Cirrhosis

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Cirrhosis

- Damage/scarring of the liver due to continuous insults; common causes
  - Hepatitis
  - Alcoholism
- May see an elevation in INR (liver makes clotting factors) even in patients not on anticoagulation
  - Usually in later stages of disease
- Yellow skin/eyes (jaundice)
- Bruising/bleeding easily
- Swelling/fluid accumulation
  - Particularly in the abdomen (ascites)
  - May also occur in the legs

Edema/Ascites

- Use of aldosterone antagonist (i.e. spironolactone)
- May be used in combo with loop diuretics to remove excess fluid from the body
- Paracentesis if significant fluid accumulation
- Target ratio of furosemide 40mg to spironolactone 100mg to maintain stable K+
- Sodium restriction is often used in combination with drug therapy
- Gynecomastia risk with spironolactone (longer duration/higher dosages)

Hepatic Encephalopathy

- Buildup of toxins in the blood due to the liver's inability to break down waste products
  - Toxins impact the brain
    - Cognitive symptoms (i.e. confusion, lethargy)
- Ammonia (NH3) accumulation can cause CNS effects/changes
- Ballpark normal ammonia – 15-45 mcg/dL
  - Potential drugs that can cause hyperammonemia; carbamazepine, valproic acid

Hepatic Encephalopathy

- Lactulose (Enulose, Generlac)
  - Reduces amount of ammonia potential in the intestine
  - Aggressiveness of dosing usually depends upon tolerability
  - Adverse effects are GI (diarrhea mostly)
  - Target dose to around 3 loose stools per day if possible
- Rifaximin (Xifaxan)
  - Mechanism of Action: Antibiotic effect which kills ammonia producing bacteria in the gut
  - Add on therapy to lactulose if ammonia levels and clinical symptoms are not improving
  - Poor systemic absorption
  - Prevents bacteria from producing byproducts that increase the amount of ammonia
- Neomycin
  - Alternative to rifaximin
  - Less evidence of efficacy
  - Ototoxicity and nephrotoxicity risks

Portal Hypertension

- Increased pressure in portal venous system
- Veins can swell and increase due to this increased pressure
  - Leading to rupture and possible bleed
    - Esophageal varices
- Management of portal hypertension and prevention of esophageal varices
  - Non-selective beta blocker (i.e. carvedilol, propranolol, nadolol)
  - Carvedilol is an option in patients who are asymptomatic (compensated) from their cirrhosis

Diarrhea and Constipation

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Changes in Regularity

- Diet
- Exercise
- Fluid intake
- Drugs
- Disease

Medical Causes of Diarrhea

- C. Diff
- Viral
- Rare bacteria (giardia etc.)
- IBS

Medical Causes of Constipation

- Hypothyroid
- IBS
- Parkinson’s
- MS
- Colon Cancer

Medications that Cause Diarrhea

- Metformin
- Acetylcholinesterase Inhibitors
- Antibiotics
- PPI’s
- GLP-1
- Colchicine
- Laxatives

Medications that Cause Constipation

- Opioids
- Anticholinergics
- CCB’s
- Bile Acid Sequestran
- Calcium/Iron

Diarrhea Treatment

- Identify Cause - Medical, Drug-induced
- Loperamide (Imodium)
  - Mechanism of Action: opioid agonist activity, but limited to the gut at low doses
  - Possibly growing risk for diversion; may get to CNS at extremely high, non-OTC doses
- Diphenoxylate/atropine (Lomotil)
  - Mechanism of Action: (Opioid and anticholinergic action)
  - Atropine helps prevent abuse
  - Controlled substance

Diarrhea Treatment

- Cholestyramine (Questran)
  - Historically a cholesterol medication
  - Can help bulk up stools
  - Lots of binding interactions with other medications that can reduce absorption
- Colestipol (Colestid)
  - Another bile acid sequestrant type medication that was developed to reduce cholesterol but is most often used for diarrhea
  - Constipating (which is what we would use it for)

Constipation Treatment

- Non-drug (fluid, fiber, exercise)
  - Ideal management
- Bulk-forming laxatives – psyllium (Metamucil), methylcellulose (Citrucel), polycarbophil (Equalactin)
  - Multiple doses per day
  - Bloating, gas are primary adverse effects
  - Slow onset of action – may take up to 2-3 days
- Osmotics - polyethylene glycol (Miralax), magnesium hydroxide (Milk of Mag)
  - Mechanism of Action: Draws large amounts of fluid in the GI tract which softens the stool and stimulates more frequent bowel movements
  - Caution with kidney impairment
    - Usually not an issue with as needed/seldom use
  - Rare risk of magnesium accumulation in kidney disease with frequent use (milk of mag)

Constipation Treatment

- Stimulants - sennosides (Senna), bisacodyl (Dulcolax)
  - Mechanism of Action: Promote contraction of the bowel
  - Rarely may cause abdominal pain as adverse effect
  - Quicker onset than bulk-forming laxatives (hours for oral); suppository onset within an hour
- Stool softener (surfactant) - docusate
  - Mechanism of Action: Surfactant that allows water and lipids to penetrate the stool which helps softens the stool
  - Usually well tolerated but efficacy is questionable
  - Less effective than other agents for acute relief of constipation
  - Stimulants and stool softeners often used in combination
    - Especially in patients on opioid therapy

Constipation Treatment

- Lubricants (i.e. mineral oil)
  - Mechanism of Action: Softens/lubricates stool
  - Avoid due to risk of pneumonitis (aspiration risk)
  - Also can prevent absorption of fat soluble vitamins
- Enemas (i.e. Fleets)
  - Mechanism of Action: Similar to Miralax
  - Rectal insertion
  - Rare, but serious - can cause electrolyte disturbances especially in patients with CKD
    - Acute phosphate nephropathy
- Lubiprostone (Amitiza)
  - Mechanism of Action: Calcium channel activator, which promotes fluid entry and secretion into the intestine
  - Nausea is primary adverse effect

GERD

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GERD

- Epigastric pain
  - Contents of the stomach (acid) into the esophagus
- Regurgitation
- Chest pain
- Sore/hoarse throat
- Foreign object sensations in the throat
- In elderly/pediatrics, may see atypical signs (i.e. dry cough)

GERD Management

- Non-pharmacologic options
  - Avoid trigger foods (i.e. spicy, chocolate etc.)
  - Avoid tight clothing
  - Weight loss
  - Frequent, smaller meals
  - Avoiding lying down after eating
  - Elevating the head of the bed

Proton Pump Inhibitors

- PPI's – omeprazole (Prilosec), pantoprazole (Protonix), lansoprazole (Prevacid), esomeprazole (Nexium), rabeprazole (Aciphex), dexlansoprazole (Dexilant, Kapidex)
  - Mechanism of Action: Inhibits hydrogen-potassium ATPase in parietal cells which prevents gastric acid secretion
  - Generally dosed 30-60 minutes before a meal for maximal effect – bedtime administration is considered less effective
  - May take a few days for max effect
  - Osteoporosis risk
  - B12 and magnesium deficiency possible
  - Trend toward increasing C. diff risk

Proton Pump Inhibitors

- May see twice daily dosing for refractory cases of GERD
- Treat GERD for up to 8 weeks and reassess use due longer term risks associated with PPIs – trial discontinuation recommended per ACG in patients who have fully responded to avoid long term PPI use
  - Attempt to maintain the lowest effective dose in patients who fail trial discontinuations
- Often PPI's get started in a hospital stay and get left on board, make sure they are frequently reassessed
- Higher risk situations like Barrett's, recurrent peptic ulcer disease, severe erosive esophagitis, chronic NSAID or corticosteroid use will be more likely to require long term PPI use

PPI Drug Interactions

- Cefuroxime (concentrations reduced) – all PPI's
- Reduced iron absorption
- Rifampin/St. John's Wort – can reduce concentrations
- Notable interactions with omeprazole/esomeprazole
  - Citalopram max 20 mg daily
  - Clopidogrel (controversial how clinically significant)
  - Pantoprazole and rabeprazole may have less inhibition on CYP2C19
  - Cilostazol (increased concentrations)

Histamine-2 blockers

- Famotidine (Pepcid), cimetidine (Tagamet), nizatidine (Axid)
  - Mechanism of Action: Antagonizes H2 receptors which reduces activity of parietal cells in the stomach; this results in a reduction in hydrogen ions in the stomach and a raising of stomach pH
  - Keep an eye out for dose adjustments in CKD
  - Possible accumulation leading to CNS problems (rare, but more likely in CKD)
  - Not quite as potent as PPI’s
  - Avoid cimetidine due to numerous drug interactions via CYP 3A4

Antacids

- Calcium carbonate (Tums, Rolaids), aluminum hydroxide (Acid Gone, Gaviscon)
- Mechanism of Action: Neutralizes stomach acid, raises pH and can help improve epigastric pain from excessive acid in the esophagus
- Identify patients with frequent use as they should be considered for stronger acid suppressing agents
- Hypercalcemia with calcium based products (rare, likely only with frequent use)
- Binding interactions common
  - Quinolones
  - Tetracycline antibiotics
  - Levothyroxine
- Constipation

Sucralfate

- Sucralfate (Carafate)
  - Mechanism of Action: Creates a film type barrier that coats the stomach and protects it from stomach acid
  - Frequent dosing bothersome for some patients (usually TID or QID)
  - Binding interactions possible
    - Administer other meds 2 hours before giving sucralfate
    - i.e. levothyroxine, warfarin
  - Option in pregnancy

Classic Medication Causes of GI Issues

- Steroids
- Bisphosphonates
- Digoxin toxicity
- NSAIDs
- Metformin
- Acetylcholinesterase inhibitors
- GLP-1
- Antibiotics

Malnutrition and Nutritional Deficiencies

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Malabsorption Disorders

- Lack of absorption of essential nutrients
- Cause
  - GI damage, alteration to GI tract
  - Surgery, Celiac disease, Crohn's
- Symptoms
  - Diarrhea
  - Weight loss
  - Poor growth (kids)
  - Anemia
  - Fatigue
  - Failure to thrive

Contributors to Malnutrition

- Cancer
- Dental Issues
- Restricted diets
- Finances
- Depression
- Taste/smell alterations
- Socially eating
- Alcoholism

Weight Loss – Medication Causes

- Digoxin
- Stimulants
- Acetylcholinesterase Inhibitors
- Diuretics
- *Be aware of timing of medication changes

Replacement of Essential Nutrients

- B12
- Vitamins A, D (most common need for supplementation), E, K
- Iron
- Thiamine
- Folic acid
- Electrolyte replenishment
  - Magnesium
  - Potassium
  - Calcium

Vitamin B12

- Deficiency
  - Can cause cognitive impairment/dementia if severe enough
  - Metformin, PPI's – possible contributors
  - Pernicious Anemia
    - Lack of intrinsic factor
    - GI absorption compromised
    - B12 injections
- Folic acid, iron, B12
  - See anemia

Thiamine

- Supplementation common for alcoholics
- Deficiency
  - Wernicke’s encephalopathy
  - Acute delirium
  - Amnesia

Vitamin D

- Treatment of deficiency
  - Vitamin D 50,000 units weekly X 8 weeks
- Maintenance
  - Vitamin D 50,000 units/month
  - Vitamin D 1,000-2,000 units/day
- Target levels >30 (some may argue a little higher)
- Medication contributors
  - Anticonvulsants (phenytoin, phenobarbital, carbamazepine)
  - Leuprolide

Parenteral Nutrition

- IV nutritional supplementation
- Use oral when possible due to risks
  - Infection risk
  - Electrolyte/fluid abnormalities
  - Hyperglycemia
  - Refeeding syndrome*
  - Liver damage

Refeeding Syndrome

- Body adaptation to replacement of nutrients after starvation period
- Lipids/protein are energy sources in fasting state
  - Shift to carbs with TPN
  - Cells shift to storing/synthesizing fat/protein
    - Requires use of electrolytes
  - Electrolyte deficiencies possible
    - Potassium
    - Phosphorus
    - Magnesium
- Close monitoring of electrolyte/fluid status when initiating TPN

Nausea and Vomiting

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Causes of Nausea and Vomiting

- Chemo
- Gastroparesis
- Motion Sickness
- Drugs
- Infection
- Panic/Anxiety attacks
- Severe Pain
- Migraine
- Pregnancy

CINV – Emetogenic Potential

- High (>90% risk)
  - Cisplatin
  - Carmustine
  - Carboplatin (high dose)
  - Cyclophosphamide (high dose)
  - Darcarbazine
  - Doxorubicin (high dose)
  - Ifosfamide (high dose)
- Moderate
  - Carboplatin
  - Cyclophosphamide
  - Doxorubicin
  - Daunorubicin
  - Irinotecan
  - Cytarabine

CINV

- High emetogenic risk
  - NK1RA + 5HT3 antagonist + dexamethasone + olanzapine
- Moderate emetogenic risk
  - 5HT3 antagonist + dexamethasone (+ NK1R antagonist if carboplatin based)
- Low emetogenic risk
  - Either 5HT3 antagonist or dexamethasone or prochlorperazine (or other phenothiazine)
- Other options
  - Metoclopramide
  - Benzodiazepines (anticipatory nausea and vomiting)

Challenges

- Huge diagnostic differential
- Polypharmacy
- Easy to treat symptoms and hard to identify cause

Classic Medication Causes of Nausea/Vomiting

- Antibiotics
- Acetylcholinesterase inhibitors
- GLP-1
- Digoxin toxicity
- Opioids
- Metformin
- NSAIDs
- Iron
- Antidepressants
- Alcohol

Medications for Nausea/Vomiting

- Serotonin receptor antagonist (5HT-3)
  - Mechanism of Action: 5HT-3 blockade likely reduces activity in the chemoreceptor trigger zone in the brain which plays a role in nausea/vomiting sensation
  - Ondansetron (Zofran), palonosetron (Aloxi), granisetron (Kytril), dolasetron (Anzemet)
  - QT prolongation risk especially when used with other prolonging agents (i.e. amiodarone)
  - Possible increase in serotonin syndrome risk

Medications

- NK1 Receptor Antagonists
  - Mechanism of Action: Inhibition of neurokinin 1 receptor which can help promote antiemetic activity
  - Aprepitant (Emend), rolapitant (Varubi), netupitant/palonosetron (Akynezeo)
  - Often used to augment ondansetron class of drugs and corticosteroids in chemotherapy caused nausea and vomiting
  - Hypersensitivity reaction possible but rare

Dopamine Antagonists

- Metoclopramide (Reglan)
  - Mechanism of Action: Inhibition of gastric smooth muscle relaxation by blocking dopamine receptors
  - Potential cause of Tardive Dyskinesia
    - Abnormal involuntary movements
    - May be unmasked by dose reduction or discontinuation (especially abrupt reductions after long term use)
  - Can exacerbate Parkinson's and other movement disorders because of the dopamine blocking effect
  - Hyperprolactinemia
- Prochlorperazine (Compazine)
  - Technically classified as an antipsychotic
  - Often used for nausea/vertigo
  - Dopamine blockade - Side effect profile similar to antipsychotics
- Chlorpromazine (Thorazine)
  - Dopamine blockade - Side effect profile similar to antipsychotics
  - Used for N/V, also may see used for hiccups

Nausea and Vomiting in Pregnancy

- Non-drug interventions
  - Small meals
  - Mild/simple foods
- Pyridoxine – first line medication, excellent safety profile
- Doxylamine
- May see these used, but we try not to
  - Chlorpromazine/prochlorperazine
  - Diphenhydramine
  - Metoclopramide
  - Ondansetron

Collateral Damage - CKD

- Fracture risk
  - Vitamin D deficiency
  - Kidney converts vitamin D to most active form
- Anemia
  - Kidney = source of EPO
- Fluid retention
- CVD
- Elevation in Parathyroid Hormone – See Hyperparathyroidism section
- Hyperkalemia

Preventing Kidney Problems

- Diabetes
  - Blood sugar control
  - ACE inhibitors/SGLT2 Inhibitors
- Hypertension management
- Smoking cessation
- Obesity management

Medications Used In CKD

- Antihypertensives – reduce the pressure on the kidney
  - Antihypertensives – target systolic BP <120 mmHg per KDIGO guidelines
  - See hypertension section for more information on individual agents
- ACE inhibitors/ARB
  - Delay progression of proteinuric kidney disease
  - Can induce acute renal failure, particularly in the setting of renal artery stenosis or use of other meds like NSAIDs

Medications Used In CKD

- SGLT-2 Inhibitors
  - Reduce proteinuria and delay progression of kidney disease in patients with albuminuria (even proven in patients without diabetes)
  - Consider starting in patients with eGFR greater than 20 ml/min
  - May consider continuing an already started agent even if eGFR drops below 20 ml/min
- Calcium Channel Blockers (non-dihydropyridines)
  - May have some benefit on proteinuria
  - Good alternative for hypertension if the patient is unable to utilize an ACE or ARB
  - Dihydropyridines less beneficial to no benefit on proteinuria
- Consider spironolactone in patients with diabetes and CKD who are already taking an ACE or ARB and SGLT2 inhibitor
- Diuretic therapy - fluid overload

Obesity

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Obesity

- BMI >30
- Complications
  - Diabetes
  - Cardiovascular risk
  - Pain/physical complications
  - Sleep Apnea
  - GERD
- Patients are often unrealistic about weight loss and may feel defeated
  - Target 5-10% weight reduction

Options for Treatment

- Diet changes/calorie reduction
- Exercise
- Medications
- Surgery

AGA Clinical Practice Guidelines

- Moderate Evidence
  - Semaglutide
  - Tirzepatide
  - Liraglutide
  - Phentermine-topiramate ER
  - Naltrexone-bupropion ER
- Low Evidence
  - Phentermine
- Avoid - Orlistat

Phentermine

- Stimulant
  - Acts via norepinephrine effects
  - Warnings/precautions regarding patient with cardiac complications/risk
    - Hypertension
    - Atrial fibrillation
  - Insomnia
- Controlled substance
  - Caution/avoid if history of addiction/drug abuse

Topiramate

- Seizure medication/migraines
- Cognitive slowing
- Combination product with phentermine

Naltrexone

- Combined with bupropion
- Opioid receptor antagonist, reduces reward-driven eating behavior
- Common side effects include nausea, headache, constipation, and insomnia
- Contraindicated in uncontrolled hypertension, seizure disorders (bupropion), and chronic opioid use

Bupropion

- Stimulating type antidepressant
- Avoid in seizures
- Smoking cessation benefit
- Combination with naltrexone

Orlistat

- Blocks fat absorption in GI tract
- Relatively safe
- Problematic oily diarrhea if patient has significant fat intake in diet
- May decrease fat soluble vitamin absorption
  - ADEK
  - Supplement with multivitamin may be necessary

Avoiding Weight+ Medications

- Antidepressants
  - Mirtazapine
  - TCA’s
  - Paroxetine
- Sulfonylureas
- Pioglitazone
- Depakote
- Antipsychotics