Pharmacology of Common Liver Diseases and Drug-Induced Liver Diseases

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Nephrology & Hypertension
Oregon State University and Oregon Health & Science University
### Regulatory actions due to DILI (1995-2005)

<table>
<thead>
<tr>
<th>Withdrawals</th>
<th>Second Line</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>bromfenac</td>
<td>felbamate</td>
<td>acetaminophen</td>
</tr>
<tr>
<td>troglitazone</td>
<td>pemoline</td>
<td>leflunomide</td>
</tr>
<tr>
<td></td>
<td>tolcapone</td>
<td>nefazodone</td>
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<tr>
<td></td>
<td>trovafloxacin</td>
<td>nevirapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pyrazinamide/rifampin</td>
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<tr>
<td></td>
<td></td>
<td>terbinafine</td>
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<tr>
<td></td>
<td></td>
<td>valproic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>zifirlukast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>atomoxetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>saquinavir/rifampin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interferon 1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>infliximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(kava, lipokinetix)</td>
</tr>
</tbody>
</table>

[http://www.fda.gov/medwatch/safety.htm](http://www.fda.gov/medwatch/safety.htm)
Hepatitis
inflammation of the liver

• Can have many causes
  – drugs
  – toxins
  – alcohol
  – viral infections (A, B, C, D, E)
  – other infections (parasites, bacteria)
  – physical damage
Alcohol & the Liver

Normal liver
Just add alcohol...
Cirrhosis
Alcohol & the Liver

• Portal Hypertension

“Caput Medusa”
Learn from the mistakes of others. You can't live long enough to make them all yourself...!
Honest...just one drink!!!

- Alcohol content differs in every drink
- There is an equivalent 10 g EtOH in:
  - 12 oz Beer
  - 4 oz wine (none-fortified)
  - 1.5 oz 80 proof (40%) liquor.
Total Per Capita Consumption in Gallons of Ethanol by State

- **1.99 or below (10)**
- **2.00-2.24 (15)**
- **2.25-2.49 (16)**
- **2.50 or over (10)**

Legend:
- **1.99 or below (10)**
- **2.00-2.24 (15)**
- **2.25-2.49 (16)**
- **2.50 or over (10)**
- **DC**
Cumulative Distribution of Alcohol Consumption in the United States

- **65% of the population are drinkers***
- **Males** reported drinking **74%** and **females 26%** of all alcohol consumed
- **73%** of the alcohol is consumed by **10%** of the population

* Individuals who reported drinking at least one drink in past 12-months

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Alcohol use, abuse, and dependence are complex behavioral traits influenced by many factors:

- Genetic and biological responses
- Environmental influences
- Stages of development, from childhood to early adulthood
Treatment
Metabolism

- 2-10% of blood EtOH excreted in lungs, urine, sweat
  - Increased clearance with high blood levels
- 90% metabolism in liver
  - Alcohol Dehydrogenase Pathway (ADH)
    - Microsomal ethanol oxidizing system (MEOS)
      - Highly inducible, (Especially during chronic EtOH)

\[
\text{EtOH} \xrightarrow{\text{ADH}} \text{Acetaldehyde} \xrightarrow{\text{ALDH}} \text{Acetate}
\]
DRUG INDUCED LIVER INJURY
Glucuronyl transferases
sulfotransferases

Acetaminophen → stable metabolites, excretion

CYP2E1, CYP3A4, CYP1A2

Glutathione transferases

NAPQI

↓

Hepatocyte damage
CLINICAL MANIFESTATIONS

• 2 to 12 hours after ingestion
  – nausea, vomiting, diaphoresis, pallor, lethargy and malaise are seen

• 24-48 hrs after ingestion
  – temporary symptomatic improvement
  – Signs of liver involvement begin at this time
    • right upper quadrant pain and hepatomegaly
    • elevations in the LFTs
    • prolongation of the PT

• 72 hours after ingestion
  – Signs of severe hepatic damage become apparent 72 to 96 hours after ingestion
Severity of acetaminophen intoxication  Relationship between plasma acetaminophen concentration (in μg/mL or μmol/L), the time after drug ingestion, and the risk of hepatic toxicity. The thick diagonal line of possible hepatic toxicity represents a 25 percent likelihood of disease. A relatively low level (such as 10 μg/mL) is safe soon after ingestion, but associated with appreciable risk at 24 hours since it reflects a high initial load which has now distributed into the tissues. (Redrawn from Rumack, BH, Matthews, H, Pediatrics 1975; 55:873.)
TREATMENT

- The mainstays of the therapy of APAP intoxication include gastric decontamination with activated charcoal and the administration of N-acetylcysteine (NAC).

- Activated charcoal avidly adsorbs APAP, reducing its absorption by 50 to 90%.

- However, activated charcoal also adsorbs NAC and, by causing nausea and vomiting, may interfere with the administration of NAC.
Dosage for NAC infusion - ADULT

• (1) 150mg/kg IV infusion in 200mL 5% dextrose over 15 minutes, then

• (2) 50mg/kg IV infusion in 500mL 5% dextrose over 4 hours, then

• (3) 100mg/kg IV infusion in 1000mL 5% dextrose over 16 hours
Management of Ascities

- Sodium restriction, diuretics and fluid removal
- Low sodium diet (250 to 500 mg per day)
- Diuretic Therapy - Aldactone, Amiloride, Dyrenium
- A paracentesis (needle puncture of the abdominal cavity) to remove ascitic fluid - reserved for patients with abdominal and respiratory impairment caused by severe ascities. Temporary and reaccumulates
- Peritoneovenous Shunt - provides continuous reinfusion of ascitic fluid into the venous system
Upper GI Bleeding
VARICEAL HEMORRHAGE

- The single most life-threatening complication of portal hypertension

- 1/3 of all patients expirances Variceal Hemorrhage

- Mortality: 25 - 30 % (underlying hepatic functional reserve)
Endoscopic Banding

A

B
Prevention of recurrent bleeding I

- Recurrent variceal bleeding rate > 70%
- **Aim**: recurrent bleeding
- **Definitive treatment**: Pharmacotherapy
  - Chronic sclerotherapy, TIPS,
  - Shunt
  - hepatic transplantation

- **Sequential treatment**: pharmacotherapy or endoscopic therapy
  - TIPS or shunt operation
  - hepatic transplantation
Prevention of recurrent bleeding II

1) Pharmacotherapy:
Propranolol (Nonselective beta-adrenergic blocker)
- heart rate: 25%
- beta blocker + long-acting nitrate: effective than sclerotherapy

2) Endoscopic therapy:
   - Most commonly used
   - Relative Clx: uncontrolled hemorrhage, noncompliant patient
     multiple major episode of rebleeding
     gastric varices or portal hypertensive gastropathy bleeding

3) Transjugular Intrahepatic Portosystemic Shunt (TIPS)
   - definitive treatment
TIPS
Transjugular Intrahepatic Portocaval Shunt
Hepatic Encephalopathy

- **Hepatic Encephalopathy**: spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of *unrelated* neurologic and/or metabolic abnormalities.
- Characterized by personality changes, intellectual impairment, and depressed level of consciousness.

**Clinical Findings:**
- Signs of Advanced Liver Disease
- Diurnal Sleep pattern
- Asterixis
- Hyperreactive deep tendon reflexes
- Decerbrate posturing (less common)
- Focal neurologic defects (less common)

**Lab Findings:**
- ↓K+ ↓Na+
- Elevated Ammonia
- Additional Labs are useful to exclude other causes of brain dysfunction
Precipitating Factors

Precipitating Factors of HE:
Increase Levels of Ammonia:
• Increased Protein uptake
• GI bleeding
• Infection
• Constipation
• Hypokalemic Metabolic Alkalosis
• Renal Failure
• Hypovolemia

Other Causes not related to Increased ammonia:
• Hypoxia
• Sedatives or tranquilizers

Ammonia Production:
► NH3 is produced in the GI tract by via deamination of glutamine and urease activity of colonic bacteria
► The liver clears the majority of portal vein ammonia by converting it to urea or glutamine
Enhance Ammonia Excretion

• **Lactulose: currently first line treatment**
  – Disaccharide that ↑ acidity of the gut thereby promoting formation of NH₃ → NH₄⁺
    • Dose 45-90 g/day goal is 2-3 stools/day, pH<6
    • Can also be given as an enema 1-3L 20% lactulose
    • SE: abdominal cramping, diarrhea, flatulence
    • 70-80% pts found to improve on lactulose

  – Lactitol found to have same efficacy with less adverse effects
Additional Modalities

• **Antibiotics** reduce urease producing bacteria
  – *Rifaximin* more effective than lactulose
  – *Neomycin*: originally thought to be as effective as lactulose, but recent randomized trial comparing it to placebo reported no difference
    • Also associated with ototoxicity and nephrotoxicity, limiting long term use
  – *Metronidazole*, *and Vancomycin*: found to be effective in limited clinical trials and are better tolerated than neomycin.

**All these antibiotics can cause alteration in gut flora leading to bacterial overgrowth, their usage is limited to pts unable to tolerate lactulose.**
## Viral Hepatitis - Overview

### Type of Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source of virus</strong></td>
<td>Feces/Oral</td>
<td>blood/ blood/ blood/</td>
<td>blood/ blood/ blood/</td>
<td>blood/ feces</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shellfish</td>
<td>body fluids</td>
<td>body fluids</td>
<td>body fluids</td>
<td></td>
</tr>
<tr>
<td><strong>Route of transmission</strong></td>
<td>fecal-oral</td>
<td>percutaneous percutaneous percutaneous</td>
<td>percutaneous percutaneous</td>
<td>fecal-oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>permucosal</td>
<td>permucosal</td>
<td>permucosal</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic infection</strong></td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>pre/post-exposure immunization</td>
<td>pre/post-exposure immunization</td>
<td>blood donor screening; risk behavior modification</td>
<td>pre/post-exposure immunization</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>
## Recommended Doses and Schedules of Hepatitis A Vaccine

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>No. Doses</th>
<th>Doses EL.U.* (ml)</th>
<th>Schedule (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children and adolescents</td>
<td>2-18 years</td>
<td>3</td>
<td>360 (0.5)</td>
<td>0, 1, 6-12</td>
</tr>
<tr>
<td>Adults</td>
<td>&gt;18 years</td>
<td>2</td>
<td>1,440 (1.0)</td>
<td>0, 6-12</td>
</tr>
</tbody>
</table>

*ELISA units
Hepatitis B Vaccine Formulations

- Recombivax HB (Merck)
  - 5 mcg/0.5 mL (pediatric)
  - 10 mcg/1 mL (adult)
  - 40 mcg/1 mL (dialysis)

- Engerix-B (GSK)
  - 10 mcg/0.5 mL (pediatric)
  - 20 mcg/1 mL (adult)
Treatment of Hepatitis B

- Interferone 5 M units daily for 16 wks
- Lamivudine (3TC) 100-300 mg daily x 1 yrs
- Famciclovir 500 mg TID
- Adefovir 10 mg daily
Hepatitis C
Hepatitis C virus
Acute infection

15%

Recovery and clearance

85%

Persistent infection

Chronic hepatitis

6%
Liver failure

20%
Cirrhosis

4%
Hepatocellular carcinoma
Treating chronic hepatitis C
10 years of progress

PEG-Intron/Rebetol

% Sustained virologic response

Intron A 24 weeks: 6%
Intron A 48 weeks: 16%
PEG-Intron: 25%
Intron A + Rebetol: 41%
PEG-Intron + Rebetol: 52%
PEG-Intron + Rebetol >10.6 mg/kg: 61%

1991 2001
IL28B Genotype a Strong Predictor of SVR With PegIFN/RBV in Genotype 1 HCV

<table>
<thead>
<tr>
<th>Factor Associated With SVR</th>
<th>Whites (n = 871)</th>
<th>Blacks (n = 191)</th>
<th>Hispanics (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL28B rs12979860 genotype (CC vs TT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HCV RNA (&lt; vs ≥ 600,000 IU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline fibrosis (META VIR F0-F2 vs F3-F4)</td>
<td></td>
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</tbody>
</table>

Drug targets

HCV RNA

Translation

Fusion and uncoating

Polyprotein processing

HCV NS proteins

NS3 NS4A NS5A NS5B

telaprevir, boceprevir, simeprevir

NS3/4A protease inhibitors

RNA replication

NS5B polymerase inhibitors

N55A inhibitors

Sofosbuvir

Ledipasvir

Transport and release

Viral assembly

N55A inhibitors
AASLD and IDSA Guidelines 2014

Genotype 1 Naïve Patients:

Recommended
12 weeks

Sofosbuvir + PegIFN + RBV

IFN ineligible:
Sofosbuvir + simeprevir + RBV

Alternative
24 weeks

Simeprevir* + PegINF + RBV

IFN ineligible:
Sofosbuvir + RBV

*given for 12 weeks only
## Results

<table>
<thead>
<tr>
<th>Response</th>
<th>12-Wk Regimen</th>
<th>24-Wk Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDV–SOF (N = 214)</td>
<td>LDV–SOF + RBV (N = 217)</td>
</tr>
<tr>
<td>HCV RNA &lt;25 IU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 2</td>
<td>174/213 (82)</td>
<td>181/217 (83)</td>
</tr>
<tr>
<td>At week 4</td>
<td>210/213 (98)</td>
<td>207/214 (96)</td>
</tr>
<tr>
<td>At week 12</td>
<td>213/213 (100)</td>
<td>214/214 (100)</td>
</tr>
<tr>
<td>After end of treatment — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 4</td>
<td>211 (99)</td>
<td>213 (98)</td>
</tr>
<tr>
<td>At week 12</td>
<td>211 (99)</td>
<td>211 (97)</td>
</tr>
<tr>
<td>Virologic failure during treatment — no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse — no.</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up — no.</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Withdrew consent — no.</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
COST

• Sofosbuvir 1000/tablet= Total cost: 90K

• Boceprevir $1100/wk – Total $26,000 to $48,000

• Telaprevir $1200/wk – Total ~$49,200 (12wks)

• SOC $600/wk – PEN-INF $500 – RBV $100

PPIs Are Most Effective Drugs For Treatment of GERD

% esophagitis cases healed

Weeks of treatment

PPIs

H₂RAs

Placebo

P < 0.0005

Chiba et al. Gastroenterology 1997
Maintenance of Healing of Erosive Esophagitis (n = 375)

% patients in remission

- Omeprazole 40 mg
- Omeprazole 20 mg
- Omeprazole 10 mg
- Placebo

*P < 0.001 vs placebo

† Indicated dose
# Proton Pump Inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>20 mg Q Daily</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20 - 40 mg Q Daily*</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg Q Daily</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg Q Daily</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg Q Daily</td>
</tr>
</tbody>
</table>

* Most expensive agent
Poton Pump Inhibitors – Kinetics

Given as enteric coated granules in capsule or enteric coated tablets

Pantoprazole also given intravenously

Half life – 1.5 hrs

Since it requires acid for activation - given 1 hr before meals

Other acid suppressing agents not coadministered
Now answer this question

It is given in the previous slides that the half life of proton pump inhibitors is 1.5 hours only and these drugs are generally given once daily. How this can be justified?
Histamine $H_2$ Receptor Antagonist

Reversible competitive inhibitors of $H_2$ receptor

Highly selective,

Very effective in inhibiting nocturnal acid secretion
  (as it depends largely on Histamine)

Modest impact on meal stimulated acid secretion
  (As it depends on gastrin, acetyl choline and histamine)
<table>
<thead>
<tr>
<th></th>
<th>Cimetidine</th>
<th>Ranitidine</th>
<th>Famotidine</th>
<th>Nizatidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>80</td>
<td>50</td>
<td>40</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Relative Potency</td>
<td>1</td>
<td>5 -10</td>
<td>32</td>
<td>5 -10</td>
</tr>
<tr>
<td>Half life (hrs)</td>
<td>1.5 - 2.3</td>
<td>1.6 - 2.4</td>
<td>2.5 - 4</td>
<td>1.1 - 1.6</td>
</tr>
<tr>
<td>Duration of action (hrs)</td>
<td>6</td>
<td>8</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Inhibition of CYP 450</td>
<td>1</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose mg(bid)</td>
<td>400</td>
<td>150</td>
<td>20</td>
<td>150</td>
</tr>
</tbody>
</table>
H$_2$ Antagonists: Side Effects

• Overall, less than 3% incidence of side effects
• Cimetidine may induce impotence and gynecomastia
• May see:
  – Headaches, lethargy, confusion, diarrhea, urticaria, sweating, flushing, other effects
\( \text{H}_2 \) Antagonists: Drug Interactions

- cimetidine
  - Binds with P-450 microsomal oxidase system in the liver, resulting in inhibited oxidation of many drugs and increased drug levels
  - All \( \text{H}_2 \) antagonists may inhibit the absorption of drugs that require an acidic GI environment for absorption
H$_2$ Antagonists:
NP Implications

• Assess for allergies and impaired renal or liver function
• Use with caution in patients who are confused, disoriented, or elderly
• Take 1 hour before or after antacids
• For intravenous doses, follow administration guidelines
H₂ Blockers—Side effects & Interactions

Extremely safe drugs

Cimetidine causes gynecomastia, galactorrhea
(as it is antiandrogenic & increases orolactin level)

Cimetidine inhibits CYP450 & increases conc. of Warfarin, Theophylline, Phenytoin, Ethanol.
Pathogenesis of Stress Ulceration

Gut Mucosal Ischemia

Impaired Defense Mechanisms:
- \( \downarrow \) \( H^+ \) back diffusion
- \( \downarrow \) Mucous/bicarbonate barrier
- \( \downarrow \) Prostaglandin production
- \( \downarrow \) Epithelial renewal

Acid Secretion

H pylori

??

Stress Ulceration

Gastrointestinal Bleed

Pathogenesis of Stress Ulceration
Risk Factors for Major Bleeding

- Coagulopathy (platelets < 50,000 or PT > 16 sec)
- Acute respiratory failure (mechanical vent’n > 24 hr)
- Shock requiring vasopressor therapy
- Burns (> 30% BSA)
- Significant intracranial bleed or trauma
- Spinal injury (immobilization > 24 hrs)
- Bone marrow transplantation
- High dose corticosteroid therapy
- Gastrointestinal bleeding within 12 weeks

Detroit Medical Center Stress Ulcer Prophylaxis Guidelines
Comparison of four different pantoprazole dosing regimens in healthy patients
Median percent time above pH 3.0, 4.0, 5.0, and 6.0.

<table>
<thead>
<tr>
<th>Median % time above</th>
<th>Placebo</th>
<th>40mg bolus every 8 hrs</th>
<th>40mg initial bolus, 4 mg/h infusion</th>
<th>48 mg/hr initial 2 hrs, 8 mg/hr infusion</th>
<th>80 mg initial bolus, 8 mg/h infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 1</td>
</tr>
<tr>
<td>pH 3.0</td>
<td>22</td>
<td>6</td>
<td>49</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>pH 4.0</td>
<td>7</td>
<td>0</td>
<td>20</td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>pH 5.0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>pH 6.0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>
Helicobacter Pylori (PH or HP)
Triple Therapy

The BEST among all the Triple therapy regimen is

Omeprazole / Lansoprazole - 20 / 30 mg bd
Clarithromycin - 500 mg bd
Amoxicillin / Metronidazole - 1gm / 500 mg bd

Given for 14 days followed by P.P.I for 4 – 6 weeks
Short regimens for 7 – 10 days not very effective
Sucralfate

Salt of sucrose complexed to sulfated aluminium hydroxide

In acidic pH polymerises to viscous gel that adheres to ulcer crater

Taken on empty stomach 1 hr. before meals

Concurrent antacids, H$_2$ antagonist avoided

( as it needs acid for activation )
Misoprostol

PGE\textsubscript{1} analogue

Modest acid inhibition

Stimulate mucus & bicarbonate secretion

Enhance mucosal blood flow

Approved for prevention of NSAID induced ulcer

Diarrhoea & cramping abd. pain – 20 %

Not so popular as P.P.I are more effective & better tolerated
## THE IBD COMPARISON

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>ULCERATIVE COLITIS</th>
<th>CROHN’S</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td>wt loss, malnutrition, Smoking improves, extraintestinal manifestations more common (JSEM)</td>
<td>D, Abd pain, wt loss, malnutrition, perianal dz, abd mass, growth failure kids, associated with PSC, smoking makes worse</td>
</tr>
<tr>
<td>SITE</td>
<td>Colon exclusively</td>
<td>Colon, ileum, infrequently other sites</td>
</tr>
<tr>
<td>COMPLICATIONS</td>
<td>Cancer, Fistulas absent</td>
<td>Stricture, Fistula, &amp; cancer, Toxic megacolon absent, Perforation uncommon</td>
</tr>
</tbody>
</table>
IBD Therapy per AGA Guidelines

• Sulfasalazine and 5-ASA
  – mild to moderate CD/UC and maintenance in UC
  – ∅ use sulfasalazine for CD ileitis, instead use 5-ASA compounds such as Asacol or Pentassa
  – Sulfasalazine, not mesalamine, may ameliorate arthropathy in ankylosing spondylitis associated with inflammatory bowel disease
Sulfasalazine (Azulfidine)

Colonic bacterial cleave N=N bond and release 5-ASA

Sulfapyridine causes rash and other side-effects

5-ASA is the active molecule that works topically to decrease inflammation

5-ASA orally will get absorbed immediately and not work in the lower GI system
5-ASA (Mesalamine) Delivery Systems

Details of Mesalamine Delivery Systems

Azulfidine® (sulfasalazine)
Sulfapyridine

Azulfidine
(sulfasalazine)

Pentasa®
(mesalamine)
Controlled-release capsules

Asacol®
(mesalamine)
Delayed-release tablets

Colazal™
(balsalazine disodium)
Capsules

Dipentum®
(olosalazine)

Rowasa®

5-ASA

Microspheres

Eudragit® S

N=N

COOH

5-ASA

N=O

OH

5-ASA

NaOOC

OH

(ABA)

Inert carrier

Slide courtesy of Charles A. Sninsky, MD.

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IBD Therapy per AGA 2006 Guidelines

• Antibiotics
  – Active luminal CD (esp metronidazole)
  – Fistulizing CD
  – Postop recurrence
  – No evidence in UC
  – Pouchitis
  – Infectious complications
Perianal Disease

- Seen only with Crohn’s disease
- Rest of GI tract may have inactive disease
- Treat with antibiotics (Ciprofloxacin, metronidazole)
- Biologics very effective
IBD Therapy per AGA 2006 Guidelines

- **Steroids:**
  - Budesonide: ileal and R sided colonic CD
  - Prednisone: moderate to severe dz, failure of 1st line tx such as mesalamine (UC) or budesonide (CD)
  - Topical hydrocortisone or budesonide for d. colon inflammation
  - Perianal fistulas: steroids not useful
  - IV steroids/hospitalize if severe dz and failure of PO
  - Not recommended as maintenance tx for CD/ UC
  - If unable to taper steroid, this is indication for antimetabolite and/or infliximab
  - Monitor: bone mineral density, ophtho exam, adrenal insuff, glucose intolerance
IBD Therapy per AGA 2006 Guidelines

- Azathioprine and 6-MP:
  - For steroid-dependent IBD in order to attempt to d/c steroids
  - Measure CBC w/diff q2wk during dose adjustment
  - Thiopurine methyltransferase genotype
  - ↓ post-op recurrence in CD
  - Perianal and enteric fistulae
  - Remission maintenance in CD
  - ↓ steroid use in UC
6-MP/Azathioprine Metabolism

AZA → 6-MP → Thioinosinic acid (TIMP) → 6-thioguanine (6-TG)

AZA → 6-MP → 6-MMP

6-MMP → 6-MMP ribonucleosides

6-thiouracil

Xanthine oxidase

non-enzymatic

HPRT

TPMT

TPMT
IBD Therapy per AGA 2006 Guidelines

• Methotrexate:
  – IV MTX for induction in active CD or maintenance of remission in inactive CD
  – Induction w/ steroid withdrawal in active CD
  – Weekly IM MTX is effective for chronic active CD
  – Do not use in pregnancy
  – Insufficient evidence for induction or maintenance in UC
  – Monitor: CBC, LFT
IBD Therapy per AGA 2006 Guidelines

• Mycophenylate mofetil
  – Lack of evidence for efficacy in IBD

• Cyclosporine
  – Induction in UC
  – Efficacy for CD w/ high doses (↑toxicity)
  – Fistulizing CD w/ IV cyclosporine
  – Severe steroid-refractory UC
  – Concomitant steroids used in severe UC
  – Goal to bridge to AZA or 6-MP as maintenance tx
  – ∅ use in luminal CD
  – Fistulizing CD with bridge to AZA or 6-MP
TNF- $\alpha$ Antibodies
IBD Therapy per AGA 2006 Guidelines

- Infliximab (TNF-$$\alpha$$ antibody)
  - CD with inadequate response to conventional tx
  - If used for induction, continue w/ maintenance
  - Fistulizing CD
  - UC patients without adequate response to conventional tx
  - Withdraw or taper concomitant steroids
  - Avoid: active infection, demyelinating d/o, CHF, malignancy, screen for TB