Drug-induced Gastrointestinal Disorders

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40% of adverse drug reactions affect the GI tract, 4% of admissions to hospital are caused by drug induced disorders.
- Impairment of GI defences
- Direct injury to the GI tract
- Changes in colonic bacterial flora
Side effect NSAID on lower gastrointestinal tract

- Produce ulcers in the distal small bowel and proximal colon
- Non specific colitis
- Erosion
- Ulcer
- Diaphragm disease
- Collagenous and lymphocytic colitis
- Pseudomembranous colitis
- Eosinophilic colitis and apoptotic colopathy
- Exacerbate ulcerative colitis and diverticular disease
Non-Steroidal Anti-Inflammatory Drug-Induced Enteropathy

NSAID-induced lower gastrointestinal (GI) complications are increasing while upper GI complications are decreasing.

Lower GI events accounted for 40% of all serious GI events in patients on NSAIDs.

Capsule endoscopy and device assisted enteroscopy are available for detection of small intestinal lesions.

Capsule endoscopy studies have demonstrated that NSAIDs use in healthy volunteers raised the incidence (55% to 75%) of intestinal damage.
NSAID-induced lower GI complications (perforation, bleeding, or obstruction) are increasing while upper GI complications are decreasing.

- The ratio of upper/lower was 4.1 in 1996 and it has decreased to only 1.4 in 2005.

- Small bowel mucosal breaks were induced in 55% of healthy volunteers who had taken naproxen for 2 weeks.
### Table 1. Epidemiology of Non-steroidal Anti-inflammatory Drug (NSAID) Enteropathy

<table>
<thead>
<tr>
<th>Method</th>
<th>Period</th>
<th>Result</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Population based study</td>
<td>1996–2005</td>
<td>Ratio of upper/lower GI complication (bleeding, perforation, obstruction) is decreasing</td>
<td>8</td>
</tr>
<tr>
<td>Double blind trial (etoricoxib vs. diclofenac)</td>
<td>18 mo</td>
<td>Lower GI events accounted for 40% of all serious GI events in patients on NSAIDs</td>
<td>10</td>
</tr>
<tr>
<td>Double blind trial using capsule endoscopy (celecoxib vs. naproxen plus omeprazole)</td>
<td>2 wk</td>
<td>Small bowel mucosal breaks in 55% of naproxen</td>
<td>5</td>
</tr>
<tr>
<td>Double blind placebo controlled trial using capsule endoscopy and fecal calprotectin (diclofenac vs. placebo)</td>
<td>2 wk</td>
<td>Macroscopic injury to the small intestine in 68–75% of diclofenac</td>
<td>4</td>
</tr>
<tr>
<td>Clinical trial using capsule endoscopy (NSAIDs vs. control)</td>
<td>3 mo</td>
<td>Small intestinal mucosal injury at 71% of NSAID users</td>
<td>3</td>
</tr>
<tr>
<td>Double balloon endoscopy registry</td>
<td>2004-2005</td>
<td>NSAIDs enteropathy occurred in half of the patients taking NSAIDs</td>
<td>11</td>
</tr>
</tbody>
</table>

GI, gastrointestinal.
“Three hit” hypothesis

First, NSAIDs solubilize lipids of phospholipids on the mucosal surface, so the epithelial mitochondria are directly damaged.

Second, the mitochondrial damage depletes intercellular energy and leads to calcium efflux and to induction of free radicals, a disruption of intercellular junctions occurs, and mucosal permeability increases in the small intestinal mucosa.

Third, the mucosal barrier becomes weakened, so bile acid, proteolytic enzymes, intestinal bacteria, or toxins can easily penetrate into the epithelial cells, resulting in mucosal injury.

NSAID-induced small intestinal injuries augment through the enterohepatic circulation
Endoluminal NSAID

Combination of biochemical events compromise mucosal cell integrity
COX-1 and COX-2 inhibition (decreased PG synthesis)
Topical effect (mitochondrial uncoupling of oxidative phosphorylation)

Initial damage
Increased intestinal permeability
Increased mucosal susceptibility to damage
Chemotactic events

Enterohepatic circulation

Endogenous aggressors:
Polymorphonuclear neutrophils
Inflammatory mediators

Luminal aggressors:
Bile
Bacteria
Hydrolytic enzymes
Proteolytic enzymes

Secondary damage with
Ulceration and strictures
Blood loss
Protein loss
Enteric coated aspirin was originally designed to decrease adverse effects on the stomach, but the use of enteric coated aspirin may have shifted the damage to the distal small bowel. Low dose aspirin is not safe, and chronic low dose aspirin use induced small bowel enteropathy
NSAID-induced enteropathy is one of the most common causes of obscure GI bleeding.
CE sensitively detects NSAID-induced small intestinal injuries such as red spot, erosion, and ulcer, while NSAID-induced small intestinal injuries are not specific in endoscopic findings and NSAID-induced ulcer is hard to differentiate from other causes of ulcer such as Crohn’s disease
Suppression of gastric acid secretion by proton pump inhibitors is unlikely to provide protection against NSAID-induced damage to the small intestine. **PPIs** have been demonstrated to exacerbate NSAID-induced intestinal damage due to shifts in enteric microbial populations.
diaphragm-like stricture

- Scarring reaction secondary to ulcerative injury
- Thin, concentric, diaphragm-like septa with pinhole-sized lumen.
- Multiple, found mostly in the mid-intestine, but have also been described in the ileum and colon
- Submucosal fibrosis with normal overlying epithelium
- The mucosa between diaphragms is normal
prior to the advent of CE and small bowel enteroscopy, most studies had to rely on surrogate markers such as urinary excretion of chromium-51-labeled ethylenediaminetetraacetic acid, which shows intestinal permeability and fecal level of calprotectin, a proposed marker of intestinal inflammation.

Calprotectin is a 36 kDa calcium-binding protein constituting up to 60% of the cytosolic proteins in neutrophil granulocytes and plays an important role in inflammatory processes. It is excreted in feces and remains stable against bacterial degradation. The presence of calprotectin in feces is a consequence of neutrophils’ migration into the GI tissue.
Capsule endoscopic findings of non-steroidal anti-inflammatory drug enteropathy. There were denuded areas (A), erosions (B, C, D), and multiple variously-shaped well-demarcated ulcers (E, F).
NSAID-induced small intestinal lesions on CE include denuded areas, erosions and ulcers. A denuded area is defined as a reddened area without villi.

classified CE findings into five categories: reddened folds, denuded area, red spot, mucosal break, and blood.
NSAID Ulceration
Capsule endoscopic findings of non-steroidal anti-inflammatory drug enteropathy
TREATMENT AND FUTURE DIRECTION

- Misoprostol appeared to be capable of healing aspirin induced small bowel injury

- Selective coxibs were believed to be less injurious than nonselective NSAIDs in the small bowel as well as in the stomach

- Selective coxibs may not provide complete protection against GI toxicity
PPI have been shown to reduce the incidence of NSAID-induced gastropathy but not enteropathy
NO releasing NSAIDs

- Nitric oxide (NO) is a potent gastroprotective substance that modulates many aspects of GI mucosal defense.

- Hydrogen sulfide (H2S) has been shown to exert protective effects in the GI tract and to accelerate the healing of preexisting ulcers. H2S-releasing NSAIDs, derivatives of naproxen, diclofenac, and indomethacin have been reported.
Colonic ulcers and NSAID

- Direct mucosal irritation and secondary to suppression prostaglandin
- Non-specific colonic ulcer
diaphragm-like stricture right colon
muscularis propria layer is intact, the risk of intestinal perforation is low with endoscopic balloon dilation, which is why it is a preferred treatment modality than surgical intervention
For **nonstricture**d ileocecal lesions, discontinuation of the NSAID is usually followed by prompt improvement. A repeat colonoscopy six to eight weeks later should be performed to confirm partial or complete resolution of ulcerations and/or colitis.

For **strictures** or diaphragms causing obstructive symptoms, through-the-scope (TTS) balloon dilatation should be performed if they are endoscopically accessible. However, diaphragm-like strictures tend to be multiple, and resection of the involved intestinal segment may be required.
A 77-year-old male presented with a 10 day history of watery diarrhea without any blood, mucous or abdominal pain.

His past medical history included malignant hypertension, renal transplant for chronic renal failure, AF.

All his medications including warfarin, doxazosin, bisoprolol, allopurinol, aspirin, atorvastatin, lercanidipine, cyclosporine and prednisolone were longstanding except mycophenolate mofetil started 2 months ago.
1. Hemorrhagic polypoidal lesion at the cecum
showing extensive areas of necrosis and ulceration of the epithelium.

disrupted and withered glands.

congested blood vessels, cryptitis and withered glands.
Drug induced ischemic colitis

- Ischemic colitis can occur in patients with atherosclerosis, vasculitis, hematological disorder, dyslipidemias and cardiac arrhythmias. Various drugs (like cocaine, estrogens, danazol, vasopressin, methamphetamine, non-steroidal anti-inflammatory drugs and psychotropic drugs
Mycophenolate mofetil

- Afebrile diarrhea the commonest gastrointestinal symptom in these patients (30%)
- Reports of upper gastrointestinal tract bleed (due to gastric or duodenal ulceration), large bowel perforation and pancreatitis have been reported
- Mimicking ischemic colitis, inflammatory bowel disease or graft versus host disease (GVHD)
- It can also produce duodenal atrophy similar to celiac disease
**Common drug causes of constipation and diarrhoea**

**Constipation**
- Drugs with antimuscarinic effects (e.g. atropine, phenothiazines, tricyclic antidepressants)
- Opioids
- Mebeverine
- Peppermint oil
- Aluminium-containing antacids
- Sucralfate
- *Gaviscon*
- Iron
- Laxatives (chronic)

**Diarrhoea**
- β-blockers
- Misoprostol
- Antibiotics
- Magnesium-containing antacids
- Olsalazine
- Mefenamic acid
- Iron
- Laxatives (acute)
- Metformin
- Angiotension-converting enzyme inhibitors
- Statins
Constipation

- Antimuscarinic drugs and opiates are the main causes of drug induced constipation.
- Reduced bowel frequency (fluoeextin, mebeverine, peppermint oil).
- Drug-induced megacolon (vincristine).
Melanosis coli

- Anthranoid laxatives (e.g., cascara sagrada, and senna)
- usually develops 9 months after initiating the use of these drugs and disappears just as quickly after the drug is discontinued.
- possibly increases the risk of colonic cancer
Cathartic Colon

- Anatomic and physiologic change in the colon that occurs with chronic use of stimulant laxatives (> 3 times per week for at least 1 year).
- As fluid and electrolyte imbalance, steatorrhea, protein-losing gastroenteropathy, osteomalacia, and vitamin and mineral deficiencies.
- When the drug is discontinued, radiographic and functional changes in the colon may only partially return to normal because of drug-induced neuromuscular damage to the colon.
Diarrhoea

- *Clostridium difficile*-associated diarrhea (CDAD). Clindamycin, ampicillin, amoxicillin, and the cephalosporins.
- Microscopic colitis (NSAID, acarbose, ticlopedine, simvostatin, ppi, serterline, ...)
- Bile acids, which have a direct irritant action in the colon
- β-blockers, which act by antagonizing antiperistaltic, adrenergic stimulation
- Bisoprostol, which stimulates intestinal secretion and
- Motility
- Magnesium-containing antacids
Malabsorption

- Tetracycline chelates calcium, cholestyramine binds iron and vitamin B12, mineral oil reduces the absorption of carotene and fat-soluble vitamins, thiazide diuretics impair ileal transport of sodium, and aluminum/magnesium hydroxide precipitate calcium and phosphate ions.
- Colchicine, neomycin, methotrexate, methyldopa, and allopurinol interfere with absorption of nutrients by causing mucosal damage.
Exacerbation of ulcerative colitis

- In patients with inflammatory bowel disease, the possibility of drug-induced diarrhoea caused by olsalazine or azathioprine, and disease relapse caused by paracetamol or NSAIDs, requires careful consideration.
- Diarrhoea caused by b-blockers is common and often not appreciated by prescribers.
- Prescribers of H2-antagonists and proton pump inhibitors should be aware of the possibility of enteric infections.
Drugs that cause colitis

Antibiotics
Amoxicillin
Ampicillin
Clindamycin
Erythromycin
Cephalosporins

Drugs causing ischaemic colitis
Oral contraceptive pill
Chemotherapeutic agents — 5-fluorouracil, cisplatin danazol
Vasopressin
Clindamycin

Miscellaneous
NSAIDs
Methyldopa
Penicillamine
Gold (oral)
Novel oral anticoagulants in gastroenterology practice

- Instead of reducing the effective levels of multiple coagulation factors, the NOACs specifically target either factor Xa or factor IIa (thrombin), thereby attenuating thrombosis
- NOACs are approved for stroke prevention in AF
Rivaroxaban and apixaban, which target factor Xa

Dabigatran targets Thrombin
Rivaroxaban and dabigatran are associated with an increased risk of major GI bleeding compared with warfarin, and dabigatran is associated with an increased risk of non-bleeding upper GI symptoms such as dyspepsia and heartburn.
<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>NOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Food and drug interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Therapeutic window</td>
<td>Narrow</td>
<td>Wide</td>
</tr>
<tr>
<td>Need for routine monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Site of elimination</td>
<td>Hepatic</td>
<td>Renal and hepatic</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Reduces synthesis of factors II, VI, IX and X</td>
<td>Directly inhibit factor Xa or thrombin</td>
</tr>
<tr>
<td>Time to peak onset</td>
<td>Days</td>
<td>Hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>&gt; 36 hours</td>
<td>9-17 hours</td>
</tr>
<tr>
<td>Need for “bridging”</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td>Approved indication (USA)</td>
<td>Valvular and nonvalvular AF</td>
<td>Nonvalvular AF Prevention and treatment of VTE</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes (vitamin K, FFP, PCC)</td>
<td>No</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes (PT, INR)</td>
<td>Yes (PT, aPTT, anti-Xa, Hemoclot)</td>
</tr>
</tbody>
</table>

NOAC, Novel oral anticoagulant; AF, atrial fibrillation; VTE, venous thromboembolism; FFP, fresh-frozen plasma; PCC, prothrombin complex concentrate; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time.
<table>
<thead>
<tr>
<th></th>
<th>Bioavailability</th>
<th>Active anticoagulant present in GI tract</th>
<th>Renal excretion</th>
<th>Hepatic metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
<td>100%</td>
<td>None</td>
<td>None</td>
<td>High</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>7%</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>66%</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>50%</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Safety: major bleeding

- More in patients above 75 age with dabigatran versus warfarin
- Aspirin, clopidogrel and renal impairment increased the bleeding rate
- Dabigatran 150 mg given twice daily was associated with a higher rate of major GI bleeding than warfarin (1.85% vs 1000 patients per year 1.36%/year ) 5 additional events per 1000 patients per year
<table>
<thead>
<tr>
<th>Risk</th>
<th>Dabigatran†</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and systemic embolism</td>
<td>↓</td>
<td>↓/=</td>
<td>↓</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>=</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>↑†</td>
<td>↑†</td>
<td>=</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>↓†</td>
<td>↓†</td>
<td>↓</td>
</tr>
</tbody>
</table>

*The arrow indicates increased (†) or decreased (↓) rate of event with NOAC as compared with warfarin in pivotal trial. The equal symbol (=) indicates that the event rates were not significantly different with the NOAC and warfarin. Note that these data compare each NOAC with warfarin; there are no data directly comparing the NOACs.
†FDA-approved dose of 150 mg twice daily (BID) is depicted.
‡Not statistically significant, but a consistent approximately 10% reduction across the trials.
Bleeding rate 0.3% to 0.5% annually. Odds ratio (OR) of major GI bleeding compared with placebo approximately 3-folds.

The most common causes of upper and lower GI bleeding in the anticoagulated patient are peptic ulcer disease (18%-25%) and diverticular disease respectively.
Major GI bleeding: pathophysiology

- compared with warfarin, dabigatran and rivaroxaban preferentially increase major GI bleeding but not major bleeding in other organs, specifically causing less intracranial hemorrhage.
- active anticoagulant drug within the GI tract lumen promotes GI bleeding (e.g., from vulnerable mucosal erosions or angiectasias).
- The absorption of warfarin in contrast is 95%, and intraluminal drug has no anticoagulant activity.
- A second hypothesis is that the drugs directly injure the GI tract.
Prevention of NOAC-related GI bleeding

- Risk of GI bleeding related to dabigatran is 30% to 50% higher when it is co-administered with antiplatelet agents.
- Use of concomitant aspirin should be reserved for patients with a clear indication, such as recent myocardial infarction, particularly among patients at risk for GI bleeding.
- In patients taking chronic nonsteroidal anti-inflammatory drugs (NSAIDs) for analgesic or anti-inflammatory effects, coadministration of a gastric protective agent (eg, a PPI) should be strongly considered.
- There are no data relating Helicobacter pylori serologic status to the risk of NOAC-related GI bleeding.
Management of acute GI bleeding in patients receiving NOACs

- decision to reverse anticoagulation should "be individualized based on the potential risk of thrombosis and continued bleeding"
- Early endoscopy is encouraged, especially if an upper GI bleeding source is likely.
1-education of patients and prescribers.
2-education of patients regarding the signs and symptoms of acute GI bleeding
3-timely recognition of subacute GI bleeding (eg, through periodic hemoglobin measurement or fecal occult blood testing),
4-prompt hospital emergency department admission for major GI bleeding.
5-urgent or semiurgent endoscopic evaluation as dictated by the
Laboratory monitoring of anticoagulation

- Dabigatran has a greater effect on the aPTT than on the PT, whereas the reverse is true for the factor Xa inhibitors. Rivaroxaban has a greater effect on the PT than does apixaban.

- If the aPTT is normal in a patient taking dabigatran, it is reasonable to conclude that there is little ongoing anticoagulation effect.

- If the PT is normal in a patient taking rivaroxaban, there is likely to be little anticoagulant effect. In the case of apixaban which does not affect the PT to a significant extent, an anti-Xa assay is needed to assess drug levels.

- Dabigatran is the only NOAC to affect the thrombin time.
Interrupting anticoagulation

- risk of thrombosis versus the risk of ongoing thrombosis
- if the NOAC is held, the return of the ability to coagulate is generally rapid (12-24 hours and drug half-lives for near complete recovery). When the decision to reinitiate is made, anticoagulation is restored within hours of the first dose, unlike with warfarin where full effect takes days. In most cases, the risk of interrupting therapy temporarily (ie, 1 week) in patients with nonvalvular AF is associated with a low risk of thrombotic adverse events (0.5%/day);
esophageal injury presumed related to dadigarton
if the NOAC is held, the return of the ability to coagulate is generally rapid (12-24 hours and drug half-lives for near complete recovery).

decision to reinitiate is made, anticoagulation is restored within hours of the first dose, unlike with warfarin where full effect takes days.
Reversing anticoagulation

- No specific antidotes for the NOACs.
- In the case of severe, ongoing GI bleeding, several options are available.
  - 1-NOAC was given within 1 to 2 hours of presentation orally administered activated charcoal may limit absorption of residual drug in the stomach or duodenum.
  - 2- In life-threatening bleeding, procoagulants such as prothrombin complex concentrate (PCC) or recombinant activated factor VII may be effective.
  - 3-A mouse antibody against dabigatran, For factor Xa inhibitors, a recombinant functionally inactive form of factor Xa.
  - 4-In patients with acute renal failure and life-threatening bleeding with dabigatran, hemodialysis or hemoperfusion may be effective.
  - 5- Dialysis is less likely to hasten the elimination of rivaroxaban or apixaban because these drugs are 90% protein bound.
  - 6- Patients with life-threatening bleeding who are also taking aspirin might benefit from platelet transfusion.
Patient with acute GI bleeding taking NOAC

Initial clinical assessment
- History, including timing of last dose of NOAC
- Vital signs, physical exam
- CBC, chemistries, coagulation parameters

Mild bleeding
- Delay next NOAC and anti-platelet agent dose
- Consult with cardiologist
- Follow clinically
- Initiate non-emergent endoscopic evaluation to determine source of bleeding

Moderate-Severe bleeding
- Refer to ED
  - Standard resuscitation measures
  - Hemodynamic support
  - Close monitoring
  - Packed RBC transfusion as needed
  - Hold further NOAC or antiplatelet agents
  - Consideration of oral charcoal if NOAC ingestion <2 hours prior
  - Rapid colonic preparation if suspected LGB
  - Consider cardiology and hematology consults

Hemodynamically stable
- Continue supportive measures
- Follow clinical and laboratory parameters
- Consider deferring endoscopic evaluation for 12-24 hours to allow normal coagulation to return

Hemodynamically unstable, Life-threatening bleeding
- Continue supportive measures
- Emergent diagnostic/therapeutic endoscopy
- Consider PCC or recombinant clotting factors
- In patient receiving anti-platelet agent, consider platelet transfusion
- If poor renal function in patient receiving dabigatran, consider hemodialysis
- Consider ED and Surgical Consults
A 73-year-old woman was admitted with central chest pain for two weeks which was recurrent, occurred at rest, and was partly relieved by glyceryl trinitrate spray. There was no heartburn, dysphagia, or acid reflux. On three admissions for similar chest pain during the previous fortnight, she had had troponin assays which were not elevated and serial ECG recordings showed no acute change. Her medical history included epilepsy and psoriasis. Her medications included phenobarbitone, lansoprazole, low dose prednisolone, ferrous sulphate, alendronic acid, calcium, and vitamin D3 supplements and glycerine trinitrate spray. She was allergic to amlodipine.
Initial investigations

- The haemoglobin was 10.6 g/dl, mean corpuscular volume 76 fl and hematinics were normal.
- Leucocytes and platelets, urea and electrolytes, liver function tests and C-reactive protein were within normal limits. Her troponin assays were normal and ECG was unremarkable. Chest X-ray showed hyperinflated lung fields only.
Further development

- Upper GI endoscopy showed a large oesophageal ulcer showing sharply demarcated edge against a background of normal mucosa
Endoscopic view of large oesophageal ulcer (u) showing sharply demarcated edge (e) against a background of normal mucosa (n).
showing ulceration and granulation tissue alongside normal oesophageal squamous epithelium
<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-oesophageal reflux disease</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Herpes, CMV, Candida, EBV, HIV, TB</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td></td>
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<tr>
<td>Autoimmune conditions</td>
<td>Churg Strauss', CREST syndrome, Sjögren's syndrome, SLE, Mixed connective tissue disease</td>
</tr>
<tr>
<td>Caustic substances</td>
<td>Acids, Alkali</td>
</tr>
<tr>
<td>Chemicals</td>
<td>Weed killer</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
</tbody>
</table>
Proximal oesophagitis is almost always pathognomonic of drug-induced oesophagitis in a suggestive clinical setting and effectively excludes gastro-oesophageal reflux disease as a cause.
Anti-bacterials
- doxycycline
- tetracycline
- clindamycin
- rifampicin

Non-steroidal anti-inflammatory drugs (NSAIDs)
- aspirin
- diclofenac
- ibuprofen
- naproxen

Bisphosphonates
- alendronic acid
- risedronic acid
- disodium pamidronate

Iron formulations
- ferrous sulphate
- ferrous fumarate

Miscellaneous
- potassium chloride
- quinidine
- warfarin
- emepronium bromide
Precautions to prevent drug-induced oesophageal damage

1. Swallow several sips of water to lubricate the throat before taking a tablet or capsule.
2. Swallow tablet or capsule with at least 200ml of liquid.
3. Swallow tablets or capsules while in an upright or sitting position.
4. Do not lie down immediately after taking a tablet or capsule.
5. Inform your doctor if swallowing continues to be painful or if the tablets or capsules continue to stick in the throat.

6. Inform your doctor if you experience any side effects or if the medication does not work as expected.
PROTON PUMP INHIBITORS

- Hypertrophy and hyperplasia parietal cells
- Hyperplasia of ECL cells
- Fundic gland polyps (17% after 3 months treatment and 35% after 5 months)
- Gland dilatation
Common drug causes of oesophageal problems

Relax lower oesophageal sphincter causing heartburn
- Anticholinergic agents (e.g. procyclidine, trihexyphenidyl)
- Tricyclic antidepressants
- Calcium channel blockers
- Nitrates
- Phenothiazines

Direct mucosal injury
- Tetracyclines
- Bisphosphonates

Associated with strictures
- Potassium chloride
- Quinidine
- NSAIDs
Drug-induced xerostomia

- antiarrhythmics, anticholinergic antispasmodic agents, antihistamines, antihyperlipidemics, anti-inflammatory agents, antiulcer agents, coronary vasodilators, drugs for parkinsonism, and psychotropic drugs

- (dysphonia), taste (ageusia), chew, and swallow food (dysphagia).
Drug-induced oral lesions

- Drugs commonly associated with erythema multiforme include trimethoprim-sulfamethoxazole, sulfonamides, penicillins, nonsteroidal anti-inflammatory drugs (NSAIDs), and carbamazepine
Gingival enlargement

- phenytoin, cyclosporine, and calcium channel blockers
drug-induced GERD

- atonic lower esophageal sphincter (LES), hiatal hernia
- impaired motility of the esophagus, lessened resistance of the esophageal epithelium to injury, increased gastric secretion, and delayed gastric emptying
Some drugs (eg, anticholinergics, calcium channel blockers, ethanol, and nitrates) cause gastroesophageal reflux by inappropriately relaxing the LES.

Progesterone, theophylline, and tricyclic antidepressants also reduce LES pressure.
Nausea and Vomiting

• Both the vomiting center (VC) and the chemoreceptor trigger zone (CTZ) in the brain play an important role in inducing vomiting.

• Cisplatin has a high emetogenic potential, and vinblastine has minimal emetogenic potential.
Common drug causes of nausea and vomiting

Locally irritant
- Potassium chloride
- Iron preparations
- NSAIDs
- Theophyllines
- Azathioprine (?mechanism)
- Metronidazole

Act via the CNS
- Levodopa
- Bromocriptine
- Opioids
- Digoxin
- Chemotherapeutic agents (e.g. cisplatin, mustine, dacarbazine, cyclophosphamide)
Pancreatitis

- diuretics (thiazides, furosemide)
- sulphonamides
- azathioprine
- 6-mercaptopurine
- corticosteroids