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Medications in inflammatory bowel disease – a primer for health care providers

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IBD - epidemiology

- Incidence of CD and UC similar
- 5-10 new cases/100,000/ year
- Incidence has DOUBLED in Finland in 15 years
  - (Turunen, IBD Journal 2006)
- 20-25% of cases in childhood and adolescence
- Rare under 5 years of age (especially Crohn's)
- 10-20% of children have a family history
- Risk factors
  - Northern European or Jewish individuals
  - oral contraceptive use
  - smoking - protects against UC, increases risk of CD

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Theory of pathogenesis

Exposure of a genetically predisposed host to an environmental trigger, resulting in immunologically mediated damage against the bowel.

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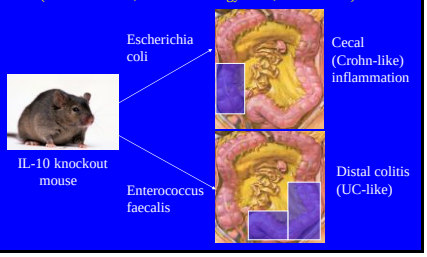
Variable phenotypes of enterocolitis in IL-10 deficient mice

(Kim and Sartor, Gastroenterology 2005;128:891-906)



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Inflammatory Bowel Disease Diagnostic Approach

- Suspect the diagnosis
  - History, Exam, CBC, ESR, Albumin
  - Possible role for serologic testing
- Exclude other etiologies
  - Stool culture, C. difficile, TB skin test
- Classify disease as CD or UC
- Determine disease location
  - Upper endoscopy, colonoscopy, UGI/SBFT
- Identify extraintestinal manifestations
  - Liver function tests, Joint, Skin, Eye exams

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IBD- presentation

Symptom/sign	CD	UC
Rectal bleeding	++	++++
Weight loss	++++	++
Growth failure	+++	+
Perianal disease	++	
Abdominal pain	++++	+++
Mouth ulcers	++	+
Erythema nodosum	+	+
Fevers	++	+
Anemia	+++	+++
Arthritis	+	+

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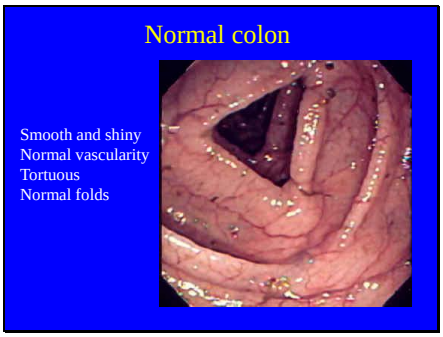

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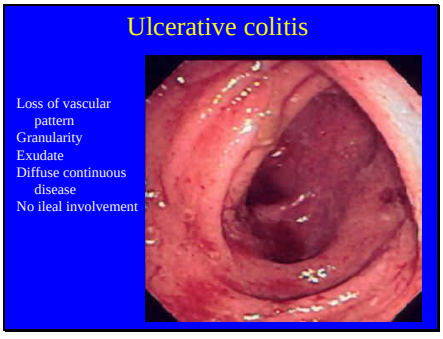

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Crohn's colitis

Deep fissures
Segmental distribution
Rectal sparing
Ileal involvement
Granulomas on biopsy

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IBD - management

- Medical
- Surgical
- Nutritional
- Supportive (psychosocial)
- Surveillance

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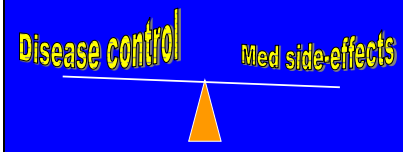
The "Balancing Act"



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What is the problem?

- Mucosal Crohn's disease and ulcerative colitis
  - Medications, surgery if medical failure
- Abdominal abscess – antibiotics and surgery
- Perianal abscess or fistula
  - antibiotics, 6MP, infliximab, surgical drainage
- Stricture – surgery
- Growth failure
  - nutrition and immunomodulators, surgery

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IBD - treatment

	CD	UC
Induction therapy		
Steroids	mod/severe	mod/severe
5-aminosalicylates	mild	mild
Nutrition	mild/moderate	not useful
CyA/tacrolimus	useful	useful
Infliximab	useful	useful
Maintenance therapy		
5-aminosalicylates	limited efficacy	useful
6-mercaptopurine	useful	useful
Infliximab	useful	useful
Methotrexate	useful	???
antibiotics	maybe useful	maybe useful

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Steroids (prednisone, budesonide)

- **Work fast**
- **Very effective**
- **Once a day**
- **Very inexpensive**
- **Fairly safe for short-term use (<3 months)**
- **Long-term experience**
- **Promote weight gain**
- **Hated by parents and kids**
- **Obvious side-effects**
  - moodiness
  - hair growth
  - facial swelling
- **Less obvious side effects**
  - growth failure
  - bone loss
  - high blood pressure

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Aminosalicylates in IBD

- Sulfasalazine
- 5 Aminosalicylates
  - Pentasa
  - Asacol
  - Colazal
  - Dipentum
  - Lialda
  - Apriso
- Effective for UC.
- Some limited efficacy for Crohn's disease
  - Induction, remission, and post-op recurrence
- Safe, though rare side effects happen

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Azathioprine and 6-mercaptopurine

- Works in up to 75% of patients with steroid-dependent Crohn's or colitis.
- Once/day medication
- More than 80% of patients have no side-effects.
- May prevent post-op recurrence in Crohn's
- About 5% do develop serious side effects
  - pancreatitis
  - low blood counts
  - infection
- Small risk of lymphoma

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A multicenter trial of 6MP and prednisone in children with newly diagnosed Crohn's disease

Markowitz et al, Gastro 2000; 119:895-902

- New onset Crohn's patients all given corticosteroids, then randomized to 1.5 mg/kg/day 6-MP (n=27) or placebo (n=28) for 18 months.
- Steroids tapered over 2 months
- After 18 months, 9% of 6MP patients vs. 47% of controls had relapsed.

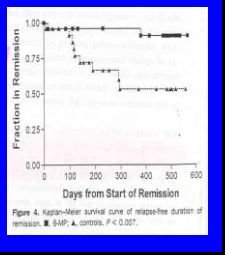

Figure 4. Kaplan–Meier survival curve of relapse-free duration of remission. ■, 6-MP; ▲, controls. $P < 0.007$.

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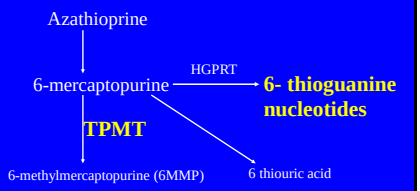
6-mercaptopurine metabolism



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Methotrexate in Crohn's

Uhlen et al, Inflamm. Bowel Dis. 2006; 12:1053

- 61 children with Crohn's resistant or intolerant to 6-MP or azathioprine
- Methotrexate weekly (median 17mg/M2)
- 80% initial response rate (29% relapse)
- MTX stopped in 10% secondary to adverse reactions
  - Hepatitis, Varicella, Zoster, Nausea

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Anti TNF inhibitors

	Infliximab	Adalimumab	Certolizumab
United States FDA approval	1998 - CD 2005 - UC 2006 - pediatric CD	2002- rheumatoid arthritis 2005- psoriatic arthritis	2008 – Crohn's
Composition	Chimeric antibody	Humanized antibody	Chimeric antibody
Monocyte apoptosis	Yes	Yes	????
Route of Administration	Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Frequency	Every two months	Every 2 weeks	Once a month

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Infliximab in ulcerative colitis

(Rutgeerts et al NEJM 2005; 353:2462)

- ACT 1 (54 week) and Act 2 (30 week) adult trials involving over 700 patients
- Inclusion criteria
  - Active UC (Mayo score 6-12)
  - Corticosteroid resistant or intolerant patients
  - Approximately 75% on concomitant ASA
  - Approximately 50% on concomitant 6MP/AZA
- Randomized to placebo, 5mg/kg, 10 mg/kg of IFX at 0,2,6,weeks then q2months
- 60% initial response, 25% remission at 1 year.

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Infliximab - adverse effects

- Usually very well tolerated
- Headache, fatigue, myalgia no greater than placebo
- Major concerns
  - Infusion reactions
    - human antichimeric antibodies
  - Disseminated tuberculosis
  - Risk of lymphoma – hepatosplenic T cell
  - Neutropenia
  - Demyelinating disease

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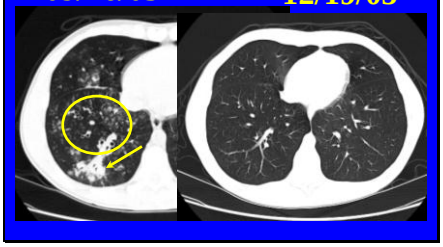

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Cyclosporine and tacrolimus for severe colitis

- Useful in severe UC or Crohn's colitis which has not responded to IV steroids.
- Randomized trials demonstrate efficacy for both.
- Most centers use IV Cyclosporine (4mg/kg/day), but oral tacrolimus has similar efficacy.
- In UC, surgery should be offered at the same time these medications are discussed.
- Initial response rate is about 80%, but up to 50% of children will proceed to colectomy even if they respond to induction by CyA or tacrolimus.

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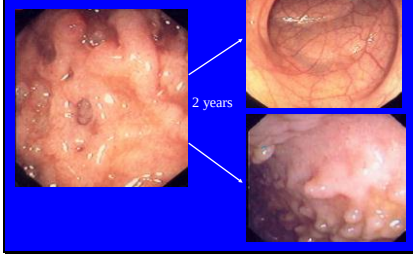
Oral tacrolimus + 6MP Outcomes



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Life is Risky

- unfortunately, everyone dies from something -

Over a lifetime, the chance of dying from:

Lightning → 1 out of 80,000
Bicycling accident → 1 out of 5,000
Drowning → 1 out of 1,000
Motor vehicle accident → 1 out of 80
Cancer → 1 out of 8
Heart disease → 1 out of 5
Anything → 1 out of 1

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IBD - management

- Medical
- Surgical
- Nutritional
- Supportive (psychosocial)
- Surveillance

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IBD- surgery

- Colectomy "cures" ulcerative colitis
  - Up to 25% develop recurrent pouchitis
  - After colectomy - 4-6 bowel movements/day
- Palliates in Crohn's disease
  - indications - stricture, abscess, fistula
  - colectomy may mean permanent ileostomy
  - patient undergoing small bowel or colonic resection has 50% recurrence risk in 5 years
  - 5 aminosalicylates, metronidazole, 6MP may postpone the recurrence risk

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Pouchitis – an ongoing issue post colectomy

Affects 30-40% of patients
Sx similar to UC
- Diarrhea
- Anemia
- Fatigue
- Abscess

Therapies
- Antibiotics
- ? clotrimazole
- Steroids
- Infliximab
- Diversion

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IBD - management

- Medical
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- Supportive (psychosocial)
- Surveillance

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IBD - Nutritional therapy

- Anorexia and growth failure are common, especially in Crohn's disease
- Etiologies
  - upper GI tract inflammation - gastritis
  - cytokine mediated anorexia - TNF and others
  - eating may produce uncomfortable symptoms
  - superimposed behavioral/psychological factors

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Nutritional therapy

- Involves administration of an elemental (e.g. Vivonex) or polymeric (e.g. Ensure) formula - either oral or intragastric feeds
- Supplemental NG feedings improve growth failure in children with Crohn's disease.
- EXCLUSIVE formula intake may bring about a remission in Crohn's disease.
- Nutrition ineffective in treating UC.
- "A hard sell in North America"

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IBD - Nutritional therapy

- Patients with active IBD frequently have laboratory test consistent with micronutrient deficiency.
- Monitoring of well patients should include routine measurement of:
  - Vitamin D status – Ca, P, 25OH vitD, PTH
  - Vitamin B12 (especially with ileal resection)
  - Zinc
  - Iron

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IBD - management

- Medical
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Psychosocial issues in patients with IBD

- Self-esteem issues
  - CD and UC occur during adolescence
  - growth failure/short stature
  - NG tube in school
  - Ostomy or surgical scar
- Conflicts with parents over appetite/eating
- Medication fatigue
- Fear of the future
  - will it ever go away?
  - concerns about cancer

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Depressive symptoms and IBD in children and adolescents

E. Szigethy et al, 2004

- Cross sectional survey of 102 children followed at Children's IBD program
- Administered Children's depression inventory
- 25% met clinical criteria for depression
- Primary risk factors
  - Active disease
  - Corticosteroid treatment

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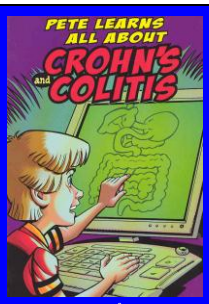

www.ccfa.org

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Conclusions

- The primary pharmacologic therapies for both Crohn's disease and ulcerative colitis are aminosalicylates, steroids, immunomodulators, and biologics.
- In addition to medications, patients require long term support and information about the other aspects of the disease
  - Nutritional
  - Psychologic
- Close multidisciplinary collaboration is essential to optimize patient outcomes.