓ likelihood of post- TIPS complications, including hepatic encephalopathy
  - If ascites recurs after initial clearance
    - TIPS venogram should be considered, and
    - TIPS revision should be performed if stenosis is identified
      - In these patients, periodic Doppler ultrasound surveillance should be considered.
    - Complications may arise from the insertion procedure, TIPS prosthesis, or presence of a shunt
  - Do **not** use indwelling catheters
    - The average bacterial infection rate is 13%
  - An automatic low flow ascites pump (not available in Canada)
    - This implantable battery powered pump transports ascites from peritoneal cavity to bladder
    - ↓ need for paracentesis, ↑ QoL / nutritional status
  - LT should be considered in patients with RA (please see diagram below)
    - Ascites after LT may take weeks to months to correct
  - Based on currently available data, NSBBs are **not** necessarily contraindicated in patients with RA.
    - However, caution is recommended in patients with hypotension, hyponatremia, or AKI.
    - There is conflicting data between studies on development of AKI and mortality.

➢ Treatment algorithm for management of RA



- All three criteria should be met for diagnosis of RA.
  - Typically, 160 mg furosemide and 400 mg spironolactone used without success
  - Post-paracentesis circulatory dysfunction (PPCD)
  - For example, MELD >18. Abbreviation: LT, liver transplant.

Printed with permission: Biggins SW, et al. Hepatology 2021;74(2):1014-1048 (Figure 3).

➢ Ascites Complications

- Hyponatremia (↓ Na_s^+)
  - Mild hyponatremia (Na_s^+ 126-135 mEq/L) in cirrhosis without symptoms does not require specific management apart from monitoring and water restriction.
    - Acute natremia much less common than chronic ↓ Na_s^+
    - Hypovolemic hyponatremia
      - Discontinue diuretics/laxatives, and provide fluid resuscitation with 5% albumin or Ringer's lactate
    - Euvolemic = treat underlying cause
    - Hypervolemic = fluid restriction, reduction/discontinuation of diuretics/laxatives
    - Give 25% albumin and/or vasopressin receptor antagonists ("vaptans")
  - Water restricted to 1,000 mL/day and cessation of diuretics is recommended in the management moderate hyponatremia (120-125 mEq/L), and
    - A more severe restriction of water intake with albumin infusion is recommended for severe hyponatremia (<120 mEq/L).
    - Greater water restriction is poorly tolerated
  - The use of vasopressin receptor antagonists in cirrhosis can ↑ Na_s^+ during treatment.
    - However, they should be used with caution only for < 30 days
      - Tolvaptan **not** approved for treatment of hyponatremia in Canada
  - The use of hypertonic saline is reserved for
    - Short-term treatment of
      - Symptomatic or
      - Severe hyponatremia, or
    - Those with imminent LT
      - Patients who undergo LT and have ↓ Na_s^+ are at risk of infections, renal failure and ODS (rare)
  - LT should be considered in patients with RA (please see diagram below)
  - When correction of chronic hyponatremia is indicated in patients with cirrhosis, the goal rate of increase of serum (Na_s^+) is 4-6 mEq/L per 24-h period, and not to exceed 8 mEq/L per 24-h period to ameliorate the risk of ODS.
    - ODS more common with advanced liver disease, alcoholism, severe ↓ Na_s^+, malnutrition and prior encephalopathy
  - Severe hyponatremia (<120 mEq/L) at time of LT → ↑ risk of osmotic demyelination syndrome (ODS) with LT.
    - A multidisciplinary coordinated care may ↓ risk of osmotic dysfunction syndrome (ODS).
- In the patient with the triad of “ascites, hyponatremia and renal dysfunction”, give the clinical factors which contribute to the worsening of the renal dysfunction (↑ Cr_s)
  - Bleeding
  - Infection, e.g., spontaneous bacterial peritonitis (SBP)
  - Treatments
    - Large volume paracentesis (LVP)
    - Diuretics

➢ Treatment (hyponatremia)

- Na^+_s < 130 mEq/L
  - Ice chips with strict ↓ intake of salt/water (500 cc/d)
  - Temporarily stop diuretics
  - Correct hypokalemia (↓ K^+_s)
    - Shifts of Na^+/K^+
    - ↑ renal glutaminase (from ↓ K^+_s) → ↑ NH_3 / ↑HE
  - Albumin solution, 25%, ≥ 40 g/L
    - Useful to treat hyponatremia in cirrhosis, not just hypervolemia, hyponatremia, including
      - Acute kidney injury (AKI)
      - Large volume paracentesis (LVD)
      - Spontaneous bacterial peritonitis (SBP)

- Na^+_s < 110 mEq/L, or severe symptoms (e.g., seizures, coma)
  - Hypertonic saline (3%)
  - Desmopressin (DDAVP)
    - Anti-diuretic synthetic analogue of V2 receptors on basolateral membrane of renal collecting ducts
  - Vasopressin receptor antagonists (vaptans)
  - Continuous veno-venous hemofiltration (CVVH)

- Hypertonic saline (3% Na) for dilutional hypovolemia
  - Use for cirrhosis-associated hyponatremia
    - Na^+_s < 110 mEq/L, or
    - Symptoms of hyponatremia
      - Cardiopulmonary stress
      - Neurological changes
        - Seizures
        - Coma
  - Acute (< 24 h) symptomatic hyponatremia
    - 100 cc 3% saline over 15-30 min, repeated maximum of 3x to ↑ Na^+_s by ~5 mEq/L in 6 h
  - Chronic hyponatremia
    - Symptomatic or severe (< 110 mEq/L)
    - 3% saline at 15-30 cc/h, to Na^+_s by ≤ 8 mEq/L per day (especially in first 24 h)
    - Complication of 3% Na infusion is ↑↑ excessive free water clearance

- Desmopressin (DDAVP)
  - For treatment of ↑↑ free water clearance after correction of hyponatremia with 3% saline.
  - DDAVP
    - Acute diuretic, analog to vasopressin
    - Binds to V2 receptors → ↑ renal water reabsorption / ↓ clearance of free water
    - The ↑ water reabsorption → ↓ Na^+_s slows the ↓ Na^+_s from 3% Na and ↓the enhanced clearance of free water (↓ Na^+_s caused by overcorrection of hyponatremia with 3% Na^+)

- Consider giving DDAVP for prophylaxis of possible excessive correction of hyponatremia using 3% Na^+
- More effective this proactive way with
  - Slower rate of Na^+_S correction
  - ↑ urine osmolality
  - ↓ urine output

  } More effective when given prophylactically

- Vasopressin receptor antagonists (vaptans)
  - Non-peptide drugs which block the action of ADH on their V1/V2 receptors
    - Location of receptors
      - V1 vascular smooth muscle
  - Tolvaptan
    - No not use in patients with cirrhosis due to complications
      - Acute kidney injury (AKI)
      - Osmotic demyelination syndrome (ODS)
      - GI bleeding
    - Exception: correction of hyponatremia pre-liver transplantation (LT) (please see next section)

- **Post-paracentesis circulatory dysfunction** (PPCD)

- Meaning of the term "post-paracentesis circulatory dysfunction" (PPCD)
  - PPCD is the triad of "ascites, hyponatremia and renal dysfunction which results from large volume paracentesis (LVP) producing ↓ effective criterial volume (ECV), and thereby possible ↑ mortality.

- **Liver transplantation** (LT)
  - In persons listed for LT with a MELD score > 11, the addition of serum sodium concentration (Na^+_S) better predicts waitlist mortality
    - Each mmol ↓ Na^+_S between 125 and 140 mEq/L is associated with a hazard ratio of 1.05 (United Network for Organ Sharing 2015)
    - The rational is related to hyponatremia being associated with
      - ↑ ICU length of stay (LOS)
      - ↑ hospital LOS
      - Renal failure
      - ↑ mechanical ventilation
      - Sepsis
      - Neurological complications
      - Effect of ↓ Na^+_S on post-LT survival is debated
        - Negative effect of hyponatremia observed in European but not in US studies

❖ **Osmotic demyelination syndrome** (ODS)

➢ Definition

- "…destruction of the myelin sheath in the pontine and extrapontine areas of the brain (cerebral cortex, subcortex, cerebellum, thalamus) … as a consequence of rapid over correction of hyponatremia…"

- Pathophysiology
  - ↑ extracellular Na+ causes osmotic movement of intracellular water, shrinking glial cells → exonal shear damage → opening of tight junctions (↑ permeability) → ↑ apoptosis → destruction of myelin sheath

- Causes/associations
  - Hyponatremia
    - Causes ODS in about 1% of LT patients
  - Other biochemical changes
    - Hypokalemia (↓ K^+_s)
    - Hypophosphatemia
    - Hypoglycemia
  - Patient
    - Men
    - Previous HE

  - "Rather than the absolute value of [serum] sodium, it is the overcorrection [of hyponatremia] over a short period of time that pass the greatest risk of development of ODS" (rate of ↓ Na^+_s)

- Clinical
  - Encephalopathy (differentiate from HE from other neurological symptoms plus typical ODS MRI) (please see below)
    - CNS
      - Agitation
      - Delirium
      - Dysarthria
      - Parkinson
      - Seizures
    - MSK
      - Ataxia
      - Dystonia
      - Quadriplegia
    - GI
      - Dysphagia

- Diagnostic imaging
  - MRI of head
    - Weighted sequences T1
      - ↓ intensity lesions
    - Weighted sequence T2
      - ↑ intensity lesion
      - Fluid-attenuated inversion recovery imaging in the central positive and extrapontine structures

- Repeat MRI may be necessary
  - Changes in MRI occur after the start of clinical symptoms

❖ Pre-liver transplantation hyponatremia

- Preoperative
  - ↓ neurological complications (e.g., ODS) but correcting hyponatremia pre-LT (≥ 120 mEq/L) correct Na^+_s to > 125 mEq/L
- Operative
  - Administer transfusions of PRBC/FFP as indicated
  - Use 0.45% saline replacement IV, as indicated
  - Treat metabolic acidosis with tris(hydroxymethyl) aminomethane (THAM) (a weak amino acid alcohol which binds CO_2 and metabolic acids)
    - Do **not** use THAM in patient with acute kidney injury (AKI)
- Continuous veno-venous hemofiltration (CVVH)
  - During LT surgery patients receive Na+ by way of IV, FFP, PRBCs
    - Replacement fluid may be by 0.45% saline
    - Correct metabolic acidosis with THAM rather than $NaHCO_3$
    - Give continuous veno-venous, hemodilution, using sterile water added to the dialysate solution

Abbreviations: ADH, anti-diuretic hormone; AKI, acute kidney injury; AQP2, aquaporin water channel protein; CO, carbon monoxide; CO_2, carbon dioxide; CVVH, continuous veno-venous hemofiltration; DAMPs, danger-associated molecular patterns; DDAVP, desmopressin; EAV, effective atrial volume; EDHF, endothelium-derived hyperpolarizing factor; FFP, fresh frozen plasma; h, hour; H_2O, water; H_2S, hydrogen sulfide; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; ICU, intensive care unit; IV, intravenous; K^+, potassium; K^+_s, serum potassium; L, litre; LOS, length of stay; LT, liver transplant; MELD, Model for End Stage Liver Disease; Na^+, sodium; Na^+_s, serum sodium; NH_3, ammonia; NO, nitric oxide; ODS, osmotic demyelination syndrome; PAF, platelet activating factor; PAMPs, pathogen-associated molecular patterns; PKA, protein kinase C; PRBC, packed red blood cells; RA, refractory ascites; RAAS, renin-angiotensin aldosterone system; SBP, spontaneous bacterial peritonitis; SNS, sympathetic nervous system; SP, substance P; THAM, tris(hydroxymethyl) aminomethane; VIP, vasoactive intestinal peptide; yr, year

❖ **Hepatic Hydrothorax** (HH)

- Transudative pleural effusion
  - Usually unilateral, R>L
  - A serum to pleural albumin gradient >11 suggests HH
- Confers a poor prognosis in hospitalized patients (74% mortality in 90 days), despite low MELD score
- May be complicated by
  - Spontaneous bacterial empyema
  - Progressive respiratory failure
  - Trapped lung, and
  - Complications of thoracentesis

- First-line therapy of HH consists of dietary sodium restriction and diuretics plus thoracentesis as required.
  - If ascites is present, then additionally perform LVP with IV albumin
- TIPS can be considered in selected patients as a second-line treatment for refractory hepatic hydrothorax (HH).
- Do **not** insert chest tube for HH (chest tubes associated with high morbidity and mortality), but
  - Consider indwelling tunneled catheters in carefully selected patients who do **not** respond to medical therapy and are **not** candidates for TIPS.
  - Indwelling tunneled catheters have ↓ infections, ↓ fluid reaccumulating and ↓ need for pleurodesis
- Patients with HH should be considered for LT
  - For MELD exception documentation, should include the following:
    - ≥ 1 thoracentesis >1 L weekly in the last 4 weeks (record date and volume)
    - Proof of transudative fluid
    - No evidence of heart failure
    - Pleural fluid culture negative on 2 separate occasions
    - Pleural fluid cytology is benign on 2 separate occasions
    - There is contraindication to transjugular intrahepatic portosystemic shunt (TIPS)
    - Diuretic refractory

❖ **Abdominal Hernia**

- Elective hernia repair in cirrhosis is best performed via a multidisciplinary approach after ascites has been controlled and the patient's overall condition, including nutritional status, has been optimized.
  - Optimal fluid control with diuretics, appropriate nutrition and conservative management with binders may improve hernias
  - LVP may paradoxically cause incarceration
  - Hernia prosthetic mesh reduces recurrence but may ↑risk of infection
- Consider TIPS insertion prior to elective hernia repair, or
  - After an emergent operation in patients with cirrhosis and uncontrolled ascites.
  - Ascites ↓ wound healing, and ↑ risks of spontaneous bacterial peritonitis (SBP)

❖ **Spontaneous Bacterial Peritonitis** (SBP)

➢ Treatment

- One-third of admitted for cirrhosis have bacterial infections including:
  - Spontaneous - SBP, bacteremia and spontaneous bacterial empyema accounting for 36% of infections
  - Urinary tract infection (UTI) (22%)
  - Skin/soft tissue infections (8%)

- The ascitic fluid should be cultured at the bedside in aerobic and anaerobic blood culture bottles before initiation of antibiotics.
  - Start empiric antibiotics after paracentesis if high suspicion for infection
  - Mortality increases by ~10% every hour without antibiotics in cirrhotics with septic shock
  - Most commonly Escherichia coli, followed by Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium
- Patients with ascites due to cirrhosis emergently admitted to the hospital should undergo a diagnostic abdominal paracentesis to rule out SBP even in the absence of symptoms/signs of infection.
- Patients with ascites who develop signs, symptoms, or laboratory abnormalities suggestive of infection should undergo workup for infection plus a diagnostic abdominal paracentesis (for cell count and bacteriological culture).
  - If the workup is negative and the patient has a pleural effusion
  - The patient should undergo a diagnostic thoracentesis.
  - Suggestive signs: fever, chills, localizing symptoms or deterioration with HE, AKI and/or jaundice
  - Paracentesis should be performed for any cirrhotic patient with ascites who is hospitalized for any reason
- The diagnosis of SBP or spontaneous bacterial empyema (SBE) is established with a fluid Polymorphonuclear (PMN) leukocyte count >250/mm^3.
  - If positive ascites culture but PMN < 250/mm^3, do **not** treat
- IV antibiotics should be started empirically in all patients with an ascites/pleural fluid PMN count >250/mm^3•
- First-line empirical antibiotic therapy for community-acquired SBP/SBE is IV third- generation cephalosporin.
- Empirical therapy with broad-spectrum antibiotics should be initiated as the first line of treatment in patients with
  - A health care-associated or nosocomial infection, or
  - Recent exposure to broad spectrum antibiotics, or
  - Who are admitted with sepsis or septic shock,
  - Carbapenem as first line for critically ill or nosocomial patients leads to higher resolution of SBP
  - Assess for history of multi-drug resistant organisms or recent antibiotic exposure
- Response to empirical antibiotic therapy may be assessed by repeating diagnostic paracentesis/thoracentesis 2 days after initiation.
  - A ↓ fluid PMN <25% from baseline indicates lack of response → broaden antibiotic coverage and further evaluation to rule out secondary bacterial peritonitis.

❖ **Hepatorenal Syndrome** (HRS-AKI)

➢ Demography

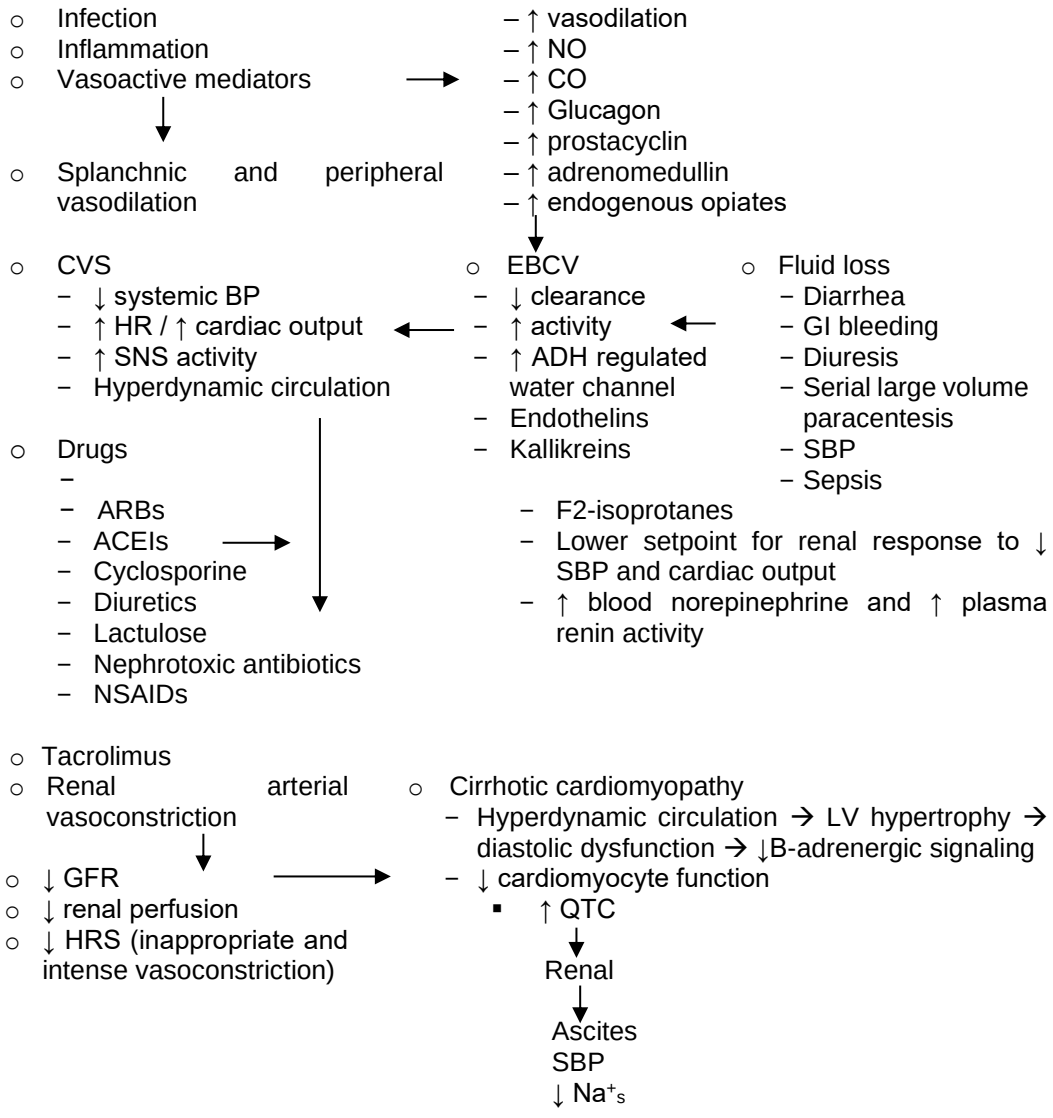
- AKI very common is hospitalized patients with cirrhosis and ascites (27-52%)
- Development of AKI associated with ↑ 30-day mortality of 29% to 44%

➢ Definition

- Inappropriate and intense vasoconstriction leading to ↑ Cr_s

➢ Pathophysiology

- When there is cirrhosis



Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ADH, antidiuretic hormones; ARBs, angiotensin receptor blockers; CO, carbon monoxide; CVS, cardiovascular system; GFR, glomerular filtration rate; HR, heart rate; HRS, hepatorenal syndrome; LV, left ventricle; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; SBP, systolic blood pressure

- ↓ renal perfusion secondary to renal vasoconstriction, mediated by ↑ activities of
  - Sympathetic nervous system
  - Renin-angiotensin-aldosterone system (RAAS)
  - Vasopressin system
- ↓ renal autoregulation
- ↓ cardiac output from cirrhosis-associated cardiomyopathy
- Immune mediated from systemic inflammation

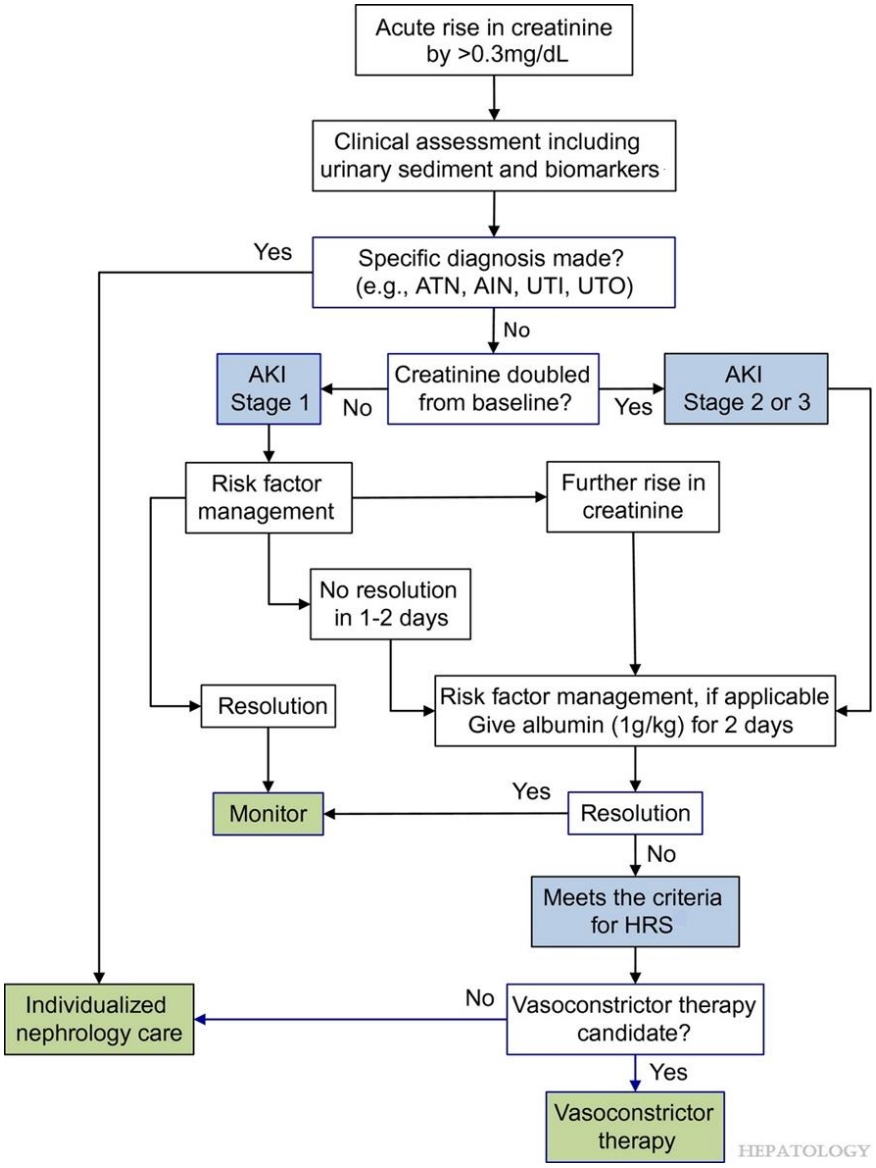
➢ Stages of AKI

- Stage 1 - ↑Cr_s >26.5 µmol/L to 2-fold of baseline
- Stage 2 - ↑Cr_s between 2-fold to 3-fold of baseline
- Stage 3 - ↑Cr_s >3-fold of baseline or Cr_s >353.6 µmol/L plus an acute increase >26.5 µmol/L, or initiation of renal replacement therapy (dialysis)
- Once AKI is diagnosed, treat precipitating factors:
  - Fluid losses
  - Bacterial infections
  - Hemodynamic instability, and
  - Potentially nephrotoxic agents (e.g., particularly nonsteroidal anti-inflammatory drugs [NSAIDs]).
  - Main causes in cirrhotics are
    - Pre-renal AKI (hypovolemia or HRS), and
    - Acute kidney injury (ATN)
  - Investigations: urine sediment, fractional excretion of sodium or urea, and urine sodium in patients receiving diuretics
- Hypovolemia-induced AKI should be managed with
  - Fluid replacement therapy
  - Correction of the cause that led to volume depletion, and
  - Diuretic withdrawal
  - Withhold NSBBs in hypotensive patients (SBP <90 mmHg)
- Differential diagnosis of AKI, HRS, and ATN is challenging and should follow the consensus criteria presented in the algorithm.
  - Diagnosis of HRS-AKI requires:
    - Cirrhosis with ascites
    - ↑Cr_s >26.5 µmol/L from baseline within 48 h, or a percent increase in Cr_s >50% which is known or presumed to have occurred within the preceding 7 days
    - Absence of shock
    - No current or recent nephrotoxic drugs
    - No structural kidney disease indicated by proteinuria (>500 mg/day), microhematuria (>50 RBC/hpf) and/or normal renal US

- Treatment
  - The treatment of choice is vasoconstrictor drugs plus albumin.
    - The preferred drug is terlipressin, administered either as IV bolus or continuous IV infusion.
    - Terlipressin not available in US or Canada
    - Give albumin 1 g/kg on day 1, then 40-50 g/day
  - In settings where terlipressin is not available (e.g., Canada), give norepinephrine (NorEpi).
    - If neither can be administered, a trial of oral midodrine (5 to 15 mg po q8h) in combination with octreotide (100 to 200 µg q8h or 50 µg/h IV) may be considered, yet the efficacy is low.
    - NorEpi given as an infusion at 0.5 mg/h up to 3 mg/h to ↑ mean arterial pressure (MAP) by 10 mmHg and ↑ urine output >200 mL over 4 h
    - Do **not** use TIPS (insufficient studies)
  - Patients should be closely monitored for the possible development of side effects of vasoconstrictors and albumin, including
    - Ischemic complications (fingers, skin, intestines, or heart), and
    - Pulmonary edema.
    - Abdominal pain (ischemia)
  - Response to terlipressin or norepinephrine is defined by
    - Cr_s decreasing to <132.6 µmol/L or
    - Return to within 26.5 µmol/L of baseline over a maximum of 14 days
    - In patients whose creatinine remains at or above the pre-treatment level for > 4 days with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued.
    - Cases with very high pre-treatment Cr_s may need longer treatment than 14 days
  - Recurrence may occur after treatment discontinuation, and should be retreated.
  - All cirrhosis patients with AKI should be considered for urgent LT evaluation given the high short-term mortality even in responders to vasoconstrictors.
    - Improvement in MELD score after treating HRS does not correlate with ↑ survival
  - Use renal replacement therapy (RRT) in liver transplant (LT) candidates with ↑renal function, or
    - Electrolyte disturbances, or
    - ↑ volume overload unresponsive to vasoconstrictor therapy
  - Initiation of RRT in patients who are not candidates for LT must be made with a clear endpoint in mind.
    - Mortality rates extremely high in patients on RRT not listed for LT despite the cause
  - In patients with suspected HRS-AKI, decisions about management including initiation of vasoconstrictor therapy and RRT should be made, if possible, by multidisciplinary teams including specialists in hepatology, nephrology, critical care, and transplant surgery.
  - Simultaneous liver-kidney transplantation may be necessary for patients who are not expected to recover kidney function post transplantation.
    - Risk factors for poor renal recovery include CKD, diabetes, unrecognized renal disease, unexpected intraoperative events, and post-transplant immunosuppression.

- Eligibility criteria for simultaneous liver-kidney transplant:
  - AKI >6 weeks with RRT (dialysis) and/or eGFR/CrCl <25 mL/min
  - CKD with eGFR <60 mL/min for >90 days with ESRD or eGFR <30 mL/min
  - Metabolic diseases
  - Safety net: Increased priority for patients on kidney waitlist between 60-365 days after liver transplantation, and is on dialysis or eGFR < 20 mL/min

➢ Proposed algorithm for the diagnosis and management of AKI in patients with cirrhosis.



Printed with permission: Biggins SW, et al. Hepatology 2021;74(2):1014-1048 (Figure 4).

PREGNANCY AND THE LIVER

- Incidence
  - 1/200
    - Hyperemesis gravidarum
    - HELLP (hemolysis, elevated LFTs, low platelets)
  - 1/1000 ICP (intrahepatic cholestasis of pregnancy)
  - 1/10,000 AFLD (acute fatty liver of pregnancy)

- Clinical
  - Palmar erythema and spider angiomas occur in two thirds of women with normal pregnancies

- Laboratory

- Liver enzymes/tests of liver function in normal pregnancy
  - Unchanged
    - AST, ALT
    - Bilirubin
    - GGT
    - INR
  - Increased
    - Alkaline phosphatase (↑ 2-400%)
    - Alpha-fetoprotein*
    - Ceruloplasmin
    - Cholesterol
    - Fibrinogen (↑ 50%)
    - Leukocytes
    - Triglycerides
    - α- and ß- globulins
  - Decreased
    - γ- globulin
    - Albumin
    - Hemoglobin
    - Platelets (>50,000)

* Moderate increase, especially with twins

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Adapted from Hay E. *Mayo Clinic Board Review* 2008: pg. 419.

❖ Drugs in Pregnancy

➢ Physiological mechanisms which contribute to the altered metabolism of some drugs during pregnancy.

- ↑ maternal blood volume (50%)
- ↓ maternal serum albumin concentration (20%)
- Progesterone → proliferation of SER
- Estrogen → proliferation of RER
- ↑ cytochrome P-450 gene products
- Increased maternal nitric oxide (NO) release during pregnancy causes maternal vasodilation, ↓ systemic vascular resistance, mean arterial blood pressure, reduced responsiveness to vasoconstrictors, resulting in maternal cardiac output rising 30-50%, sixth activation of the rennin-angiotensin system, and increased GFR as well as renal blood flow.

- The FDA category and risk of liver disease-treating drugs during pregnancy and lactation.

Drug	FDA Class	Risk in Pregnancy	Risk with Nursing
Adefovir	C	Low risk	+
Anti-rejection drugs	C	**Not recommended**	
B blockers	C 1st trimester	IUGR, fetal brachycardia, hypoglycemia	-
Cyclosporine	**D**		+
D-penicillamine	**X**	**Teratogenic**	
Interferon	C	**Not recommended**	+
Lamivudine	C	Low risk	-
Methotrexate	**X**	**Contraindicated**	
Metronidazole	B		
Octreotide*	B	Uterine ischemia	+
Penicillamine	**D**	**Significant embryopathy**	-
Ribavirin	**X**	**Contraindicated**	+
Thalidomide (IBD)	**X**	**Contraindicated**	
Trientine	C	Alternative to penicillamine	-
Ursodiol (UDCA)	B	Low risk	+

Note: Avoid the “X” medications for 6 mon before conception.

- Octreotide is useful to stop the bleeding from esophageal varices (EV) in men and in non-pregnant women
- In the setting of a pregnant woman with
  - Bleeding EV, infusion of octreotide may result in ischemia of the uterus, and the induction of premature labor, so do **not** use.

Printed with permission: Katz PO. *2008 ACG What's New in Pharmacology Course:* pg. 50.

- Medications used in gastroenterology and hepatology which have an FDA (food and drug administration, USA) "X" category of fetal risk.
  - Cyclosporine
  - D-penicillamine
  - Methotrexate (IBD)
  - Ribavirin (HCV)
  - Thalidomide

- FDA class and risk of liver transplantation-treating drugs during pregnancy and lactation.

Drug	FDA Class	Risk in Pregnancy	Risk with Nursing
○ Anti-thymocyte globulin	C	Low risk	UN
○ Mycophenolate	C	Do **not** use	+
○ OKT3	C	Probably low risk	-
○ Sirolimus	C	Do **not** use	-
○ Tacrolimus	C	Use if necessary	-

Abbreviation: UN, unknown

Printed with permission: Katz PO. *2008 ACG What's New in Pharmacology Course:* pg. 50; and Mahadevan U. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 867.

❖ Cholelithiasis in Pregnancy

SO YOU WANT TO BE A HEPATOLOGIST!

- Give the potential **genetic basis** for cholestasis of pregnancy seen in about 15% of cases.
  - About 15% of women with cholestasis of pregnancy have mutations in the MDR3 (ABCB4) gene (a phospholipid flippase that moves PC (phosphatidylcholine) from the inner to the outer surface of the hepatocyte canalicular membrane.
  - More common in women from Chile and Scandinavian countries

➢ Pathophysiology

- Changes in bile acid metabolism which occur during pregnancy, and which ↑ risk of **cholelithiasis** (but not necessarily acute cholecystitis).
  - Cholesterol
  - ↑ supersaturation of bile with cholesterol
  - ↑ bile acid pool size
  - ↑ cholic acid
  - ↓ chenic acid (chenodeoxycholic acid)
  - ↑ volume of gallbladder (fasting/fed states)
  - ↓ gallbladder contraction

A trick question

- Give the effect of pregnancy on the prevalence of cholelithiasis, and the incidence of acute cholecystitis.
  - Cholelithiasis ↑
  - Acute cholecystitis – no change from non-pregnant state

- Factors associated with ↑ risk of recurrent cholestasis of pregnancy.
  - Further pregnancies
  - Use of oral contraceptive agents (OCAs)
  - Cholecystectomy for ↑ risk of cholelithiasis, cholecystitis, pancreatitis
  - Use of progesterone during subsequent pregnancy

- Use of estrogen
  - The increased risk of biliary sludge (10-30%) and cholelithiasis (2-3% of all pregnant women) during pregnancy is due to
    - Estrogen-associated with increased transport of cholesterol into bile from the liver
    - Solubilization of this cholesterol as the result of reduced hepatobiliary transport of bile acids and phospholipids
    - Slowing of gallbladder emptying contributes to the formation of stones
    - Pregnancy-associated increase in estrogens increases the risk of biliary pain in 28% of pregnant women who had pre-existing gallstones

❖ **Viral hepatitis** may flare in pregnancy, and gallstones form in pregnancy, and both these as well as pre-existing gallstones may become symptomatic.

➢ Differentiating between viral hepatitis versus symptomatic gallstones in pregnancy.

Findings	Viral Hepatitis (flaring in pregnancy)	Gallstones
○ Nausea/vomiting	Yes	Variable
○ Abdominal pain	Variable	Variable
○ Pre-eclampsia	No	No
○ Cholestasis	Mild to marked	Marked
○ AST/ALT elevation	High	Low
○ Coagulopathy	Rare and late (acute fulminant)	No
○ Hepatic failure	Rare	No
○ U/S	Nonspecific	Dilated bile ducts, stones
○ Management of mother and child	Support HBV – Lamivudine for mother, mT_3 HBIG at birth for child; immunize child HCV – none; check child at 18 wk	Support, avoid cholecystectomy if possible

Please see: Swan MG. Chapter 58. In: Therapeutic Choices. Grey J, Ed. 6th Edition, Canadian Pharmacists Association: Ottawa, ON, 2011, Table 4: Cholestatic Liver Disease, page 776-777.

❖ Cirrhosis in Pregnancy

➢ Complications of cirrhosis in the pregnant patient.

- ○ In the pregnant woman with cirrhosis, the maternal mortality rate is 10%, and there is a 3-25% risk of abortion, premature birth and perinatal death.
- ○ In the pregnant woman with portal hypertension, 18-50% will bleed during pregnancy from esophageal varices

❖ Liver Disorders seen only in Pregnancy

- The trimester (T) in pregnancy of the onset and treatment of liver diseases unique to pregnancy.

Liver Disease	Onset	Treatment
○ Hyperemesis gravidarum	T1	− Supportive care, rehydration
○ Intrahepatic cholestasis of pregnancy (ICP)	T2-3	− Ursodeoxycholic acid (UDCA) or cholestyramine − Preterm delivery if fetal compromised
○ Pre-eclampsia and eclampsia	T2-3	− Antihypertensive drugs, magnesium sulphate
○ HELLP syndrome	T3	− Induction of delivery
○ Acute fatty liver of pregnancy	T3	− Consider early induction of delivery

Abbreviations: HELLP, characterized by hemolysis, elevated liver enzymes and a low platelet count; T, trimester

Printed with permission: Jutta K, et al. Nat Clin Pract Gastroenterol Hepatol 2008; 5(8): 430-43 (Table 1)

➢ **T1-first trimester**

- Nausea and vomiting in pregnancy
  - Nausea and vomiting are common in pregnancy, usually beginning by week 4 to 6, and settling by week 20.
  - Hyperemesis gravidarum (HG) is severe, persistent vomiting which requires medical therapy
  - The PUQE score (pregnancy-unique quantification of nausea and emesis) may be used to assist in directing therapy for HG

- **Hyperemesis Gravidarum** (HG)

➢ Mechanisms for the development of hyperemesis gravidarum (HG), and its associated conditions.
  - Gastroparesis – estrogen, progesterone
  - Obesity (↑ estrogen)
  - Gastric infection –H. pylori
  - Hormone changes
    - HCG
    - Estrogen
    - Progesterone
    - Thyroid hormones
    - Leptin

➢ Associations
  - Female fetus
  - Hydrops fetalis
  - Multiple gestation
  - Personal/family history
  - Trisomy 21 (Down syndrome)
  - Trophoblastic disease

Abbreviation: HCG, human chorionic gonadotropin

➢ **T2 – Second Trimester**

- **Intrahepatic cholestasis of pregnancy** (ICP)

➢ Demography
  - Present in 2% of pregnancies in America, 6% in Chile and Scandinavia
  - 10-15% of first-degree relatives of women with ICP also develop ICP
  - 3rd trimester

- Pathophysiology
  - Usual cholestatic effects of estrogen in pregnancy, plus
  - Genetic predisposition (imitations in canalicular transporters for bile acids, phospholipids and cholesterol [amino phospholipid flippase], as well as FXR, the nuclear regulator of bile acid synthesis)

- Risk factors
  - Previous ICP (50% recurrence)
  - Multiple pregnancies
  - Multiple gestations
  - Descent
    - Chilean
    - Scandinavian

- Clinical
  - Usual presentation is painless jaundice and pruritus, possibly due to elevated serum bile acid concentrations
  - Generalized pruritus of skin especially on palms & soles but no rash
  - Second or third trimester (T_2, T_3)
  - Fetal complications
    - Usually occur after 32 weeks and include
      - Intrauterine growth retardation
      - Fetal distress
      - Premature labour
      - Stillbirth (fetal death rates in ICP are two-fold increased, usually occur between 37-40 weeks, are associated with much higher concentrations of serum bile acids, and may be sudden and intrauterine
    - For this reason, the fetus should be delivered early [36-37 weeks of pregnancy]
    - The newborn may have meconium ileus
    - When serum bile acids > 40 µmol/L, ↑ risk of complications
    - Increase risk for
      - Prematurity
      - Still birth
      - Spontaneous preterm labour and delivery,
      - Fetal compromise,
      - Fetal cardiac dysrhythmias
      - Meconium-stained amniotic fluid, and intrauterine fetal death

- Maternal complications
  - Vitamin K deficiency
  - Coagulopathy postpartum hemorrhage
  - Pruritus and abnormal laboratory tests resolve with delivery
  - Recurs 40-60%) with subsequent gestations
  - Increased risk for cesarean delivery due to fetal compromise
  - Can recur with subsequent use of oral contraceptives (OCAs) and hormonal fluctuations
  - Recurrence of ICP (~50%)
  - ↑ risk of need for cesarean section delivery
  - ↑ risk of
    - Cholelithiasis
    - Cholestasis with use of OCAs
    - Cholecystitis
    - Pancreatitis

Schutt VA, and Minuk GY. *Best Practice & Research Clinical Gastroenterology* 2007; 21(5): pg. 778.

➢ Laboratory

- ↑↑↑ serum alkaline phosphatase, bilirubin, and serum bile acids > 10 µmol/L
- ALT/AST may be ↑ 20x
- LEs/LFTs fluctuate

Abbreviations: Les, liver enzymes; LFTs, liver function tests

➢ Histopathology

- Liver biopsy is **not** necessary to make the diagnosis, but would show intrahepatic central lobular cholestasis, with bile plugs in canaliculi and hepatocytes

➢ Prognosis

- Fetal and maternal outcomes of intrahepatic cholestasis of pregnancy.

Maternal Outcome	Fetal Outcome
○ Pruritus and abnormal laboratory tests resolve with delivery ○ Recurs 40-60%) with subsequent gestations ○ Increased risk for cesarean delivery due to fetal compromise ○ Can recur with subsequent use of oral contraceptives (OCAs) and hormonal fluctuations	– ↑ risk for ▪ Prematurity ▪ Still birth ▪ Spontaneous preterm labour and delivery, ▪ Fetal compromise, ▪ Fetal cardiac dysrhythmias, ▪ Meconium-stained amniotic fluid, and intrauterine fetal death

➢ Treatment

- Benefits of ursodeoxycholic acid (UDCA) in the management of cholestasis of pregnancy
  - ↓ concentration of bile acids in maternal serum and amniotic fluid
  - ↑ transport of bile acids in placenta
  - ↓ cholestatic potential of progesterone during pregnancy
  - ↓ pruritus
  - ↓ fetal distress, premature delivery, stillbirth
- The role of SAM (S-adenosyl – L- methionine) in the treatment of cholestasis of pregnancy.
  - SAM may enhance the benefit of UDCA (ursodeoxycholic acid) in cholestasis of pregnancy.
- The types of drugs used to treat pruritus in patients with cholestatic liver disease.
  - Drugs
    - ↓ degree of cholestasis: UDCA
    - Antidepressants (SSRIs)
    - Cannabinoid agonist
    - Changes in opioidergic neurotransmission: naloxone, naltrexone
    - Changes in threshold to experience nociception: dronabinol
    - GABAergic changes: gabapentin
    - Hepatic enzyme (cP452) inducers: rifampicin, metronidazole, phenobarbital
    - IV propofol
    - Non-absorbable anion exchange resins: cholestyramine
    - Sedation (antihistamines)
    - Serotonin antagonists: ondansetron
  - Invasive procedures
    - Biliary drainage
    - MARS (extracorporeal albumin dialysis)
    - Plasmapheresis
  - UV light
  - Liver transplantation – removes cause of cholestasis

Adapted from: Kremer AE, et al. *Drugs* 2008;68(15):2163-82.

- **T3 – Third Trimester**

- ICP, ALF and HELLP

Acute fatty liver of pregnancy (AFLP), the HELLP syndrome* and intrahepatic cholestasis of pregnancy (ICP) occur only in pregnant women.

➢ Distinguishing characteristics

	ICP	AFLP	HELLP
• Mother			
○ % Pregnancies	0.1–1.0	0.005–0.01	0.2–0.6
○ Time of onset in pregnancy	T3	Second half of pregnancy, or postpartum	Second half of pregnancy, or postpartum
○ Trimester	(2 or) 3	3 or postpartum	3 or postpartum
○ Maternal mortality (%)	0	7–18	1–25
○ Presence of preeclampsia	No	50%	Yes
○ Typical clinical features	Pruritus ↑ serum ALT/AST ↑ fasting bile acids	Liver failure with mild jaundice, coagulopathy, encephalopathy, hypoglycemia, DIC	Hemolysis Elevated serum liver tests Thrombocytopenia (often <50,000/μL)
○ Nausea/ vomiting	Rare	Yes (80%)	Yes
○ Abdominal pain	Rare	Yes (60%)	Yes (100%)
➢ Laboratory			
○ Cholestasis	Marked	Modest and late	Mild or absent
○ ALT	Mild to 10–20-fold ↑	5–15-fold, ↑ variable	Mild to 10–20-fold ↑
○ Bilirubin	<5 mg/dL (<85 μmol/l)	Often <5 mg/dL (<85 μmol/l)	Mostly <5 mg/dL (<85 μmol/l)
○ Fetal/perinatal mortality (%)	0.4–1.4	9–23	11
○ Recurrence in subsequent pregnancies (%)	45–70	20–70 (carriers of LCHAD mutations) Rare (others)	4–19

	ICP	AFLP	HELLP
○ Coagulopathy	No	In severe cases, late	Early: thrombocytopenia Late: DIC
○ Hepatic failure	No	Yes (70% when severe)	Rare
• Imaging			
○ U/S	Normal	No change or fatty liver	Areas of necrosis, infarction, or hematoma
• Liver biopsy	Cholestasis	Microvesicular fatty infiltration	Periportal patchy, hemorrhagic necrosis, Fibrin deposition Perisinusoidal mild microvesicular fat
• Treatment			
○ Management of mother and child	UDCA, vitamin K	Early delivery (cesarian section) increased risk of AFLP in next pregnancy, check LCHAD in fetus (unknown risk of recurrence of AFLD)	Early delivery (cesarian section) for severe uncontrolled pre-eclampsia (hemolysis, seizures)

UDCA is low risk after first trimester and is effective for cholestasis of pregnancy.

Abbreviation: LCHAD: α-subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase; HELLP, hemolysis, elevated serum liver enzymes, low platelets

Adapted from: EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. J Hepatol 2009; 51(2), 237–267 and Myers RP, et al. *First Principles of Gastroenterology* 2005. pg. 652.

- **HELLP** (HEMOLYSIS, ELEVATED LFTS, LOW PLATELETS) **SYNDROME**

➢ Definition

  - The HELLP (hemolysis, elevated liver enzymes, low platelet) syndrome is a form of pre-eclampsia liver disease.

Danger sign!

A woman in the second trimester of pregnancy with RUQ (right upper quadrant) pain, nausea and vomiting, should be suspected of having HELLP, rather than focusing just on gallbladder disease.

➢ Demography

  - Pre-eclampsia occurs in 5-10% of pregnancies, and accounts for 20% of maternal deaths (Van Dyke 09)
  - Preeclampsia occurs in about 4% of pregnancies, and HELLP occurs with about 12% of women with severe eclampsia
  - Pre-eclampsia and the HELLP syndrome usually occur in the 3rd trimester, but in 28% HELLP occurs in the early postpartum period.

➢ Pathophysiology

  - Both HELLP and AFLP may be associated with maternal defects in the mitochondrial oxidation of fatty acids arising from deficiency of **LCHAD** (long-chain 3- hydroxyacyl- CoA dehydrogenase).
  - LCHAD in fetus: "AFLP may develop regardless of maternal genotype if the fetus is deficient in LCHAD and carries at least one allele for the G 1528C LCHAD mutation" (Sleisenger & Fordtran's gastrointestinal and liver disease 2010, page 635)". In cases of AFLP the mother, father and child should be tested for the G1528C LCHAD mutation" (Sleisenger & Fordtran's gastrointestinal and liver disease 2010, page 636)
  - ↓ carnitine palmitoyltransferase
    - Both HELLP and AFLD are associated with defects in fatty acid oxidation and prenatal genetic diagnosis may be performed in pregnant women in affected families

- The role of deficiency of the mitochondrial fatty acid oxidation enzyme LCHAD (long-chain 3-hydroxyacyl-coenzyme A dehydrogenase) in AFLD.
  - ↓ ability of fetus to oxidize long-chain fatty acids (LCFA), sometimes from a mutation causing ↓ LCHAD activity.
  - LCFA from fetus are transferred from fetus to placenta to mother.

- If the mother is heterogeneous for LCHAD, she will accumulate LCFA as microvesicular fat, and will develop
  - Hepatic steatosis
  - HE (hepatic encephalopathy)
  - ALF (acute liver failure)
- If the newborn child has LCHAD deficiency, she/he has ↑ risk of fatal, fasting non-ketotic hypoglycemia over next several months – must check the newborn for their LCHAD levels.

- The maternal and fetal factors implicated in the pathogenesis of HELLP.
  - Pathophysiology relates to the fetal and maternal sides of the placenta
  - Even if there are no signs of preeclampsia at the time of delivery, about 30% of cases of HELLP will develop eclampsia after delivery

  - Mother
    - ↑ sFlt1 (soluble form-like tyrosine kinase 1 (an antagonist of VEGF [vascular endothelial growth factor] and an antagonist of PIGF [placental growth factor])
    - ↑ sEng (soluble endoglin, which reduces the formation of capillaries)
    - ↑ procoagulant (e.g., factor V Leiden, anticardiolipin antibody)
    - ↑ systemic vascular resistance
    - ↓ plasma volume
    - ↓ LCHAD (long-chain 3-hydroxyacyl – CoA dehydrogenase), which when reduced leads to ↓ mitochondrial oxidation of fatty acids)
  - Fetus
    - On the fetal side, the high capacity low resistance placental vessels do not develop, which leads to ↓ blood flow to the fetus from the placenta, fetal ischemia and intrauterine growth retardation
      - ↓ trophoblast invasion of wall of uterus
      - Dilation of spiral arteries
      - ↓ uteroplacental perfusion

➢ Clinical
  - Associations
    - Hyperreflexia
    - Peripheral edema
    - Disseminated intravascular coagulation (DIC)
    - Abruption placentae
    - Budd-Chiari syndrome (hepatic vein thrombosis)

- Often associated with preeclampsia
  - ↑ systolic blood pressure (SBP)
  - Proteinuria
  - Peripheral edema
- Mortality rate
  - Mother 20%
  - Fetus 20%
- Recurs
  - 1/3 of future pregnancies
- There is an increased risk of **recurrence** of HELLP in women with severe
  - Hypertension
  - Chronic renal disease
  - Lupus anticoagulant, or
  - Women with a liver transplantation (or other organ transplantation)

➢ Diagnosis

- Required for diagnosis
  - Hypertension (sustained systolic blood pressure of ≥ 140/90 after week 20 of pregnancy, in women whose blood pressure was previously normal)
  - Hypertension-associated end organ damage (e.g., liver damage in HELLP syndrome)
- Proteinuria (≥ 300 mg urinary protein per 24 h, or 30 mg/dL urine [dipstick #1])
- While abdominal ultrasound may be reliable to detect intrahepatic complications of HELLP, imaging is not reliable to prove the absence of AFLP (the liver must contain > 30% before the abdominal ultrasound becomes reliably positive for steatosis).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Using the presence of ↑ serum values of AFP (alpha-fetoprotein) is **not** widely recommended as a screening test for hepatocellular cancer (HCC).

- In the setting of a pregnant woman with cirrhosis or chronic HBV infection who has been found to have an ↑ serum AFP, what are the differential possibilities besides HCC?
  - Mother
    - Physiological (↑ AFP in normal pregnancies)
    - Hydatidiform mole
  - Fetus
    - Down syndrome
    - Neural tube defects

- Laboratory
  - The extent of laboratory abnormalities does **not** reflect the severity of HELLP
  - Lab' abnormalities
    - Hemolysis (from microangiopathic hemolytic anemia) unconjugated hyperbilirubinemia
      - ↑ LDH
      - ↓ haptoglobin
    - ↑ ALT, AST
    - ↓ platelets
  - In keeping with the hemolysis ("H") in HELLP
    - The peripheral blood smear may show schistocytes
    - There may be increased serum LDH (lactate dehydrogenase)
    - Although transaminases are often increased 6x (median, 249 U/L for serum aspartate aminotransferase), values > 1000 may occur.
  - In HELLP, there are:
    - The usual laboratory findings of hemolysis (H).
    - The elevated liver tests (EL) include a wide range of changes in ALT/AST, further increased in alkaline phosphatase, and jaundice in 5-40% depending on the extent of patchy ischemic necrosis and fibrin deposition, and hemolysis.
    - The thrombocytopenia (LP) may be associated with low fibrinogen, increased fibrin degradation products and renal dysfunction.
  - Fetal hypoxia may develop quickly, with sudden intrauterine death, so early delivery of the fetus is recommended. Fetal mortality is 3-23%, and maternal mortality is up to 3.5%.

Clinical Alert

- In the pregnant woman with Wilson disease who develops hemolysis and acute liver disease at the time of delivery, in addition to suspecting the HELLP syndrome, consider and exclude acute Wilson disease.

- Histopathology
  - The usual patchy hepatic necrosis may lead to confluent necrosis, hepatic hematoma, and even hepatic rupture requiring surgical intervention or hepatic artery embolization.
  - Fibrin deposit in sinusoids → focal ischemic necrosis → periportal hemorrhage subcapsular hematoma hepatic rupture.
  - Maternal and fetal mortality from a free rupture is 50-100%.
- Treatment
  - Urgent delivery of the fetus

- **Acute Fatty Liver in Pregnancy** (AFLP)

➢ Demography

- Seen in 1/1000 pregnancies
- AFLP accounts for 16-70% of severe liver disease as well as maternal and fetal deaths during pregnancy

➢ Pathophysiology

- Impaired mitochondrial beta-oxidation or oxidative phosphorylation of fatty acids, resulting in mitochondrial damage, ↓ ATP production, and destruction of hepatocytes
- Associated with pre-eclampsia in 30%, genetic abnormality in LCHAD (long chain 3-hydroxyacyl-CoA-dehydrogenase) in 20%, possibly other as yet unknown genetic mutations, and the use of drugs such as ASA/NSAIDs
- When mother is LCHAD heterozygote but fetus is homozygote, the risk of AFLP is 43%; when the fetus is a heterozygote or normal, the risk of AFLP is 2.7%

➢ Pathophysiology

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  - LCFA from fetus are transferred from fetus to placenta to mother.
  - If the mother is heterogeneous for LCHAD, she will accumulate LCFA as microvesicular fat, and will develop
    - Hepatic steatosis
    - Hepatic encephalopathy (HE)
    - Acute liver failure (ALF)
  - If the newborn child has LCHAD deficiency, she/he has ↑ risk of fatal, fasting non-ketotic hypoglycemia over next several months – must check the newborn for their LCHAD levels.

- Clinical
  - The presentation is that of acute liver failure, including hepatic encephalopathy, coagulopathy, jaundice, ascites, hypoglycemia, renal impairment and pancreatitis
  - Intrauterine fetal mortality may be as high as 32%, and maternal mortality rates of 5-26%.
- Laboratory
  - The level of the altered serum transaminases do not reflect the severity of the liver damage and failure. In addition to an elevated INR, anti-thrombin III levels are often increased as well
- Differential

Ticks and Treats

- Overlap - questions are often asked of candidates to distinguish between AFLP (acute fatty liver of pregnancy) and HELLP.
- It is helpful that AFLP does not usually have thrombocytopenia.
- ALT/AST may be increased in patients with AFLP; although this increase may not be as high as in HELLP
  - In the individual patient this relative elevation of differences in ALT/ AST is not useful.
- Beware, AFLP is not considered to be a “preeclamptic liver disease”, but about 50% of AFLP may actively have associated pre-eclampsia.
- Both HELLP and AFLP may be associated with inherited defects in the beta oxidation of fatty acids.
- And don’t forget
  - AFLP is associated with severe pericentral (zone 3) microvesicular fat
    - HELLP may be associated with fatty liver, albeit not as severe as the pericentral microvesicular fat of AFLP.

- Treatment
  - Urgent delivery of the fetus is required; test the mother and infant for LCHAD mutations

Abbreviations: AFLP, acute fatty liver of pregnancy; LCHAD, long chain 3-hydroxyacyl-CoA-dehydrogenase

Clinical Gem

- After an episode of AFLP, the microvesicular steatosis may progress!

❖ **LIVER DISEASES OCCURRING IN PREGNANCY WHICH ARE NOT UNIQUE TO PREGNANCY** (cautions to be considered when treating the following liver conditions during pregnancy).

- **Autoimmune hepatitis** (AIH)
  - Maintenance medications for autoimmune hepatitis (AIH) should **not** be stopped during pregnancy
    - Even with these being continued, there is ↑ risk ofspontaneous abortion (12%) and perinatal deaths (7%).

- **HAV infection**
  - Hepatitis A has low risk in pregnancy, and only requires supportive care for the mother.

- **HBV infection**
  - HBV vaccine results in ↓ risk in pregnancy.
  - Lamivudine is low risk treatment for HBV infection in pregnancy.
  - Do **not** give **Interferon** and **ribavirin** in pregnancy (if appropriate, use lamivudine, tenofovir)
  - Vertical transmission from mother-to-child is the commonest route for HBV infection
    - Depending upon the viral load, may be 80-90%.
  - Babies born to HBV positive mothers should receive HBIG and HB vaccine at birth, and further vaccination at
    - 1 and 6 mon of age, then
    - 18 mon of age

- **HCV infection**
  - HCV infections are the result of vertical transmission, which are rarely transmitted to fetus
  - Risk for HCV infection is 30% if the mother is both HCV and HIV positive.
  - HCV – do **not** treat in pregnancy

- **HDV infection**
  - HDV may be transmitted at the same time as HBV.

- **HEV infection**
  - Because of underlying chronic liver disease
    - Rare to become pregnant if HEV infected
    - Prognosis variable
    - ↑ stillbirths
    - High bilirubin → kernicterus in fetus
  - Transmission of HEV is vertical
  - HEV hepatitis in pregnant women is associated with
    - ↑↑ rate of fulminant hepatic failure, and
    - Maternal/fetal death (especially in Africa and Asia)

- **HSV**
  - ↑ risk of herpes simplex hepatitis during pregnancy
    - May present with markedly
      - ↑↑ transaminases, or
      - Fulminant hepatic failure.

- **PBC/PSC/ICP**
  - UDCA has low risk after first trimester and is effective for intrahepatic cholestasis of pregnancy (ICP), and for primary biliary cholangitis (PBC).
    - UDCA us not of benefit in patients with primary sclerosing cholangitis (PSC), neither with/without pregnancy.

- **Portal hypertension**
  - Propranolol – avoid after first trimester (fetal cardiotoxicity)
  - Nadolol has a long half-life – Do **not** use.

- **Wilson disease** (WD)
  - Penicillamine should be avoided (teratogenic), or dose reduced to half during pregnancy
    - If necessary, switch to trientine
    - May switch to oral zinc only if previous Cu^{2+} removal was complete, as indicated by a normal 24 h urine copper concentration
    - The woman of childbearing potential who has WD is usually not able to conceive because of associated amenorrhea and infertility.
  - If the couple wishes to become pregnant, the planned mother should be treated with chelation therapy until normalization of 24 h urine copper level before planned pregnancy, then maintained through/after pregnancy on oral zinc (Zn).
    - If conception occurs without prior stoppage of the chelation therapy, or without confirmed normalization of 24 h urinary copper extraction, and switching to zinc po,then reduce the dose of the penicillamine currently being used, but do **not** completely stop.

- The reason why some form of copper-lowering therapy should be continued even when D-penicillamine is teratogenic in humans
  - When therapy for Wilson disease is suddenly stopped during pregnancy, the sudden release of copper from storage sites causes RBC hemolysis, with possible development of acute liver failure (ALF) and death.
    - The only successful treatment for ALF due to withdrawal therapy in a pregnant with WD is emergent liver transplantation.
  - If a woman with Wilson disease is planning/hoping to become pregnant, switch from D-penicillamine to trientine (not teratogenic in humans), or to oral zinc after normalization of 24 h copper management.
  - If patient has previously been adequately treated with chelation therapy, and is being managed with zinc po, if pregnancy occurs, simply continue oral zinc.

ALCOHOLIC LIVER DISEASE (ALD)

➢ Definition: ALD is a disorder associated with the intake of excessive amounts of alcohol over prolonged periods of time, leading to acute and / or chronic compensated / decompensated liver disease.

➢ Pathophysiology

- Alcohol intake
  - Metabolizing enzymes
    - ADH (alcohol dehydrogenase)
      - Main enzyme at < 10 mM alcohol
    - CYP2E1 (cytochrome P450 2E1)
      - Main enzyme at > 10 mM alcohol (self-inducible, i.e., alcohol increases CYP 2E1)
    - Catalase
    - ALDH (aldehyde dehydrogenase)

Alcohol -------→ Acetaldehyde

Acetaldehyde ---$\xrightarrow{\text{ALDH}}$> Acetate

- Role of acetaldehyde
  - Acetaldehyde forms adducts with reactive residues (oxidatively modified proteins or small molecules
  - Antibodies form against these adducts (e.g., MAA [malondialdehyde and acetaldehyde])

- Methionine metabolism
  - Methionine is acted upon by methionine adenosyl transferase (MAT) to form S-adenosyl-methionine (SAM)
    - SAM usually is acted upon in the transmethylation pathway, forming S-adenosyl homocysteine (SAH)
      - In ALD, there is ↓ MAT and ↓ SAM → ↓ transmethylation → ↓ DNA RNA, histones, biogenic amines, phospholipids
  - SAH and ↓ SAM
    - ↑ SAH and ↓ SAM/SAH ratio → ↓ transmethylation reactions → ↓ SAM
  - ↓ SAM →
    - ↓ glutathione in mitochondria → mitochondria dysfunction
    - ↑ LPS (lipopolysaccharide)
      - Stimulated release of TNF → ↓ mitochondrial function
      - ↑ IL-10 from monocytic cells
    - ↑ homocysteine, ↑ SAH
    - ↑ SAH and ↑ homocysteine
    - ↑ hepatocyte sensitivity to TNF-mediated destruction

- ↑ hepatocyte sensitization from
  - ↓ glutathione in mitochondria
  - ↑ SAH
  - ↓ proteasomes
  - ↓ THF, ↓ methionine
- Alcohol ↓ folic acid absorption and metabolism, including
  - ↓ 5-mTHF (5-methyltetrahydrofolate [THF])

- Hypoxia
  - Alcohol
  - ↑ O_2 uptake by liver
  - ↑ lobular O_2 gradient
  - ↑ NADH / NAD+ → ↑ HIF (hypoxia-inducible factor) 1 and 2 genes → mitochondrial dysfunction
  - When alcohol ↓, HIF
  - Reperfusion injury, especially in centrilobular area

- Mitochondria dysfunction
  - ↑ TNF impairs function of mitochondria
  - ↑ $NADH/NAD^+$ ---→ ↑ generation of superoxidase
  - In ALD, ↓ transport of glutathione into mitochondria
  - Glutathione-depleted mitochondria → ↑ sensitive to damage by TNF
  - ↑ depolarization leads to
    - ↑ membrane permeability
    - ↑ apoptosis of hepatocytes

- Redox state (oxidative-reduction state)
  - Alcohol → ↑ CYP 2E1 → leaking of electrons → ↑ oxidative stress
  - ↓ ATP
    - ↓ metabolism of
      - Carbohydrate
      - Fat (e.g., steatosis)
  - ↑ oxidants: ↑ ROS (reactive oxygen species), ↑ RNS (reactive nitrogen species), ↑ oxidative stress
  - ↓ antioxidants
  - ↑ cell injury
    - ↑ membrane lipid peroxidation
    - ↑ protein and DNA oxidation
    - ↑ NF-kB (nuclear factor kappa B) → ↑ TNF

- Dysregulated proteasome system
  - ↓ removal of proteins damaged by oxidative stress

- Dysregulated cytokine production
  - ↑ hepatocyte
    - IL-8, IL-18
      - ↑ apoptosis → sustains ↑ proinflammatory cytokines
    - Neutrophil chemotactic peptide
    - Angiogenesis factor
  - Kupffer cells
    - NF-kB → TNF-α
    - IL-10
  - Sinusoidal endothelial cells
    - Adhesion molecules
  - Stellate cells
    - TGF-β → fibrosis
  - ↑ intestinal permeability → ↑ LPS
  - ↑ apoptosis of hepatocytes → ↑ release of IL-8 (neutrophil chemoattractant), IL-18 (primes TNFα release, and type 1 helper T cell response)
    - ↑ TNF-α inducible IL-6, IL-8, Il-18, MCP-1 (monocyte chemoattractant protein 1)
  - As well as ↑ pro-inflammatory cytokines, there is ↓ anti-inflammatory cytokines

- Autoimmune changes
  - Mutation in CTLA-4G (cytotoxic T lymphocyte-associated antigen 4G) allele actives T cell function.
  - Hydroxyethyl radical from breakdown of alcohol modifies CYP 2E1
  - Modifies CYP2E1 plus CTTA-4G mutation → ↑ anti-CYP2E1 autoantibodies
  - Activation of HSC and Hepatic Fibrosis
  - NKT (natural killer T) cells
    - Altered proportion of NKT cells in periphery and parenchymal tissue may ↑ risk of NASH

NON-ALCOHOLIC FATTY LIVER DISEASES (NAFLD: Simple Steatosis, and Non-Alcoholic Steatohepatitis [NASH])

➢ Pathogenesis

- Diet
  - ↑ n-6 PUFAs
    - Linoleic acid
    - Arachidonic acid
  - ↓ N-3 DUFAs
  - ↑ CHO / fructose →
    - ↑ hepatic lipogenesis
    - ↑ inflammatory pathways
  - Altered gut microbiotica

- Genetics
  - Genetic polymorphism in PNPLA3 (patatin-like phospholipase domain) containing germline-encoded mechanisms of pattern recognition, affecting innate immunity
    - Pathogen-associated molecular patterns (PAMPs)
      - TLR (toll-like receptors
      - Nucleotide-binding oligomerization domain (NOD)
    - Damage-associated molecular patterns (DAMPs)
      - NLR leucine rich repeat containing receptors

- GI Tract
  - Abnormal control of food intake
  - ↑ dietary fat, carbohydrate
  - ↑ VLDL, apo B-100
  - ↑ free fatty acids (FFAs)
  - ↑ fat / ↑ CHO to liver
    - ↑ lipogenesis (↑ TG in liver)
    - ↑ insulin resistance
  - Bacterial toxins
    - ↑ reactive oxygen species (ROS) → ↑ oxidative stress
  - Gut lipopolysaccharides (LPS)
    - Endo-/ exotoxin-mediated release of proinflammatory cytokines and inflammasomes
  - Altered intestinal microbiome

- Toll-like-receptors (TLRs)
  - TLR2
    - Ligands for bacterial, fungi and protozoal products
    - Saturated fats in diet ↓ protective role of TLR2s
  - TLR4
    - ↑ activity in response to LPS (lipoprotein polysaccharides)
  - TLR9
    - Endosomal TLR9 recognizes unmethylated Cp6 motifs-a direct role not identified in NAFLD
  - DNA viruses / lipopolysaccharides (LPS) speculated to be of importance

- Adipocytes
  - ↑ FFA / ROS
    - Activation of macrophages / immune system → ↑ lipoptosis
    - ↑ insulin-resistant adipocytes → ↑ FFAs

- Adipose tissue
  - ↑ Visceral fat (non-peripheral fat)
  - ↑ Portal FFA
  - ↑ Cytokine production
    - ↑ NF-kB
    - ↑ IL-6
    - Lysosomal destabilization (↑ TNF-α)
  - ↑ ROS, ↑ CYP 2E1
  - ↓ Adiponectin
  - ↑ leptin, ↑ leptin resistance
  - ↑ FFA (long chain fatty acids)
    - Mitochondrial dysfunction → ↓ ATP, ↑ mitochondrial DNA damage
    - ↓ adiponectin

- Imbalance (↓ lipolysis / ↑ lipogenesis)
  - ↑ FFA → ↓ Lipolysis of adipocyte TG
  - ↓ FFA β-oxidation by mitochondria
  - ↑ esterification into triglyceride (TG)

- Synthesis of
  - Phospholipids
  - Cholesteryl esters
- ↑ CYP 2E1
  - ↑ ROS
  - Hepatic insulin resistance
- ↑ Lipogenesis
- Accumulation of triglyceride-derived toxic lipid metabolites activates intracellular inflammatory pathways within hepatocytes and Kupffer and other immune cells, in resemblance to defects within adipocytes.
- PPAR-α
  - FA oxidation
  - Oxidative stress
- Regulation by
  - Adiponectin
  - Catecholamines
  - Glucagon
  - Growth hormone
  - Insulin
  - Leptin

- Liver
  - Metabolism
    - ↑ insulin, ↑ insulin-resistance
    - ↑ leptin, ↑ leptin resistance
    - ↑ VLDL
    - ↓ adiponectin
  - Mitochondria
    - ↓ β oxidation of FFA
    - ↑ synthesis of FFA
      - ↓ respiratory chain complexes
      - ↓ ATP
      - ↑ ROS, ↑ PPAR γ, ↑ TNF-α
      - ↑ DNA damage
    - ↑ SREBP1 / ↑ CHREBP → ↑ TG synthesis
    - ↓ Apo B-100 (also ↓ β oxidation) → ↓ fat transport out of liver → ↑ TG in liver
  - ↑ CYP 2E1
    - ↑ leak of electrons → ↑ ROS, ↑ RNS → ↑ NF-kB → ↑ TNF-α
    - ↓ ATP
    - ↓ antioxidant
    - ↑ membrane lipid peroxidation
    - ↑ protein / DNA oxidation
    - ↑ hepatic insulin
    - ↑ synthesis of PL, CE

- Types of hepatocyte injury and death
  - Apoptosis
    - FFAs cause
      - Lysosomal permeabilization / destabilization → activation / release of cathepsin B
      - Mitochondrial dysfunction
      - Lipotoxicity
      - ↑ FAS protein expression
      - ↑ TNF / TNF -1R expression
    - Programmed cell death
  - Necrosis
    - Accidental cell death in response to
      - ↓ ATP
      - ↑ ROS
  - Necroptosis
    - Receptor-induced, caspase-independent cell death
    - CYP2E1-dependent receptor-interacting protein (RIP) expression
    - RIP-1 – RIP-3 dependent TRAIL-induced receptors
- Terminal events
  - May play a role in NAFLD via NLRP3 and IL-1 signaling
  - Lytic release of cellular compounds
    - Necrosis
    - Pyroptosis
  - Breakdown of cellular components with instant plasma membranes
    - Apoptosis
    - Autophagia
  - Pyroptosis caspase-1 dependent cell death

- Hepatic stellate cells (HSC)
  - ↑ Apoptosis, ROS → ROS paracrine stimulation of HSC
  - Altered ATP homeostasis
  - Angiotensin
  - Connective tissue growth factor
  - Connective tissue growth factor
  - Extracellular matrix
  - Growth factors
  - Leptin-associated production of TGF-β by Kupffer cells
  - Mechanical stiffness of extracellular matrix (ECM)
  - Oxidative stress (ROS)
  - PDGF (platelet-derived growth factor)
  - Pro-inflammatory cytokines
  - Signals from Kupffer and endothelial cells

- I**nitiation of activation** of HSCs.
  - Activation of hepatic stellate cells (HSC) leads to collagen deposition and the potential for cirrhosis.
  - The HSC is the central effector in hepatic fibrosis
  - HSC undergoes activation through a two-phase process
    - Initiation
    - Maintenance
  - Initial liver injury results in hepatocyte cell apoptosis with generation of apoptotic bodies, reactive oxygen species (ROS), and paracrine stimulation of HSCs.
  - LPS from the gut also stimulate HSCs.
  - Growth factor signaling
  - Fibrogenic signaling pathways
    - TGFB1
    - CTGF/CCN2
  - Adipokine signaling pathways
    - Leptin
    - Jak, PPARγ
  - Neuroendocrine pathways
    - Cannabinoid receptor signaling
    - Opioid signaling
    - Serotonin
    - Thyroid hormones
- In the initial phase, the hepatocyte becomes sensitized to additional activation by upregulating various receptors.
- The hepatocyte begins to secrete autocrine growth factors, chemokines, and ECM.
- Activation → down-regulation of inhibitory MHC class I molecules
- ↓ lipid droplets from HSC

- **Maintenance** of HSC activation
  - The perpetuation phase is the maintenance of HSC activation.
  - This maintained HSC activation involves changes in HSC proliferation, chemotaxis, fibrogenesis, and contractility.
  - Fibrocytes derived from the bone marrow transdifferentiate into myofibroblasts, and may increase ECM production.
  - Increased ECM enhances mechanical stiffness of the ECM can be sensed by and activate HSCs.
  - The contribution of dendritic cells to fibrosis is not well understood, but may include NK cell-mediated HSC killing.

- ↑ PDGFR
  - PDGF signals partially through ERK activation and also through AKT via mTOR mediated protein synthesis regulation.
  - PDGF activation also allows for influx of Ca^{2+} ions, which contributes to gene regulation
  - In addition to PDGF, several other growth factors can activate tyrosine receptors which lead to Akt activation and then either mTOR or JNK activation.
  - TGFβ recruits Smad 2/3, leading to their phosphorylation and stimulation of fibrogenic gene expression.
  - Emerging pathways of importance of fibrosis include contributions from adipokines (leptin), neuroendocrine signals (2-AG), TLR signaling, and angiogenic signals (VEGF), among other.

Abbreviations: FFA, free fatty acids; HSC, hepatic stellate cell; ROS, reactive oxygen species

❖ Regulated changes in gene expression which occur during activation of HSCs.

- Transcription factors and targets (modulation of the activity of transcription factors)
  - Transcription factors which activate the transcriptional targets of HSCs: Ets-1, Mef 2, CREB, EGR-1, vitamin D receptor, Foxf1, Jun D, and C/ERPB
  - HSC activation: α_1 and α_2 chains of type I collagen – α – SMA, TGFB1, TGF receptors MMP-2, and TIMPs I and 2
  - HSC inactivation (anti-fibrotic) – Lhx2 (LIM homeobox gene 2) - FOXO1 (forkhead box gene, group O)
  - Development and differentiation (factors expressed by HSCs)
  - Dominant – positive
    - b HLH (basic helix-loop-helix transcription factors)
    - E box DNA hexanucleotide sequence for b HLH binding
    - Myo D, SREBP-1c, C-Myb and C-Myc
  - Dominant – negative (antifibrotic)
    - I d proteins
    - C/ERPα

- Nuclear receptors
  - Farnesoid X receptor (FXR)
    - RXR and FXR dimerize after “sensing” bile acids.
    - The dimerized RXR and FXR activate SHP.
    - SHP suppresses the expression of the collagen gene.
  - Pregnane X receptor (PXR)
    - PXR is activated by steroids, certain drugs, xenobiotics and antibiotics.
    - PXR dimerizes with RXR and induces cytochrome P450 enzymes.
  - Peroxisome proliferators-activated nuclear receptors (PPARs)
    - ↓ HSC activation – expression of collagen gene.
  - Retinoid responsive RXR and RAR.

- Epigenetic regulation (methylation of promoters)
  - "Epigenetics refers to changes in DNA methylation and associated histone modifications that influence the chromatin states and impact gene expression patterns, without affecting the sequence of the target DNA."
  - Activation of HSC leads to "global" reduction in methylation.
  - ↑ CBF1 and MeCP2 result in ↓ IKB by way of promoter methylation.
  - IKB repression results in de-repression of NFKB activity.
  - ↑ NFKB increases the survival of HSCs.

- Inflammasomes
  - Proinflammatory multiprotein complexes consisting of a Nod-like receptor (NLR) protein or a PYHIN protein
  - Sense pathogen-associated molecular pattern (PAMPs)
  - Damage-associated molecular patterns (DAMPs) and are key to the production of the proinflammatory cytokines IL-1β IL-18.
  - Reactive oxygen species (ROS) activate the NLRP3 inflammasome and their generation is triggered by many DAMPs.
  - Increased ROS generation is a proinflammatory insult in the progression of NAFLD.
  - Nod-like receptor (NLR) proteins
    - Form cytoplasmic multiprotein complexes, known as inflammasomes
    - Inflammasomes (adaptor proteins) contain apoptosis-associated speck-line protein containing
      - CARB
      - Serine protease caspase-1
  - A signaling pathways regulating HSC activation
    - PDGF
      - PDF signals partially through ERK activation and also through AKT via mTOR mediated protein synthesis regulation.
      - PDGF activation also allows for influx of Ca2+ ions, which contributes to gene regulation
      - In addition to PDGF, several other growth factors can activate tyrosine receptors which lead to Akt activation and then either mTOR or JNK activation.
    - TGFβ
      - TGFB recruits Smad 2/3, leading to their phosphorylation and stimulation of fibrogenic gene expression.
    - Others
      - Emerging pathways of importance of fibrosis include contributions from
        - Adipokines (leptin)
        - Neuroendocrine signals (2-AG)
        - Toll-like receptor (TLR) signaling
        - Angiogenic signals (VEGF), among others

- Micro RNA
  - "micro RNAs (mi RNAs) represent a family of small non-coding RNAs controlling translation and transcription of many genes"
  - TGFB, LPS and NF-kB down-regulate the miR-29 family of miRNAs
  - ↓ mi-R-29 enhances hepatic fibrosis (i.e. mi-R-29 is anti-fibrotic)
  - Post-translational regulation of transcription factors
    - Acetylation
    - Glycosylation
    - Phosphorylation
    - Prenylation
    - Sumoylation

❖ Pancreas

- Insulin resistance
  - Obesity
    - ↑ serum insulin
    - ↑ serum lipid
    - ↑ β cell apoptosis
    - ↑ type 2 diabetes mellitus (T2DM)
    - ↓ Insulin secretion

❖ Muscle

- ↓ Mitochondrial function
- ↓ VO_2 max
- ↑ Insulin resistance

❖ Macrophage immune system

- In obesity, activation of macrophages/immune system contributes to the development of dysfunctional, insulin-resistant adipocytes that release excessive amounts of FFA and cause insulin resistance and lipoapoptosis in distant tissues (liver, muscle, pancreatic beta cells, vascular bed, other).

Abbreviations: ATP, adenosine triphosphate; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β

LIVER TRANSPLANTATION (LT)

- **Non-GI adverse effects of immune suppression**
  - Commonest adverse effects of immune-suppressive drugs frequently used afterorthotopic liver transplantation.

Adverse Effect	Cyclosporine	Tacrolimus	Glucocorticoids	Azathioprine	Mycophenolate Mofetil	mTOR Inhibitors
Alopecia	-	+	-	+	+	-
Arterial hypertension	+++	++	+++	-	-	+
Bone marrow suppression	+	+	-	+++	+++	++
Dermatitis	-	+ (rash, pruritus)	+	-	-	++ (oral ulcers, acne)
Gastrointestinal** Toxicity	+	+	+	+ pancreatitis	+++ (gastritis and/or diarrhea)	++
Hirsutism and/or gingival hyperplasia	+	-	-	-	-	-
Hyperglycemia and diabetes mellitus	-(?)	+	+++	-	-	-
Hyperlipidemia	++	+	++	-	-	+++
Impaired wound healing	-	-	+	+	+	++
Lymphoma malignancy	++	++	-	?	?	-
Myalgia arthralgia	-	-	+	+	-	++
Nephrotoxicity	+++ (K^+, Mg^{2+})	+++ (K^+, Mg^{2+})	-	-	-	+ proteinuria
Neurotoxicity[a]	++	++	+ psychiatric	-	+ headache	-
Osteoporosis	+	+	+++	-	-	-
Pneumonitis	-	-	-	-	-	+

  - Note that each agent has other specific adverse effects in addition to those listed inthe table. [a]Neurotoxicity includes mainly peripheral neuropathy, headaches, tremor, convulsions,akinetic mutism, and insomnia.

? , Incidence unknown; - not reported; + rarely reported; ++ commonly reported; +++ veryfrequently reported adverse effect limiting usage of the drug.

Printed with permission: Benten D, et al. Nat Clin Pract Gastroenterol and Hepatol 2009;6:1:23-36 (Table 1).

- Gastrointestinal (GI) complications of transplant immunosuppression
  - Infections
    - Bacterial: Yersinia enterocolitica, Clostridium difficile
    - Viral: CMV (especially for MMF), HSV
    - Fungal: Candida albicans, candida tropicalis
    - Parasites: Microsporidia, Strongyloides, *H. pylori* (70% in renal transplant recipients,and 60% in hemodialysis patients)
  - Mucosal injury and ulceration
    - Diarrhea, constipation dyspepsia (especially tacrolimus and MMF)
    - Ulcerations: stress/NSAID ulcers
      - Giant gastric ulcers (>3cm, especially in lung transplant recipients)
    - Diverticular disease: complicated diverticulitis (perforation, abscess, Phlegmon,fistula); especially with polycystic kidney disease
    - Perforations: early, late (especially from diverticulitis or CMV colitis)
  - Biliary tract disease
    - Cholecystectomy (often as an emergency, high mortality rate [MR])
    - Cholelithiasis
  - Pancreatitis
    - 5% in LTx, MR 64%
    - High mortality rate (64%)
  - Liver
    - Acute cellular rejection
    - Acute early cellular rejection of graft occurs in the first few weeks after liver transplantation
    - Chronic rejection occurs in 10% of liver transplant recipients, especially in HCV infection
    - Recurrence of initial condition/retransplantation
    - Post liver transplantation steatosis
      - Steatosis occurs in as many as a third of persons following a liver transplantation (LT), with a histological diagnosis of NASH occurring in about 10% of these persons.
  - Post-transplant diabetes and cardiovascular disease
    - Early after liver transplantation, transient hyperglycemia occurs in 40% of patients,and 9-21% have persistent hyperglycemia (new onset diabetes)
    - Hyperlipidemia occurs in 20-50% of liver transplant patient, with a 2.6x ↑ risk of coronary artery disease (CAD) and 20% of deaths occurring 3 yr after liver transplantation coming from CAD

BILIARY TREE AND GALLBLADDER

GALLSTONES (CHOLELITHIASIS)

- Types
  - Composition
    - Cholesterol
      - Crystals of cholesterol monohydrate
      - Calcium bilirubinate
      - Calcium carbonate / phosphate
    - Pigment
      - Calcium bilirubinate
    - Mixed
    - Rare
      - Calcium carbonate
      - Calcium-fatty acids
  - Site
    - Intrahepatic
      - Brown pigment
    - Gallbladder
      - Cholesterol >> black pigment
    - Bile duct
      - Mixed
  - Physical state of cholesterol
    - Low concentrations
      - Monomers of bile acids (BA)
    - Critical micellar concentration (CMC)
      - Simple micelles are spontaneously formed with BA monomers
        - Small (~ 3 nm diameter)
        - Disk-like macromolecular aggregates
        - Solubilize and incorporate
      - Cholesterol
      - Phospholipids (mostly lecithin, with some phosphatidylethanolamines and sphingomyelin) to form mixed micelles (~ 4-8 nm diameter)
    - Biliary vesicles
      - Secreted by hepatocytes
      - Composed of cholesterol monohydrate crystals and phospholipids
      - Large (40-100 nm diameter)
      - Multilamellar spherical structures
      - As the gallbladder (GB) absorbs H_2O, the GB bile becomes concentrated
      - The stability of the biliary vesicles determines the stability of bile molecular rearrangements for example, at high concentrations of BA, there are the biliary vesicles may transform into mixed micelles

➢ Pathophysiology

- Gallstones are usually formed from cholesterol, bilirubin, or a mixture of the two.
- The steps leading to bilirubin gallstones will be covered in the next section on bilirubin metabolism.

- Genetic (Formation of cholesterol gallstones)

  - A number of observations suggest that there may be genetic factors leading to an ↑ risk of gallstones. These include studies in:
    - First Nations (Indigenous) persons
    - Siblings with gallstones
    - Monozygotic twins with gallstones
    - Relatives of index persons with gallstones

  - Abnormalities associated with the formation of cholesterol (CH) gallstones

− ↑ hepatic uptake of HDL-C	▪ CETP (cholesterol ester transfer protein)
− ↑ intestinal CH absorption and ↑ hepatic VLDL synthesis	▪ Apolipoprotein (APO) E and B gene polymorphisms
− 7α-hydroxylase (CYP7A1) gene variant	▪ ↓ conversion of CH (cholesterol) to BA (bile acids) in the "neutral" pathway
− ↓ Phospholipid secretion	▪ ABC B4 (aka MDR3 [multidrug resistant gene 3]) missense mutation of phosphatidylcholine (PC) transporter in hepatocyte CM ▪ ↓ CYP7A1 ▪ ↑ HMG-CoA reductase ▪ ↓ bile PC (phosphatidylcholine) ▪ ↑ bile cholesterol
− ↑ CH secretion	▪ Variant of ABCG5/-G8 on CM of the hepatocytes
− Aberrant splicing of CCK-IR (cholecystokinin-1 receptor)	▪ ↓ gallbladder motility

  - There are over a dozen genes and gene predicts that have been identified (please refer to Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Saunders/Elsevier, Philadelphia, 2020, chapter 65, for a lot of Human Cholesterol Gallstone [LIH] gene and gene Products).

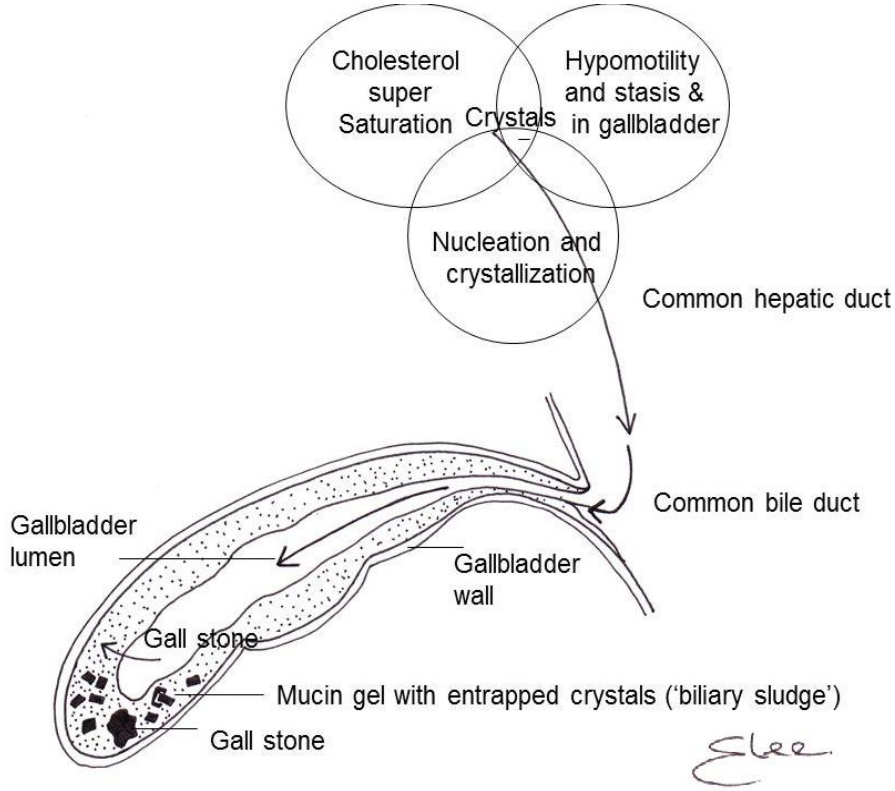
- Cholesterol handling by the hepatocyte is determined by the following:
  - CH uptake across the sinusoidal membrane (SM) from LDL, HDL
  - Chylomicron remnant (CMR) secretion of
    - CH across SM in VLDL back into portal blood
    - As CH in N-HDL (nascent HDL), using ABCA1
  - Metabolism
    - De Novo synthesis of CH from acetate, through HMG-CoA reductase
    - Esterification of CH to cholesterol ester (CE) by way of ACAT
    - 7α-hydroxylation of CH to bile acids (BA) by
      - CYP7A1
      - CYP27A1
  - Transfer of CH across AM by ABCG5/-G8

Abbreviations: ACAT, acyl-coenzyme A: cholesterol acyltransferase; CM, canalicular membrane of hepatocytes; CMR, chylomicron remnants; CYP27A, 27-hydroxylase ("acidic" pathway); CYP7A1, cholesterol 7α-hydroxylase ("neutral" pathway); HDL-L, high-density lipoprotein; HMG CoA, 3-hydroxyl-3-methy glutaryl-coenzyme A; LDL, low-density lipoprotein; SM, sinusoidal membrane of hepatocytes; VLDL, very-low-density lipoprotein

- Liver

➢ Role of the liver in the control of cholesterol homeostasis

- HMG-CoA reductase controls the rate of synthesis of cholesterol in the hepatocytes.
- CH is also taken up across the hepatocyte sinusoidal membrane (SM), mixed with synthesized hepatic cholesterol, and exits the hepatocyte across the canalicular membrane (CM) and into the ductules, as part of the EHC.
- The major means of eliminating cholesterol from the body is by their hepatic conversion to bile acids, acting through the activity of 7α-hydroxylase.
- Other routes of elimination of small amounts of CH from the body includes
  - Synthesis of steroid hormones
  - Sloughing of skin and intestinal epithelial cells
  - Loss in the bile
  - Loss in the feces.
- If the concentrations of bile acids, cholesterol, phospholipids or bilirubin are abnormal in the bile, the lipids may be insoluble.
- The bile becomes "lithogenic"; lipid becomes insoluble in bile, and gallstones are formed.
- Conditions required for cholesterol stones to form, may be
  - Too much cholesterol in the bile, or
  - Too little bile salt to solubilize the cholesterol.



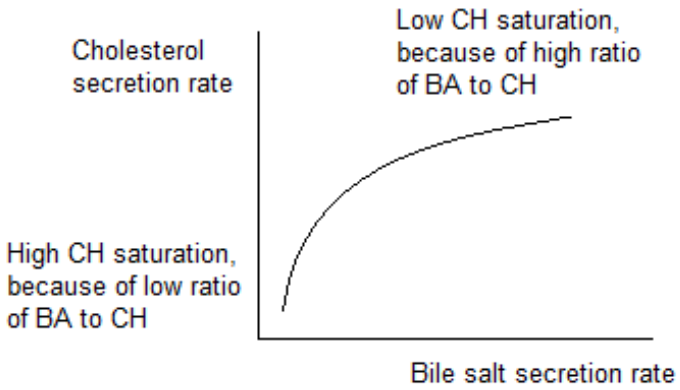
- Gallbladder
- ↓ motility
  - Contractile of gallbladder (GB)
    - ↑ parasympathetic
    - ↓ sympathetic
  - ↑ fasting residual GB volumes
  - ↓ response to cholecystokinin (CKK)
  - Likely important in patients with cystic fibrosis (CF), pancreatic insufficiency

- Mechanisms leading to “hypomotility” by which the gallbladder contributes to the formation of gallstones.
    - Fasting period
        - ↑ volume
        - ↑cholesterol absorption (“loss of capacity for selective absorption of biliary cholesterol and phospholipids”) by GB

        → ↑ stiff sarcoplasmic membranes
        → ↓ activation of G-proteins in muscularis propria
        → ↑ storage of CE
        → ↑ inflammation and proliferation
        → ↓ motility

- Cholesterol Supersaturation and Lithogenicity of Bile.

The formation of bile saturation with cholesterol which may occur normally with fasting.



Abbreviations: BA, bile acids; BS-S, bile salt secretion rate; CH, cholesterol; CH-S, cholesterol secretion rate

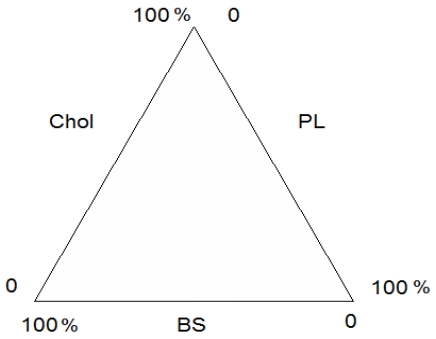
- Sludge
    - Cholesterol monohydrate crystals, Ca bilirubinate, mucin → radiolucent cholesterol stones
    - Black stones – hypersecretion of bilirubin conjugates into bile
        - Hemolysis
        - Cirrhosis
    - Pigmental gallstones are seen in patients with chronic hemolytic anemia, liver disease, and with total parenteral nutrition (TPN) feeding.

- Food
    - With fasting, the secretion rates of bile salts (BS) and cholesterol (CH) are both low, but there is proportionally more CH (ratio of BA /CH is low, so there is CH saturation → “sludge” from lithogenic bile)
    - As bile salt secretion rate and flow increase with feeding, there is proportionally more BA than CH ratio of BA / CH is high, and the CH is solubilized.

- Postprandial
  - ↓ binding of cholecystokinin (CCK) to CCK-1 receptors
  - ↓ emptying continues bile supersaturation
  - ↑ post-emptying (residual) volume
- Interdigestive
  - ↓ filling
  - ↑ lithogenic hepatic bile enters duodenum
  - ↓ cholesterol solubilization
- ↑ mucin glycoproteins
  - Binds CH, PL, BA
  - ↑ nucleation factors
  - ↓ anti-nucleation factors
  - ↑ vesicles fusion / aggregation
  - ↑ mucin in lithogenic bile

- Lithogenicity of bile
  - ↑ hepatic secretion of cholesterol (lithogenicity and supersaturation)
  - ↓ cholesterol solubility
  - ↑ cholesterol nucleation and crystallization
  - Intestinal factors (EHC), e.g., altered, ↓ luminal bile acid concentration
  - ↓ gallbladder motility ("hypomotility")
  - Genetic factors, including LITH (lithogenic) genes
  - The lithogenicity of bile is finally determined by the molar % of cholesterol (CH), phospholipids and bile acids. The amount of CH available for transport across the sinusoidal membrane (SM) of the hepatocyte is determined by a balance between entry of CH across SM, exit across the SM (the sinusoidal membrane), metabolism in hepatocyte cytosol, and exit across the canalicular membrane (CM).
  - In the presence of nidation factors, nucleation and crystalization occurs, and over time, gallstones form.
  - Nucleation and crystallization of cholesterol in bile
    - An imbalance of pronucleating and anti-nucleating factors in the gallbladder leads to cholesterol nucleatic and nidation.
    - Cholesterol nucleation and crystallization are initiated in vesicles, so that the stability of vesicles determines their stability in bile.
    - Protein and non-protein factors (accelerate the nucleation and crystallization of cholesterol in bile, leading to the supersaturation of cholesterol and the formation of biliary sludge or cholesterol gallstones).
  - Mucins
    - Hypersecretion of mucins by gallbladder mucosal cells
    - Gel-forming mucins: MUC2, MUC 5AC, MUC 5B
      - ↑ gallbladder mucin, mucin glycoprotein complexes (nidation)
    - Form disulfide-stabilized aggregates of mucin gels which bind to lipids, bilirubin, Ca^{2+}
    - Create a scaffolding to hold crystals of cholesterol
    - Mucin gel of glycoproteins and calcium bilirubinate provide a surface for nucleation
    - Nucleation proceeds with cholesterol monohydrate crystals plus the mucin matrix

- Bile composition
  - ↑ bile lipid > 3 g/dl
  - ↑ hydrophobicity of bile salt pool
  - ↑ bile salt-to-phospholipid (lecithin) ratio
  - ↑ cholesterol-to-lecithin ratio in vesicles
  - ↑ Ca^{2+}
  - ↑ deoxycholate in bile
- ↓ apolipoproteins A I and A II
- ↓unnamed slightly acidic glycoprotein
- Equilibrium phase diagram and triangular co-ordinates



Abbreviations: BS, bile salt; CH, cholesterol; PL, phospholipids

- In normal persons, gallbladder bile may become supersaturated with cholesterol for a short interval during fasting.
  - The components are expressed as moles percent (%)
  - If cholesterol saturation index (CSI) > 1, bile is saturated, and cholesterol can precipitate and form crystals
  - The number of phases in the cholesterol (CH)-, phospholipid (PL, lecithin)-, mixed bile salt (BS) system is shown.
  - If cholesterol saturation index (CSI) is > 1, bile is saturated, and cholesterol precipitates and form crystals
  - The maximal solubility of cholesterol is determined by the relative molar percentages of cholesterol, phospholipids and bile acids
  - When the bile is supersaturated with cholesterol, unstable unilamellar vesicles form.
  - Multilamellar vesicles then form from the unstable unilamellar vesicles.
  - This allows for the quantification of the degree of saturation of bile with cholesterol
  - This quantification of cholesterol saturation is the CSI (cholesterol saturation index), aka the lithogenic index
  - Examples of CSI
    - < 1, unsaturated
    - 1, saturated
    - > 1, supersaturated (↑ risk of forming gallstones)

- Small Intestine
  - Cholesterol
    - ↑ intake
    - ↑ efficiency of absorption
  - Bile acids
    - ↓ transit time
      - ↑ gram + anaerobic bacteria → ↑ 7α-dehydroxylase activity
      - ↑ conversion of 1° cholic acid to 2° deoxycholic acid
      - ↑deoxycholic → ↑ lithogenicity of bile
    - ↓ ileal absorption
    - ↓ hepatic synthesis / secretion of bile acids
    - Interruption of enterohepatic circulation (EHC)
      - Disorders of liver
      - Biliary tract obstruction
      - Ileal resection
      - Small intestine bacterial overgrowth
      - Bile acid binding drugs

GALLSTONE DISSOLUTION

- UDCA (ursodeoxycholic acid) to prevent stone formation
  - Gallstones are frequent after bariatric surgery, when the patient is on a very low-calorie diet.
  - As a result, there is
    - ↑ liver synthesis of cholesterol
    - ↑ gallbladder (GB) mucin
    - ↓ GB motility
  - Giving UDCA prophylactically reduces gallstones from ~30%
- Criteria for use of UDCA
  - Functioning gallbladder on HiDA scan
  - Radiolucent stones
  - Patent cystic duct
  - Dissolution rates depend upon size of stones

Size, mm	Rates
< 5	70%
< 10	49%
>10	29%

- Recurrence of stones when stopping UDCA after initial successful dissolution, 50% in 5 yr
  - Current indication
    - Use to prevent development of cholelithiasis in high-risk persons (e.g., bariatric surgery, short bowel syndrome)
    - ↓ risk of biliary pain and acute cholecystitis, even without dissolution of stones
    - Safe to use in pregnancy

PANCREAS

PANCREATIC SECRETION

- Acinar and Ductular Secretion

➢ Acinar cells

- Digestive enzymes
  - Lipids
  - Protein
  - Carbohydrate
- Prevention of autodigestion
- Basal and stimulated secretion
- NaCl and H_2O secretion

➢ Duct cells

- Alkaline fluid and H_2O secretion
- Glycoproteins (mucins)

- Basal Secretion of Enzymes During Fasting

➢ Basal Secretion	○ Low	– MMC I
	○ Increases	– MMC II, III
	○ Low again	– MMC IV
➢ Cyclic pattern	○ MMC I – IV	– Sympathetic
		– Parasympathetic
	○ MMC II, III	– CCK

Abbreviation: CCK, cholecystokinin; MMC, migrating myoelectric complex

- Pancreatic Acinar Cell Regulated Secretion of Fluid: Secretin
  - Secretin
    - Gastric H^+ in duodenum → act on duodenal S cells → ↑secretin release
    - Secretin → stimulation of H_2O and HCO_3^- from pancreatic duct cells
    - Duodenal contents need to be alkalinized to provide
      - Full activity of secreted pancreatic digestive enzymes
      - Activate of proenzymes to active enzymes (e.g. trypsinogen)
      - Optimal solubilization of luminal contents

- Stimulated (Regulated) Secretion of Pancreatic Enzymes by Acinar Cells

➢ Phases
- Cephalic (10% to 20%*)
  - Ach
  - GRP
  - VIP
- Gastric (50% to 80%)
  - Ach
  - Gastrin
- Intestinal (~20 %)
  - CCK
  - Secretin

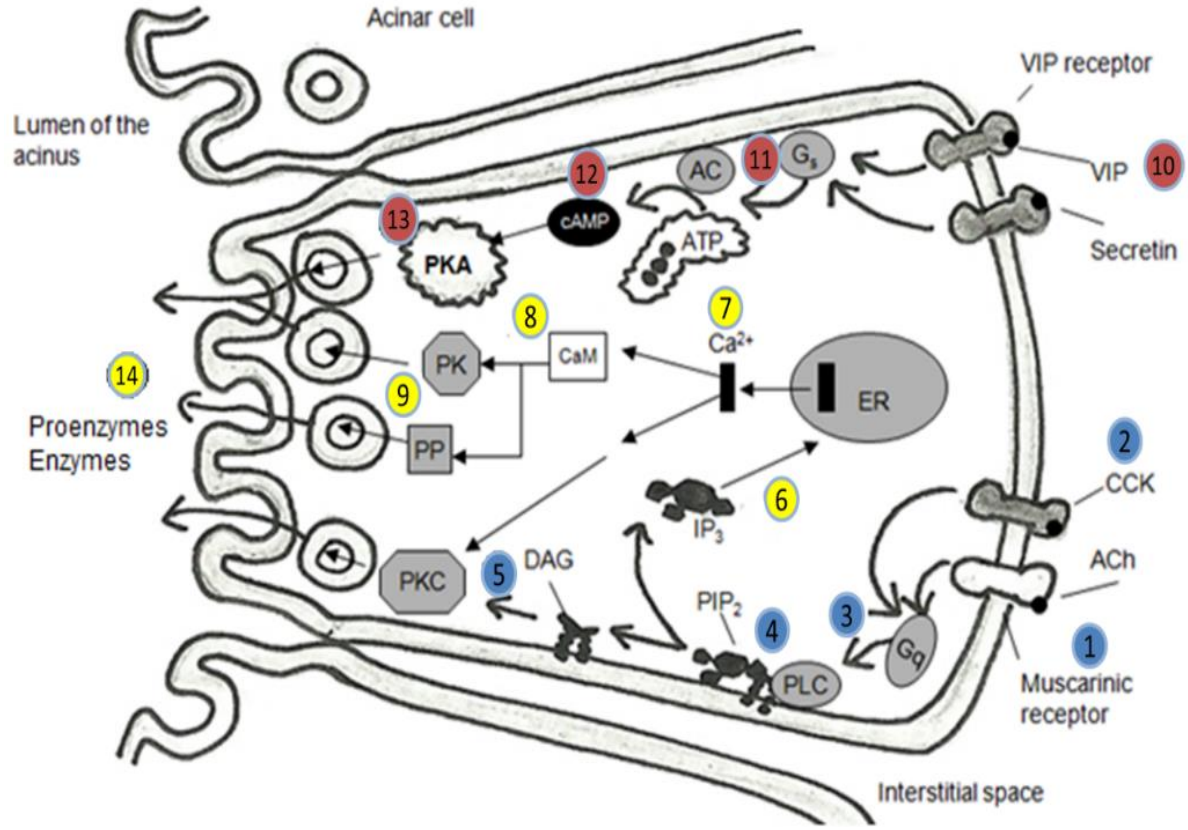
➢ Regulated secretion
- 5-10 x > basal secretion

*% of daily pancreatic enzyme secretion

Abbreviations: Ach, acetylcholine; CCK, cholecystokinin; GRP, gastrin-releasing peptides; VIP, vasoactive intestinal peptide

- Pancreatic Acinar Cell Regulated Secretion of Enzymes: Cephalic Phase
  - DVC (Dorsal vagal complex)
    - Hypothalamus
    - Mammillary bodies
  - Vagal efferents
    - Activated
  - Pancreatic ganglia release
    - Acetylcholine (Ach)
    - Gastrin releasing peptide (GRP)
    - Vasoactive intestinal peptide (VIP)

- The Pancreatic Acinar Cell Secretion of Protein (Enzymes and Proenzymes)



Adapted from: Boron Walter F. and Boulpaepemile L. *Medical Physiology*, Second Edition,. 2009; page 916.

- Stimulation and Intracellular Events of Pancreatic Secretion of Proenzymes/Enzymes: Ach to PKC
  - Ach binds to muscarinic 3 (M3) receptors on acinar cell (1).
  - CCK binds to CCK receptor (CCK-R) on acinar cells (2).
    - CCK-R subject to desensitization
  - Ach-M3 plus CCK-R stimulate Gq (3).
  - Gq forms Phospholipase C (PLC) (4).
  - PLC acts on PIP_2 to form DAG and IP_3
  - Diacylglycerol (DAG) acts on PKC (5).

- IP_3 to S-R / VIP-R
  - IP_3 acts on endoplasmic reticulum (ER) (6).
  - ER causes ↑ Ca_i^{2+} (7).
  - ↑ intracellular calcium ion (Ca_i^{2+}) acts on calmodulin (CAM; 8).
  - CaM acts on protein kinase (PK) and PP (9).
  - Intestinal phase of pancreatic enzyme secretion:
    - Secretin and vasoactive intestinal peptide (VIP)
    - Bind to their receptors (10) on the basal membrane (BM) of the acinar cells

- cAMP to ZGM
  - S-R and VIP-R activate Gs to stimulate adenyl cyclase (AC; 11).
  - AC acts on ATP to form ↑ cAMP (12).
  - Cyclic AMP (cAMP) activates PKA (13).
  - The protein kinase (PK) A, PK, PP and PKC alter the phosphorylation of structured and regulatory proteins to insert the zymogen granule membranes (ZGM) into the apical membrane (AM) of the acinar cell (14).

- AA, RER, SV, GC
  - Amino acids (AAs) in the portal blood (PB) are taken up by acinar cells.
  - Rough endoplasmic reticulum (RER) in acinar cells synthesize enzymes and proenzymes.
  - Small vesicles (SV) containing pancreatic enzymes are formed in RER.
  - Pancreatic transcription factor (PTF-1) binds to pancreatic consensus element (PCE).
  - SV leave RER and traffic to Golgi complex (GC).

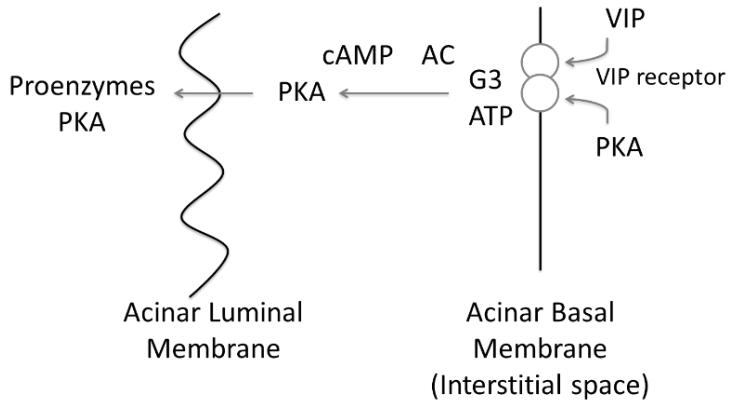
- ZG Insertion into Acinar Membrane
  - Large membrane bound “condensing vacuoles (CV)” form in Golgi.
  - The pancreatic enzymes leave the Golgi in membrane-bound “zymogen granules (ZG)”.
  - ZGs containing the pancreatic enzymes / proenzymes traffic to inner side of membrane of side of acinar cell.
  - Most ZG traffic to and bind to inner side of acinar membrane.

- Release of Zymogen Granules Enzymes Into Intralobular Ducts
  - Enzymes in zymogen granule (ZG) are released into lumen of intralobular ducts (IDs) in the pancreas.
  - The membrane of the ZG detaches from the membrane.
  - The acinar cell membrane reseals.

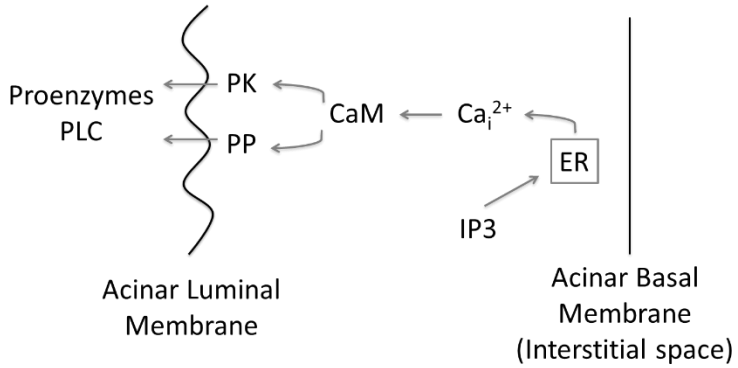
- ZG-T, Autophagosomes and Autolysosomes
  - Zymogen granule minus its membrane becomes an “empty” zymogen granule.
  - The empty zymogen granule traffics back to the Golgi of the acinar cells.
  - New condensing vesicles form, and the system recycles.
- Autophagosomes, Lysosomes and Autolysosomes: Cathepsin Band L
  - Some zymogen granules containing trypsinogen (ZG-T) are not secreted from acinar cell into IDs.
  - ZG-T is taken up by autophagosomes of acinar cells.
  - Autophagosomes fuse with lysosomes, becoming autolysosomes.
  - In the autolysosomes, the granules containing the proteolytic enzymes are degraded by lysosomal enzymes cathepsin B and L.

Abbreviation: ID, intralobular duct

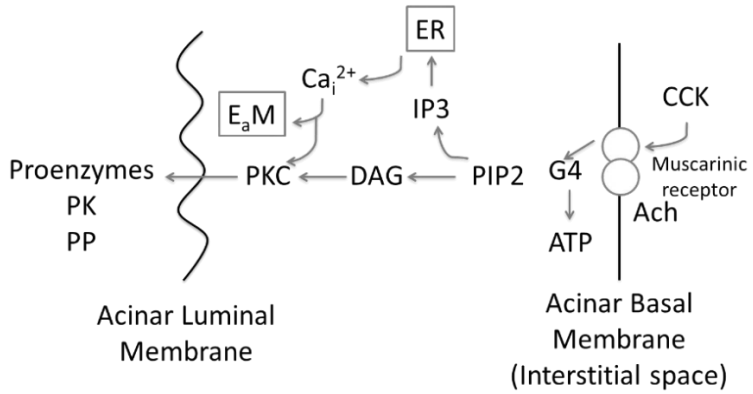
- VIP and Protein Kinase A (PKA)



- Ca_i^{2+}, IP3 and Protein Kinase C (PKC) / Protein Lipase C (PLC)



- CCK, Ach and Protein Kinase (PK) /Protein Phosphatase (PP)



- CCK and CCK-RF
  - CCK
    - Peptides, AA, FA → ↑ mucosal CCK-RF into duodenal lumen → ↑ CCK from duodenal I cells into portal blood
  - Pancreatic acinar cells → Enzymes
  - Pancreatic duct cells → Alkaline fluid (HCO_3^-, H_2O)

Abbreviations: AA, amino acids; CCK-RF, cholecystokinin releasing factor; FA, fatty acids

- Duodenum
  - I cells
    - Release CCK into PV
      - Trypsin insensitive
      - Important in digestive phase
  - Mucosa
    - Release CCK-RF into DL
      - Trypsin sensitive
      - Important in digestive and interdigestive phases
  - During feeding (digestive phase), trypsin is released, CCK-RF is trypsin-sensitive, and thus there is CCK-RF ↓ → ↓ CCK

Abbreviations: DL, duodenal lumen; PV, portal vein

- Intracellular Events of Pancreatic Secretion: Desensitization
  - When acinar cells have been stimulated by peptides such as CCK or VIP, and the hormonal stimulus is removed and then is reapplied, the receptors become desensitized.
  - Because of the desensitization of the CCK and VIP receptors, secretion becomes less than what would have been seen with the initial stimulation.

❖ Let's Review This Difficult Concept Again

- Food
  - Peptides
    - ↑ CCK
  - AAs
    - ↑ trypsin
  - FAs
    - ↑ CCK-RF
- With ↑ trypsin, CCK-RF ↓

- Effects of food on pancreatic acinar enzyme secretion depends on balance between release of
  - CCK by peptides in duodenal lumen
  - Trypsin by amino acids, and its effect on CCK-RF

- Pancreatic Enzymes

Enzymes (secreted in their active form)	Proenzymes
○ Amylase ○ Carboxylesterase ○ DNase ○ Lipase ○ RNase ○ Sterol esterase	• Endopeptidases ○ Trypsinogen – Cationic – Anionic – Mesotrypsinogen – Chymotrypsinogen ○ Kallireinogen ○ Chymotrypsinogen ○ Proelastase • Exopeptidase ○ Procarboxypeptidase A,B ○ Pyrophospholipase ○ Procolipase

❖ A Lot Can Go Wrong in the Synthesis and Secretion of Tryptic Enzymes

- Any block in enzyme from acinar cell secretion →
  - ↑ intracellular ZG
  - ↑ ZG uptake into autophagosomes
  - ↑ autophagosome-lysosome fusion
  - Depletion of adequate lysosomal cathepsin B and L
  - ↑ release of trypsinogen into cytoplasm of pancreatic acinar cells → pancreatitis
  - ↓ degradation of lysosomal enzymes

➢ Clinical Correlations

- Acute Pancreatitis
  - Activation of proenzymes
  - Spillage of active enzymes into pancreatic tissue
  - Autolysis/destruction
- Pancreatic insufficiency
  - Maldigestion/malabsorption
    - Fats, protein, carbohydrates: malnutrition
    - Fat soluble vitamin deficiency
    - Steatorrhea

ACUTE PANCREATITIS

- Definitions
  - Acute pancreatitis is "……an event triggered by sudden pancreatic injury that is followed by sequential inflammatory responses" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 901).
    - Alternate definitions: ...an acute inflammatory process of the pancreas with variable involvement of other regional tissue or remote organ systems" (Feldman M., et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 9th Edition. Saunders/Elsevier, Philadelphia, 2010, page 931).
    - "…best defined clinically by a patient with [or all of the following criteria: (1) symptoms such as epigastric pain, consistent with the disease; (2) a serum amylase or lipase greater than three times a year limit of normal; or (3) radiologic imaging consistent with the diagnosis, usually using computed tomography (CT) or magnetic resonance imaging (MRI) (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Saunders/Elsevier, Philadelphia, 2020, chapter 58).

- Pathophysiology
  - Failure of the normal mechanisms of protecting pancreas from autodigestion by trypsin and the pancreatic proenzymes activated by trypsin.
  - The pancreatic enzymes digest carbohydrates (amylase), proteins and lipids (lipase, phospholipase, colipase, carboxyl ester lipase), and nucleic acids.
  - These are secreted either in an active form, or in an inactive form as proenzymes (endo-/exopeptidases) which require activation by enterokinase and by trypsin.
  - Acute pancreatitis may be caused by or associated with genetic defects which disrupt mechanisms which normally protects the process from trypsin associated injury, and therapy increases the susceptibility of the pancreas.
  - Activation of complement and kinin systems
  - Associated genetic abnormalities
    - $SPINK_1$ (aka PSTI, pancreatic secretory trypsin inhibitor) mutations, resulting in loss of the normal effect of inactivating 20% of trypsin activity.
    - $PRSS_1$ (cationic trypsinogen gene)
  - Associated environmental abnormalities e.g.
    - ↑ serum triglyceride
    - ↑ serum Ca^{2+}

- Disassociation
  - Between continued synthesis but blocked secretion of pancreatic enzymes
  - Enzymes accumulate in acini, causing damage
  - Possible colocalization of pancreatic enzymes in the lysosomes
- Disruption of tight junctions
  - Pancreas: loss of paracellular barrier of acinar cells and intralobular pancreatic duct cells
  - GI tract: ↑ translocation of gut bacteria / lipopolysaccharide
- Microcirculatory changes
  - Vasoconstriction
  - Release of VCAM-1 (an endothelial adhesion molecule)
    - Prostaglandins (PGs)
    - Platelet activating factor (PAF)
    - Leukotrienes
  - Ischemia
  - AV shunting in gut (plus ischemia → GI bleeding)
  - Possible reperfusion injury
- Immune changes
  - Activation of complement and release of C5a
  - Recruitments of PMNs and macrophages
  - ↑ proinflammatory cytokines
  - ↑ mediators of inflammation
    - Arachidonic acid metabolites
    - NO (nitric oxide)

- Acute alcohol-associated pancreatitis
  - Direct effect of alcohol and its “toxic” metabolites on pancreatic acinar cells.
  - ↑ lithogenicity of pancreatic fluid (alcohol-related ↑ secretion and viscosity of pancreatic juice → precipitation of protein (such as GP-2) → formation of pancreatic stone (crystals of calcium carbonate, polysaccharides, fibrillar proteins, and a gel-like matrix)
  - Acute but, sometimes subclinical pancreatitis → scarring of preductular area → stasis of ductules → progression to fibrosis
  - Acute pancreatitis activates trypsin → ↑ inflammation → ↑ cytokines → activates pancreatic stellate cells → fibrosis

HEREDITARY PANCREATITIS

- Definition
  - Hereditary pancreatitis is "……recurrent acute or chronic pancreatitis in an individual from a family in which the pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in an autosomal dominant pattern."
    - Caused by mutations in $PRSS_1$ (cationic trypsinogen) gene
    - Clinical phenotype: recurrent acute pancreatitis
    - Penetrance of genotype to phenotype 80%
  - Familial pancreatitis is "…. pancreatitis from any cause that occurs in a family with an incidence [of pancreatitis] that is greater than would be expected by chance alone, given the size of the family and incidence of pancreatitis within a defined population" (familial may or may not be caused by a genetic defect).
    - Usually caused by
      - SPINK1 mutations, or
      - CFTR – SPINK1 genotypes atypical (homozygous or atypical compound heterozygous.
  - Tropical pancreatitis is "……a form of early age-onset, non-alcoholic chronic pancreatitis occurring in tropical regions what is often clustered among family members, and that has a complex genetic basis."
    - SPINK1 N34S mutations are common
  - Some mutations of CFTR, SPINK1, and PRSS1 genes are associated with acute recurrent or chronic pancreatitis.
  - All patients with such mutations do **not** necessarily develop acute recurrent or chronic pancreatitis.

- Cationic trypsinogen ($PRSS_1$) [protease serine 1]) gene. There are 3 forms of trypsinogen
  - $PRSS_1$ cationic trypsinogen (65%)
    - There are numerous gene mutations in $PRSS_1$.
    - These mutations may be Ca^{2+}-dependent or independent.
    - The main genetic mutations in $PRSS_1$ are $R_{122}H$ and $N_{29}I$ mutations.
    - $PRSS_1$ gene mutation is associated with hereditary pancreatitis.
    - The $R_{122}H$ is a "conversion mutation" which alters the high-fidelity regulatory mechanism of $PRSS_1$.

- The $R_{122}H$ and $N_{29}I$ mutations of $PRSS_1$ result in
  - ↑ activation, or
  - ↓ inactivation
- The switch on/off represents a process to enhance trypsin activity ("gain-of-function").

- $PRSS_2$ anionic trypsinogen (30%); ("CFTR, cystic fibrosis conductance regulator gene")
- $PRSS_3$ mesotrypsin

- PST_1 (aka $SPINK_1$ [serine protease inhibitors Kazal type 1])
  - An acute phase reactant
  - Colocalized in zymogen granules in the pancreatic acinar cells.
  - Secrete with trypsin
  - Presents the premature activation of trypsinogen in the pancreatic acinar cells.
  - Mutations, or polygenic mutation of CFTR- $SPINK_1$ are associated with familial pancreatitis.
  - Acts as the first line defense against prematurely activated trypsinogen
  - Co-mutations such as with CFTR or $PRSS_1$ increase the risk of fibrosis.
  - ↑ $SPINK_1$ with inflammation of pancreas
    - $SPINK_1$ N34S is the commonest $SPINK_1$ mutation
    - $SPINK_1$ mutations lead to less trypsin inhibition.
  - These loss-of-function polymorphisms are important
    - When acute pancreatitis occurs.
    - When there is recurrent premature activation of trypsin (e.g., CFTR or PRSS, mutation).

CHRONIC PANCREATITIS

- Definition
  - Chronic pancreatitis "….. is a process that usually begins with recurrent pancreatitis and ends with immune-related destruction of the pancreas and widespread glandular fibrosis" (Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th Edition. Saunders/Elsevier, Philadelphia, 2020, chapter 59).
  - Chronic pancreatitis displays chronic inflammation as well as fibrosis.
  - The fibrosis of chronic pancreatitis results from immune-mediated process (e.g. TGF-β and IL-10) which activate the pancreatic stellate cells.

- Pathophysiology (alcohol abuse)
  - Direct injury by alcohol or a metabolite
    - Liver
      - Acetaldehyde
    - Pancreas
      - FAEs (fatty acid esters) → ↑ Ca_i^{2+}
  - Oxidative stress
    - Production of free radicals
    - ↑ peroxidation of membrane lipids
  - CCK
    - Alcohol-associated ↑ sensitivity of acinar cells to CCK
    - Redirection of CCK-mediation zymogen granule exocytosis from apical to basolateral membrane of acinar cell.
  - Genes / enzymes
    - Alcohol-associated
      - Altered expression of genes responsive to physiologic stress
    - Over
      - ↑ expression / activity of necrosis / apoptosis
  - Stellate cells
    - ↑ activity of pancreatic acinar cells associated stellate (myofibroblastic) cells
      - ↑ extracellular matrix → ↑ fibrosis → ischemia
      - ↑ proliferation
      - Phagocytosis
    - Alcohol / alcohol metabolites
    - Cytokines (from necrosis of cells)
    - Growth factors (PDGF, TGF-B1)
    - Transcription factors
    - Angiotensin II
    - Autocrine factors
  - Protein (plugs)
    - Alcohol stimulates pancreatic secretion of fluid with ↑ protein, ↓ volume and HCO_3^-

- Gain of function gene mutation, leading to SAPE
  - CFTR (cystic fibrosis transmembrane conductance regulator gene)
  - PRSS1 (cationic trypsinogen gene)
  - SPINK1 (a trypsin inhibitor)
  - These genetic mutations are hypothesized to lead to repeated episodes of acute pancreatitis, which set in motion a process that leads to chronic pancreatitis (SAPE, sentinel acute pancreatitis event)

Abbreviations: Ca_i^{2+}, intracellular Ca^{2+}; CCK, cholecystokinin; PDGF, platelet-derived growth factor; TGF, transforming growth factor

- Pathogenesis of pain (in patients with pancreatitis)
  - Nerves (neuroimmune interaction)
    - ↑ number and diameter of nerves in the pancreas
    - ↑ inflammation around these nerves and ganglia
    - Axons release pain mediators, such as
      - Substance P
      - CERP
      - Glutamate
  - GAP-43 (growth associated protein 43)
    - ↑ NGF (nerve growth factor) and TrkA (NGF receptor)
    - ↑ endogenous proteases
  - CCK
    - ↑ sensitivity of pancreas to stimulation by CCK
    - ↑ duct pressure
    - Redirecting pancreas enzymes to basolateral rather than apical portion of acinar cells

- Factors responsible for the development of **diabetes mellitus** in patients with chronic pancreatitis.
  - Loss of islet cells
    - From chronic pancreatitis disease process
    - From resection of pancreas
    - ↑ amylase → ↑ insulin resistance
  - Hepatic insulin receptors
    - ↓ number
    - ↓ function

INDEX

Note: Page number followed by f and t indicates figure and table respectively.