

Inflammatory Bowel Disease (2009)

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Inflammatory Bowel Disease (IBD)

- Ulcerative colitis (UC)
- Crohn's disease (CD) (regional enteritis)
- Systemic disease (arthritis, uveitis, liver disease, etc.)

Epidemiology of IBD

- 1 million in USA (15,000-30,000 new cases/year)
- 3-6 new cases/100,000/year (UC), 4.3-6.8/100,000/year (CD)
- Total cases = 35-70/100,000/year (UC), 20-40/100,000/year (CD)
- M = F
- Peaks in 20's-30's, Ashkenazi Jews

Comparison of CD and UC

	CD	UC
Malaise, fever	common	uncommon
Rectal bleeding	Approx. 50%, intermittent	common
Abdo tenderness	common	may be present
Abdo mass	very common	not present
Abdo pain	very common	usual
Fistulas	very common	rare
Rectal disease	approx. 20%	almost 100%
Diffuse, continuous, symmetric	uncommon	very common
Aphthous, linear ulcers	common	rare

Comparison of CD and UC (cont'd)

	CD	UC
Ileal involvement	very common	rare
Asymmetry	very common	rare
Strictures	common	rare
Transmural	common	rare

Extraintestinal Manifestions of IBD

- Liver: chronic active hepatitis, cirrhosis, primary sclerosing cholangitis (3%), gallstones, cancer
- Musculoskeletal: arthritis (up to 15%), ankylosing spondylitis (1-2%)
- Eye: iritis, uveitis, conjunctivitis (10%)
- Skin/mouth: variety of lesions (10%)
- Kidney: oxalate stones
- Above "wax and wane" with intestinal dz except spinal and liver dz

Colon Cancer and IBD

- UC: 10-15 years, risk incr. (30% with 35 years) → surveillance colonoscopy every year
- CD: less established association

Sulfasalazine (SASP)

History

- 1930's-bacterial etiology of rheumatoid arthritis
- 1940's-clinical use in IBD
- 1970's-kinetics, ADR, MOA

SASP (cont'd)

Mechanism of Action:

- Antibacterial activity
- Local and systemic immunity-lymphs, IgG
- Arachidonic acid metabolism-PG, Thr, leukotrienes
- Free radical scavengers (5-ASA)
- Inhibit PAF, histamine release (mast cells)

SASP (cont'd)

Clinical Use:

- UC: initial tx
maintenance tx (dose-dependent)
good if concurrent arthritis (DMARD)
- CD: virtually no role except postop CD

SASP (cont'd)

Adverse Effects

- 10-45% incidence (*sulfapyridine*)
- Dose-related: N, V, anorexia, dyspepsia, HA, oligospermia, esp. during 1st 8-12 wk of tx
- Idiosyncratic: rash, hepatotoxicity, hematologic, neuropathy, bloody diarrhea, serum sickness

SASP (cont'd)

Dosing

- 1-6 gm/day in 2-4 divided doses (adults)
(4-6 gm/day acute, 1-4 gm/day maintenance)
- 50-100 mg/kg/day in 2-4 divided doses (peds)
- Give folate to prevent anemia
- Pregnancy and lactation not contraindication, despite sulfa (? incr. congenital anomalies in UK study)

Oral Salicylates

5-ASA delivery systems via:

- Coated forms: Pentasa, Asacol, Rowasa, Claversal, Salofalk
- Conjugation to itself: Olsalazine (Azodisalicylate)
- Conjugation to inert carrier – balsalazide

Clinical Use

- UC: as effective as SASP with fewer ADRs, less effective than oral CS
- CD: no role

Oral Salicylates (cont'd)

- Initial Dosing – mesalazine 2-6 g/d, balsalazide 6.75 g/d, olsalazine 1.5 -3 g/d
- Maintenance dosing – mesalazine 1-2 g/d, balsalazide 2.5 g/d, olsalazine 1.5 g/d
- ? qd vs. divided doses (only shown for Salofalk brand)
- Sustained-release qd brands are different story
- 5-ASA ↓ colon cancer risk in UC (SASP does not)

Oral Salicylates (cont'd)

Adverse Effects:

- Beware cross-reactivity with SASP (20%)!
- Nephrotoxicity with Asacol
- Secretory diarrhea, esp. with olsalazine (slow dose titration, give with meals)
- No oligospermia

+++ expensive so use only if SASP-intolerant or males wishing to start family

Topical Salicylates

- **5-ASA, 4-ASA**
- UC only:
 - ☞ Supps-rectum
 - ☞ Foam-proximal sigmoid colon
 - ☞ Enemas-up to splenic flexure
 - ☞ Topical ASA superior to top. CS and oral 5-ASA
- Active dz: 1-4 g/d, maintenance 1g/d → thrice weekly
- Best to use PR alone or PR + PO salicylate in combo for active distal dz

Corticosteroids (CS)

- Revolutionized management of severe dz in UC and CD
- Topical, intravenous, oral preps available
- PO budesonide limited role (isolated moderate ileocecal CD) (can induce remission but weaker than traditional CSs + no role in maintenance)

Corticosteroids (cont'd)

Clinical use

- UC acute Tx (induce remission)
- ☞ Proctitis, use local CS (enema/foam)+oral/top SASP/5-ASA
- ☞ Mild dz, po prednisone (20 mg/d)+local CS X 4 wks, then taper (1/8-1/6 per week)
- ☞ Mod. dz, po prednisone (20-40mg/d)+local CS X 6 wks, then taper as above
- ☞ Severe dz, IV (1-2 mg/kg/d methylprednisolone) with failures to CSA or infliximab or surgery
- UC maintenance Tx: ineffective in maintaining remission
- CD acute Tx: see UC acute Tx (induce remission)
- CD maintenance Tx: ineffective in maintaining remission

Corticosteroids (cont'd)

Adverse Effects

- See pharmacology texts
- Topical HC/prednisolone potentially toxic due to considerable absorption through bowel wall
- Safe in pregnancy/lactation (don't withhold tx if indicated)
- Childhood
 - ☞ Growth retardation
 - ☞ Balance with growth retardation due to dz
 - ☞ Growth improves with nutrition and remission
 - ☞ Adult-type regimens (wt. basis)
 - ☞ Alternative-day regimens don't work
- Osteoporosis: Ca, vit D, + bisphosphonate

Antimicrobials (CD only)

- **Metronidazole**
 1. Perianal dz (10-20 mg/kg/d), pouchitis (ileal reservoir)
 2. ADRs-nausea, metallic taste, alcohol intolerance, neuropathy in 50% with long-term use
 3. Can use in pregnancy
 - **Ciprofloxacin**-alternative in perianal CD (500-750 mg bid), pouchitis – better tolerated
 - Cipro + metro or cipro + rifiximin promising (use low metro doses of ≤ 1 g/d)

Immunosuppressives

6-mercaptopurine (6-MP), Azathioprine (AZA) are DOC's

Clinical use

- UC: induces and maintains remission and CS-sparing
- CD: induces and maintains remission, fistulas close, CS-sparing, requires 4-6 months to show effect
- Inverse relationship of WBC ct. and efficacy (? dosing strategy)
- Equieffective in UC + CD
- ? start earlier in dz course – more CS-sparing + ↓ hospitalizations

Immunosuppressives (cont'd)

Adverse effects

- Bone marrow suppression: dose-related, 1.5-2 mg/kg/d gen. safe, CBC qwk X 4-6 wk then decrease frequency to monthly
- Allergic reaction: rash, fever, joint pain in 2%
- Pancreatitis: in first 3-4wk (3%)
- Superinfection: < 2%
- Neoplasia: little evidence for increased risk (B cell lymphoma assoc. with EBV)
- Children: no undue toxicity
- Pregnancy: use at time of conception not indication for abortion (transplant data), prefer contraception during and for 3 mo. following tx use
- Allopurinol interaction! (use febuxostat)

Immunosuppressives (cont'd)

Recommendations for UC

- Pt. prefers medical tx prior to surgery and failed other med. modalities
- CS toxicity, continuous CS (> 15 mg/d > 6 months) needed, needs ≥ 2 courses of CS/yr. or relapse within 6 wk of D/C CS
- Universal dz, continually active and hasn't had dz long enough to be at cancer risk

Immunosuppressives (cont'd)

Recommendations for CD

- Chronic, active dz unresponsive to SASP/ASA, CS, metronidazole (abscesses, SBO)
- CS toxicity and continuous CS needed
- Fistulae present
- Prior to extensive surgery
- Maintenance of remission

Can AZA/6-MP be stopped after long quiescent disease?

- No since 1/2 will quickly relapse

Can 6-MP be used in AZA-intolerant?

- Yes but only if AZA intolerance was characterized by nausea/vomiting/flu-like illness/rash

Immunosuppressives (cont'd)

Cyclosporin (CSA)

- Severe, active CD/UC failing CS (IV)
- If fails CSA, don't try another agent (go to surgery)
- No role in maintenance tx (use PO CSA to "bridge" to AZA, 6-MP, MTX, etc.)
- ADR: renal, hepatic, ↑ BP, hirsutism, etc.

Methotrexate (MTX)

- Works in CS-refractory and -dependent (25 mg IM once/wk.)
- ? Work faster than 6-MP/AZA and in 6-MP/AZA nonresponders/intolerant
- ADR: hepatic, bone marrow, pulmonary, fetal (folate 5 mg qwk [3 d after Mtx])

Miscellaneous Drugs

Antidiarrheals

- Loperamide, diphenoxylate, codeine
- Avoid in acute attacks (toxic megacolon)

Iron

- Avoid in acute attacks

Cholestyramine

- Bile salt-assoc. diarrhea post-surgery

Probiotics

- Clear evid. of efficacy is lacking

Hormone Replacement Therapy

- Protects vs. active disease and may allow flares to be managed with non-immunosuppressants (both UC, CD)

Infliximab (Anti-TNF alpha Antibody)

- Tx of moderate-severe active CD in pts with inadequate response to alternative tx (5 mg/kg IV at 0, 2 + 6 wks)
- Tx of enterocutaneous fistulizing CD (5 mg/kg at 0, 2, 6 weeks)
- Maintenance of CD (give q 8wk) - only in AZA/6-MP/MTX failures
- "Rescue" of fulminant UC in single dose (like CSA) - if fails, infliximab, don't try another agent (go to surgery)
- 30% do not respond at all + not all responders respond fully
- Concurrent AZA/6-MP/Mtx, etc. ↑ + prolongs response (safety risk: lymphomas!)
- Adults (peds need RCTs)
- No role (yet) in maintenance of UC

Infliximab (cont'd)

- **ADRs:** infusion rx, hypersensitivity rx, autoimmunity, immunosuppression
- Devel. antibodies (murine protein) (↓ response, immed. infusion rxs, serum sickness-like or delayed infusion rx (if latter, change to fully human anti-TNF tx like adalimumab))
- Same MOA as thalidomide, so avoid in pregnancy
- CS-sparing
- TB risk-screen before use, INH (start 2 mo. before)
- Drug-induced lupus
- Avoid live attenuated vaccines within 3 months of Tx

Adalimumab

- Fully-humanized anti-TNF antibody
- o/w similar to infliximab in virtually all ways
- 160 mg SC loading → 80 mg SC at 2 wk. → 40 mg SC every other wk. (every wk. in rare cases)

Certolizumab

- Fully-humanized anti-TNF antibody
- o/w similar to infliximab in virtually all ways
- 400 mg SC at wks. 0, 2 and 4 than 400 mg SC q 4 wks.

Natilizumab (Anti- $\alpha 4\beta 7$ Integrin Antibody)

- 1st of selective adhesion molecule inhibitors
- Better as maintenance than induction agent in CD
- 300 mg IV q 4 wk
- Withdrawn from market last year due to cases of progressive multifocal leukoencephalopathy (neurodegen. dz due to Jakob-Creutzfeld virus) but reapproved by FDA with restricted labeling

Postoperative CD

- Use metro 400 mg BID X 3 mo. (if tolerated)
- Low risk for recurrence: no tx or 5-ASA 2-2.5 g/d X 3 mo.
 - : scope at 6 mo. + tx based on endo results
 - mild endo signs: none or 5-ASA
 - mod.: AZA/6-MP (5-ASA if intol.)
 - severe: AZA/6-MP (biologic if intol.)
- High risk for recurrence: maintain on AZA/6-MP or start these 2-3 mo. preop
 - : scope at 6 mo. – severe endo signs, start biologic
- Scope annually thereafter
