Practice Guidelines Management of IBD

Dipendra Parajuli

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Management of IBD

Overview of pharmacologic agents

1. 5-ASA Compounds
2. Steroids
3. Antibiotics
4. Immunomodulators
5. Biologic agents

5-Aminosalicylic Acid (5-ASA) Drugs	
Mesalamine preparations	
Enteric-coated	Asacol
	Claversal
	Salofalk
	Rowasa
Controlled-release	Pentasa
Prodrugs	
	Sulfasalazine
	Olsalazine (Dipentum)
	Balsalazide (Colazal)

Which 5-ASA?

Plasma 5-ASA concentrations are approximately 2 µmol/l for sulphasalazine, Pentasa, olsalazine, or balsalazide, compared with >6 µmol/l for Asacol

(Travis,Gut, 2002;51:548-549)

The systemic exposure to 5ASA, as measured by urinary excretion of total 5ASA, and the faecal excretion of total 5ASA is comparable for all oral mesalazine formulations and pro-drugs.

(Sandborn WJ, Aliment Pharmacol Ther. 2003 Jan;17(1):29-42.)

Intolerance to sulfasalazine fairly common

Nausea, vomiting, dyspepsia, anorexia, and headache.

More severe, but less common, adverse effects

Allergic reactions, pancreatitis, hepatotoxicity, drug-induced connective tissue disease, bone marrow suppression, interstitial nephritis, nephrotoxicity, hemolytic anemia, or megaloblastic anemia.

Abnormal sperm counts, motility, and morphology sulfasalazine but not seen with the mesalamine preparations

Approximately 80% of the patients intolerant to sulfasalazine are able to tolerate olsalazine, mesalamine, and balsalazide

A Cochrane review of 11 trials (1598 pts) Sulfasalazine (SAS) more effective than other 5-ASA drugs for maintaining remission in ulcerative colitis (odds ratio (OR) 1.29, CI 1.06–1.57).*

Cochrane review of maintenance therapy, SAS less tolerated than 5-ASA

5 ASA Vs placebo OR 1.16 (CI 0.62–2.16)

5 ASA Vs Sulfasalazine pooled OR 0.38 (CI, 0.25 to 0.57)**

** (Travis ,Gut 2002;51:548-549)*

***(Sutherland et al: Cochrane Database Syst Rev. 2006 Apr 19)*

5 ASA Compounds

5 ASA Safety – all seem to be very safe
– A/E monitoring recommended but ?evidence base

5-ASA acts on and is metabolized by intestinal epithelial cells. Consequently, ulcerative colitis (a mucosal disease) is more susceptible to treatment by 5-ASA than transmural Crohn's disease.

5 ASA –chemopreventive

5 ASA –chemoprevention

Adjusted Odds Ratios for Most Influential Variables for Colorectal Cancer Risk			
Variable	Odds Ratio	95% CI	P Value
No 5-ASA treatment	—	—	—
Any 5-ASA treatment	0.47	0.22-1.0	0 .05
Mesalamine			
<1.2 g/day	0.18	0.02-1.92	0 .16
≥1.2 g/day	0.19	0.06-0.61	0.006
Sulfasalazine			
<2 g/day	0.93	0.22-3.91	0 .92
≥2 g/day	0.85	0.32-2.26	0.75
Other (olsalazine, balsalazide)			
Variable doses	1.21	0.08-18.97	0.89

CI = confidence interval.
Eaden J, et al. Aliment Pharmacol Ther. 2000;14:149.

Infliximab

INDUCTION OF REMISSION IN PATIENTS WITH ACTIVE CROHN'S DISEASE

Targan et al, N Engl J Med 1997; 337:1029
Hanauer et al, The ACCENT I randomised trial. Lancet 2002;359:1541.

INDUCTION OF REMISSION IN FISTULIZING DISEASE

Present et al, N Engl J Med 1999; 340:1398.
Sands et al, N Engl J Med 2004; 350:876.

MAINTENANCE OF RESPONSE AND REMISSION

substantial clinical benefits (compared with episodic) in patients who achieved remission with initial infliximab induction

- Increased likelihood of achieving and maintaining remission
- Improves quality of life
- Decreases corticosteroid requirements
- Reduces the likelihood of developing antibodies to infliximab
- Results in fewer hospitalizations

Accent I Trial

MAINTENANCE OF RESPONSE AND REMISSION

Patients without fistulizing disease

ACCENT I

Patients with fistulizing disease

ACCENT II Study - Sands et al, Clin Gastroenterol Hepatol 2004; 2:912.

More patients had complete absence of draining fistulas at 54 weeks.

Longer time to loss of response

ULCERATIVE COLITIS

Infliximab Vs placebo in severe to mod severe UC not responding to conventional treatment.
Randomized double-blind trial

End points
Primary- colectomy or death 3 months after randomization.
Secondary - clinical and endoscopic remission at that time in patients who did not undergo operation.

CONCLUSIONS: Infliximab 4-5 mg/kg is an effective and safe rescue therapy

Jarnerot G et al,Gastroenterology. 2005 Jun;128(7):1805-11.

Infusion reactions

- Acute infusion Rxn

SOA, hypotension, urticaria, fever, and/or chills.
typically mild
redc in the IV rate and adm APAP and/or H2RA

Delayed type hypersensitivity-like infusion Rxn

Myalgia, Rash, Fever , Polyarthralgia , Pruritus, Edema, Urticaria , Sore throat, Dysphagia, H/A
H2RA and/or steroids

Pts receiving concomitant immunosuppressive therapy are less likely to develop infusion reactions

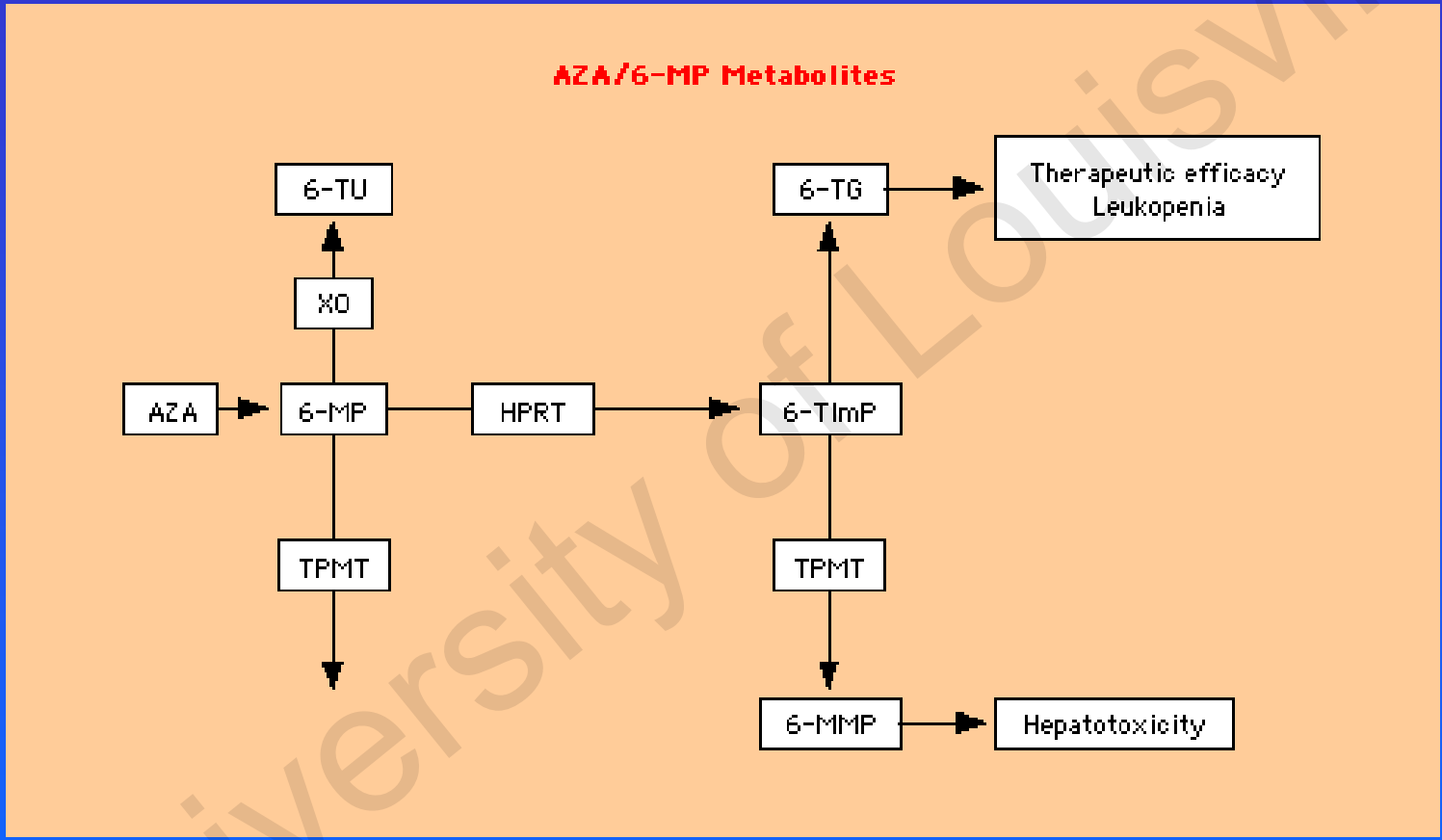
Prevention of recurrence

Anaphylaxis- Do not infuse again

Delayed hypersensitivity Rxn or a lupus like reaction
treatment can be attempted again

measures to reduce the likelihood of future reactions
- Scheduled dosing Vs Intermittent
- Recommended infusion rate (if needed slowed even further)
- Use of a concurrent immunomodulator
- Premedicate with IV steroids/H2RA/APAP

Testing for TPMT polymorphisms



6-TU (6-thiouric acid), 6-MMP (6-methylmercaptopurine, 6TImP (6-methyl-thioinosine 5'-monophosphate), (6-TG) 6-thioguanine.

Testing for TPMT polymorphisms

Population

89 % - wild type TPMT- normal or "high" activity

11 % - heterozygous -low activity

0.3 % - homozygous TPMT mutations- negligible activity.

Defcy of TPMT

- excessive production of 6-TG- with bone marrow tox

Higher than average TPMT activity

- may remain refractory to conventional doses of AZA or 6-MP
- 6-MMP correlate with liver toxicity

RECOMMENDATIONS

TPMT Testing

- Reasonable to consider in all patients in whom AZA or 6-MP is being considered (Insufficient data to suggest that it should be mandatory.)
- Should be performed in pts known to have developed leukopenia or elevated liver function studies during previous treatment

Testing for 6-TG and 6-MMP levels

-Greatest value in nonresponding patients (? non-compliance)
- In patients with detectable levels, it may reveal preferential metabolism toward 6-MMP (Consider alt immunomodulator)

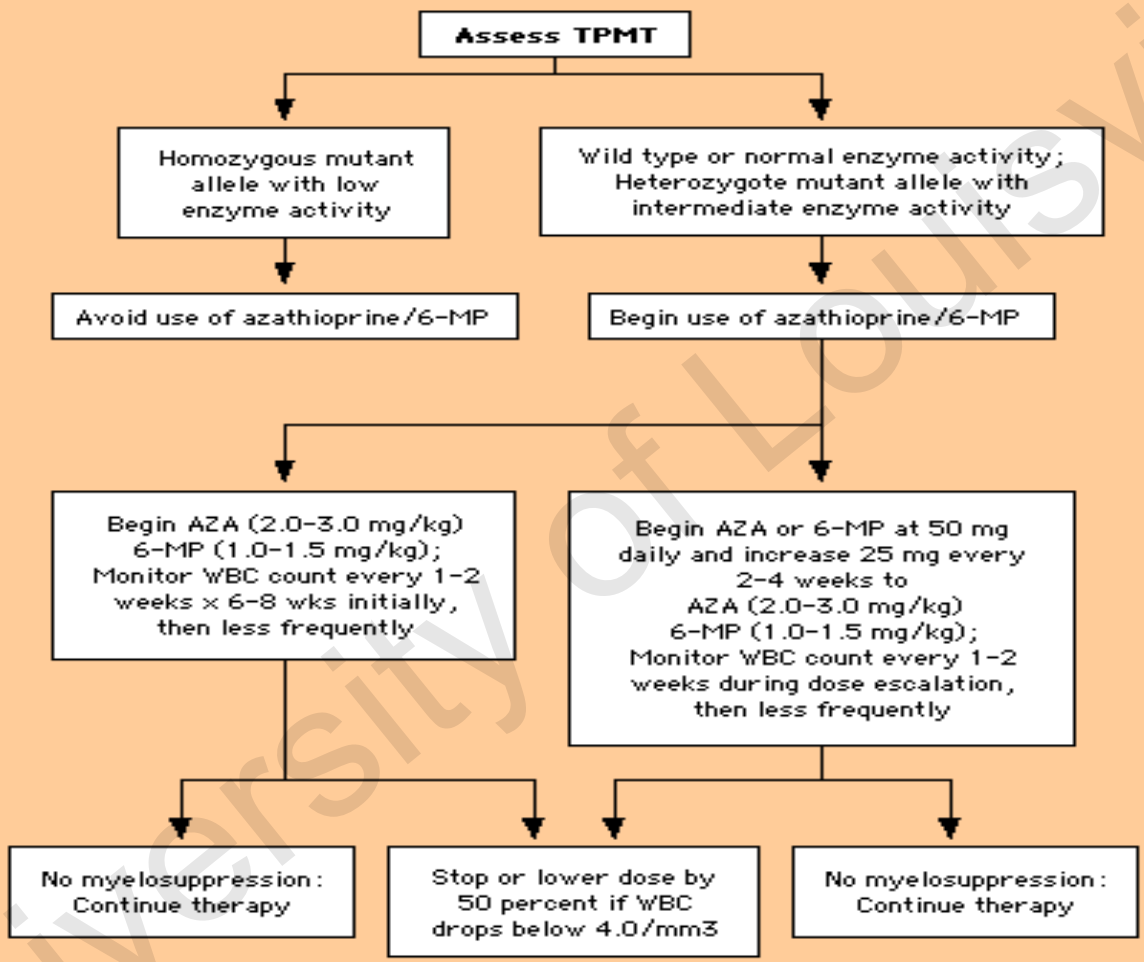
6-MP and AZA induce TPMT activity (Measure while on therapy)

Majority of patients who develop myelosuppression while taking AZA do not have detectable TPMT gene mutations

Those with high TPMT activity may be predisposed to forming potentially hepatotoxic levels of 6-MMP possibly increasing the risk for hepatotoxicity with an aggressive dosing regimen.

The safety, efficacy, and cost-effectiveness of these approaches are unproven.

Another Sggested but Unproven Approach for the Initiation of Therapy with Azathioprine or 6-Mercaptopurinein Patients with Inflammatory Bowel Disease†



TMPT: thiopurine methyltransferase; AZA: azathioprine; 6-MP: 6-mercaptopurine.

†Adapted with permission from: Lichtenstein, GR. Use of laboratory testing to guide 6-mercaptopurine azathioprine therapy. Gastroenterology 2004; 127:1558. Copyright © 2004 Elsevier.

ULCERATIVE COLITIS

Natural History of UC

Mortality – prob. no excess mortality now

1950's – 25% mortality in first severe attack

Colectomy

29% of patients with a severe attack of UC during the same hospital admission

Further 14% within 1 year of that admission

On day 3

if more than 8 stools/d

or 3-8 stools/d + CRP > 45 mg/l

85% will need colectomy

Travis et al,Gut, Vol 38, 905-910, 1996

UC – Clinical Course

Extent of Disease at Diagnosis

- Pancolitis 36. 7%
- Left sided proctocolitis 17. 0%
- Proctitis 46. 2%

Extension of Disease over time

- 54% 5-28 yr FU (Farmer et al 1993)
- 10-30% 10 yr FU (Farmer & Brown 1972; Powell-Tuck et al 1977; Ayres et al 1996)

Relapse Rates

- First year after diagnosis 50%
- 3-7yrs after diagnosis:
  - In remission 25%
  - Relapse every year 18%
  - Intermittent relapses 57%
- At any one time only 50% of patients in remission (Langholz et al 1994)

Colectomy Rates – by extent of disease at presentation

- Pancolitis 5 yr 32-44%
- Proctosigmoiditis 5yr 4-9 % (Ballinger 2000)

UC - Assessment of Disease Severity

Clinical

Truelove and Witts' Activity Categories

Severe	Diarrhea > 6 motions/day, with blood PM temperature > 37°C Average pulse > 90 beats/min Anemia with hemoglobin ≤ 75% ESR > 30 mm/hr
Moderate	Intermediate between mild and severe
Mild	Diarrhea < 4 motions/day, non-bloody No fever No tachycardia Anemia "not severe" ESR < 30 mm/hr

UC - Assessment of Disease Severity

Sigmoidoscopic

0—Normal mucosa
1—Loss of vascular pattern
2—Granular, nonfriable mucosa
3—Friability on rubbing
4—Spontaneous bleeding, ulceration

Laboratory Data

CRP/ ESR
HGB
Serum alb.
Neutrophilic leukocytosis/ band cells

Disease limited to the rectum, or even the rectosigmoid, rarely causes a rise in CRP, unless the disease is particularly severe.

St. Mark's Clinical Illness Score

Item	Points	Range
General health	0–3	Good to unable to work
Abdominal pain	0–2	None to prolonged
Bowel frequency	0–2	< 3 to > 6 per day
Blood in stool	0–2	None to more than trace
Stool consistency	0–2	Formed to liquid
Anorexia	0–1	Absent to present
Nausea/vomiting	0–1	Absent to present
Abdominal tenderness	0–4	None to rebound
Extraintestinal manifest.	0–3	None to severe (or >1)
Temperature	0–2	Normal to > 38°C
Sigmoidoscopy	0–2	Nonhemorrhagic to spontaneous bleeding

Defining Extent of Disease

Proctitis

Left Sided - Upto Splenic flexure

Extensive/Pancolitis- Beyond Splenic Flexure

Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee

Asher Kornbluth, M.D. and David B. Sachar, M.D.

American Journal of Gastroenterology
Volume 99 Page 1371 - July 2004

Quality of evidence

Grade A:

- Homogeneous evidence from multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials,
- Sufficient statistical power.

Grade B:

- Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta analysis.

Grade C:

- Evidence based on clinical experience, descriptive studies, or reports of expert committees

APPROACH TO MANAGEMENT

Goals of treatment

- Inducing and then maintaining remission of symptoms and mucosal inflammation to provide an improved quality of life.

Global assessment of the patient should include attention to

- extraintestinal manifestations,
- general health concerns,
- and quality of life issues.

Quality of life

- function at school, work or in personal relationships
- social and emotional support
- financial resources
- adequacy of patient education regarding their disease

MILD-MOD. ACTIVE DISTAL COLITIS

Evidence Base A

- Oral 5 ASA, topical mesalamine, or topical steroids
- Topical mesalamine agents are superior to topical steroids or oral 5 ASA
- Oral + topical 5 ASA > effective than either alone
- In patients refractory to oral 5ASA or topical corticosteroids, mesalamine enemas or suppositories may still be effective

The unusual patient who is refractory to all of the above agents in maximal doses, or who is systemically ill, may require treatment with oral prednisone in doses up to 40–60 mg per day (Evidence C).

The therapeutic plan largely determined by the pt's preference

- Both oral or topical therapy are effective
- Topical mesalamine is superior to oral 5ASA

Oral 5 ASA Compounds

- Generally act within 2–4 wk
- Effective in 40–80% of patients

Topical therapy

Mesalamine - suppositories or enemas
Hydrocortisone - foam or enemas.

Distance reached

Suppositories - approx. 10 cm (Proctitis)
Foam - approx. 15–20 cm
Eenemas - splenic flexure (Lt sided Colitis)

Topical Mesalamine

- effective in inducing and maintaining remission

Topical corticosteroids

Effective for induction NOT for maintenance

100 mg hydrocortisone enema
10% hydrocortisone foam,

Budesonide
- budesonide enema not yet available in US
- at least as effective as the hydrocortisone, fewer A/E

Advantages of topical therapy

- quicker response time
- less frequent dosing schedule than oral

REMISSION MAINT. IN DISTAL DISEASE

Evidence A

- Topical Mesalamine are effective in the maintenance of remission in patients when dosed even as infrequently as every third night
- Oral 5ASA agents are also effective
- Combination of oral and topical mesalamine is more effective than the oral mesalamine alone

Topical corticosteroids NOT effective for maintaining remission in distal colitis

MILD-MODERATE EXTENSIVE COLITIS: ACTIVE DISEASE

Begin therapy with oral sulfasalazine
(daily doses titrated up to 4–6 g / day)
OR an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-ASA moiety (Evidence A).

Oral steroids are generally reserved for patients who are refractory to oral 5ASA +/- topical therapy, or for patients whose symptoms are so troubling as to demand rapid improvement (Evidence C).

6 MP/AZA

Effective for patients who do not respond to oral prednisone but are not so acutely ill as to require intravenous therapy (Evidence C).

Effective in pts who do not respond to, or cannot be weaned from steroids.

Slow onset of action; up to 3–6 months to optimal effect

RECOMMENDATIONS FOR MILD-MODERATE EXTENSIVE COLITIS: MAINTENANCE OF REMISSION

5 ASA

- All 5 ASA effective in reducing relapses (Evidence A).

AZA or 6-MP

- steroid-sparing agents for steroid-dependent pts
- maintenance of remission not adequately sustained by 5 ASA
- occ. for steroid-refractory pts who are not acutely ill (Evidence C).

SEVERE COLITIS

Severe colitis refractory to max. PO prednisone, oral 5 ASA and topical medications, or the patient who presents with toxicity should be hospitalized for a course of IV steroids (Evidence C).

Failure of sig. improvement within 7–10 days is an indication for either colectomy (Evidence C) or IV Cyclo - sporine (Evidence A)

Infliximab – New evidence

Usual steroid dose=

equivalent to 300 mg of hydrocortisone or

60 mg of methylprednisolone

NO benefit with higher doses

continuous infusion Vs bolus therapy has not been subjected to a controlled trial.

<u>ABX</u>

oral Vanc or IV Falgyl or Cipro

No therapeutic benefit

Broad-spectrum antibiotics ususally include for patients with signs of toxicity, or with worsening symptoms despite maximal medical therapy

Impt to r/o CMV superinfection in pts with severe colitis who do not respond to maximal immunosuppress.

IV Cyclosporine

Both 4 mg/kg/ day and 2 mg/kg/day equally effective

Addition of 6MP/ AZA

- indicate a significantly higher long-term success rate when added during the oral cyclosporine phase
- ideal dose or time to add 6-MP or AZA not known

IV Cyclosporine

Long Term Outcomes – Steroid-resistant (3 Series)

Centre	Pt No	Initial Response %	Long Term Remiss. %
Nottingham	22	91%	53% at 3yr
Oxford	50	56%	40% at 2yr
Dublin	46	69%	26% at 2yr

Hawkey et al, Alimentary Pharmacology & Therapeutics, Oct98, Vol. 12 Issue 10, p973

Jewell DP et al, Eur J Gastroenterol Hepatol. 1998 May;10(5):411-3

SURGERY

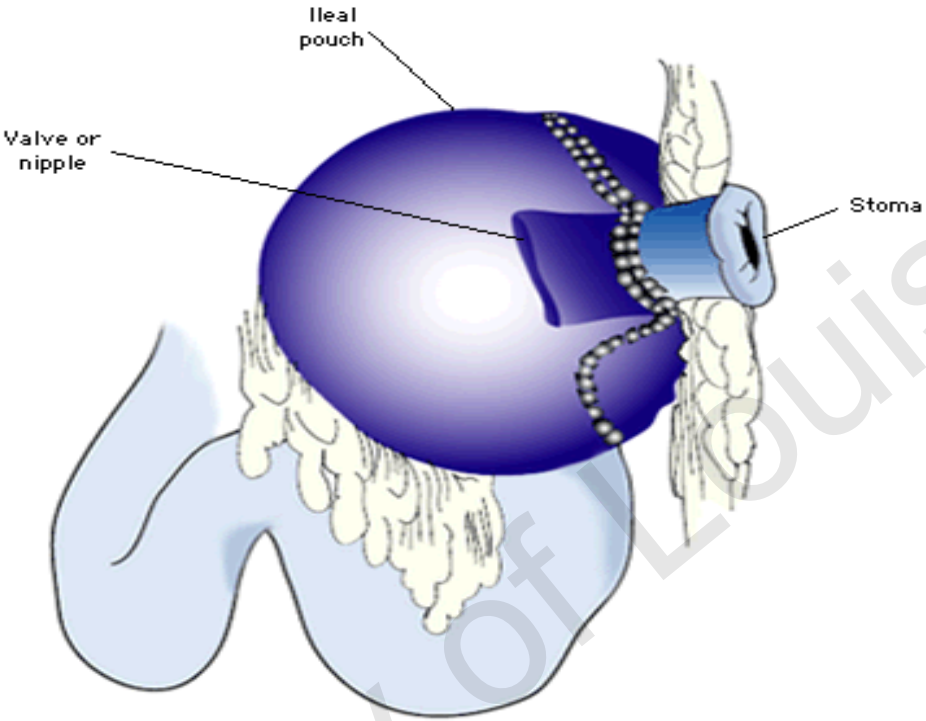
Absolute indications

Exsanguinating hemorrhage, perforation, and documented or strongly suspected carcinoma (Evidence C).

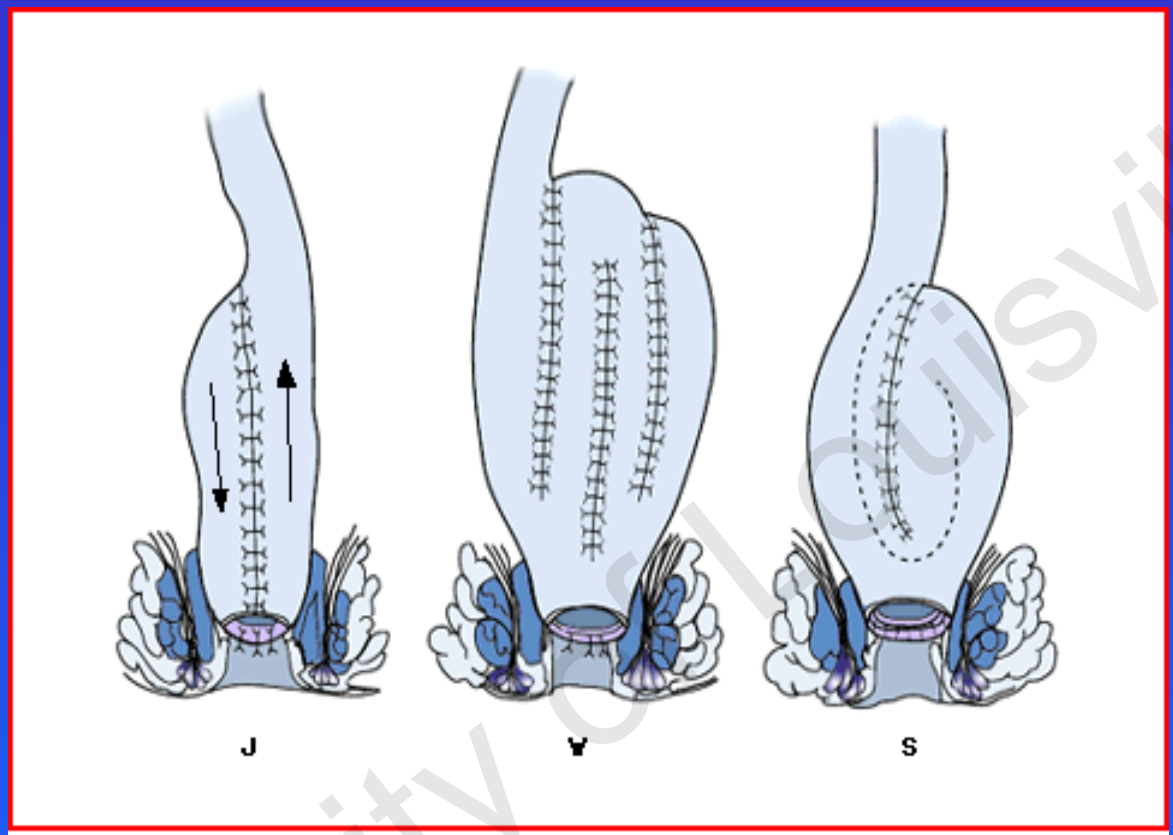
Other indications

- Severe colitis +/-toxic megacolon unresponsive to conventional maximal medical therapy,
- Patient with less severe, but medically intractable symptoms or intolerable medication side effects (Evidence C).

No prospective RCT comparing medical treatment to surgery for any indication in UC



The continent ileostomy The ileal pouch is formed from a loop of ileum, folded on itself as a U, and sutured along with antimesenteric borders. The limbs are then incised, exposing the mucosa, and the nipple valve is fashioned. The pouch is closed and positioned as shown underneath the abdominal wall. Note that the stoma is flush with the skin. (Adapted from Pemberton, JH, Phillips, SF. Ileostomy and its alternatives. In: Gastrointestinal and Liver Disease, 6th ed, vol 2, Feldman, M, Sleisenger, MH, Scharschmidt, BF (Eds), WB Saunders Company, Philadelphia 1998. p. 1764. Reproduced with permission from Mayo Foundation, Copyright ©1999. Mayo does not endorse any organizations or non-Mayo products that may appear in this Website. Materials copyrighted by Mayo may be reprinted for personal use only. Permission to reprint or electronically reproduce any document in part or in its entirety for any other reason is expressly prohibited, unless prior written consent is obtained from Mayo.)



Ileal pouch-anal anastamosis Anatomy of the J, W, and S ileal pouches used for anastomosis to the anal canal (ileal pouch-anal anastomosis). (Adapted from Pemberton, JH, Phillips, SF. Ileostomy and its alternatives. In: Gastrointestinal and Liver Disease, 6th ed, vol 2, Feldman, M, Sleisenger, MH, Scharschmidt, BF (Eds), WB Saunders Company, Philadelphia 1998. p. 1765. Reproduced with permission from Mayo Foundation, Copyright ©1999. Mayo does not endorse any organizations or non-Mayo products that may appear in this Website. Materials copyrighted by Mayo may be reprinted for personal use only. Permission to reprint or electronically reproduce any document in part or in its entirety for any other reason is expressly prohibited, unless prior written consent is obtained from Mayo.)

UC - MORE RECENT THERAPIES

- Immunomodulators
- Heparin
- Nicotine
- Probiotics/antibiotics
- Short Chain Fatty Acids
- Heavy metals
- Miscellaneous
- Biologicals
- Experimental – Leukocytapheresis

Methotrexate

Author	Trial Design	Pt No	Outcome
Egan 99	dose-rand. s/c 15/25mg/wk uncontrolled	32	17% rem at 6 wks
Paoluzi 02	i/m 12.5mg/wk aza-intolerant uncontrolled	10	8/10 rem at 26 wks
Fraser 02	oral 20mg/wk (mean) aza-intolerant uncontrolled, retro	22	57% rem at 36 mnts

Other Immunomodulators

Tacrolimus

Fellerman 02

- iv-oral tacrolimus in 38pts steroid resistant
- Colectomy Rate - early 34%
  - 2 year 50%

Cyclophosphamide

Stallmach 03

- Crohn's only
- Encouraging pilot study – 7pts - uncontrolled

Medical Management of Crohn's Disease

DEFINITIONS OF SEVERITY

Mild to moderate

- Ambulatory patients
- Able to tolerate an oral diet
- No dehydration, toxicity, abdominal tenderness, mass, or obstruction or wt loss >10%

Moderate to severe

- Pts who have failed Tt for mild to mod Dz
- Pts w prominent Sx- fever, weight loss, Abd pain/Tenderness, intermittent nausea/ vomiting, or anemia

Severe-fulminant disease

Pts with persisting Sx despite Tt with steroids or patients presenting with high fever, persistent vomiting, intestinal obstruction, rebound tenderness, cachexia, or an abscess

Remission

Patients who are asymptomatic either spontaneously or after medical or surgical intervention.

Patients requiring steroids to remain asymptomatic are not considered to be in remission

Mild–moderate active disease

Ileal, ileocolonic, or colonic

- Oral aminosalicylate

- ABX

  Metronidazole / Ciprofloxacin

- Budesonide

Sulfasalazine

- Sulfasalazine in ileitis-response rates 0 to 20 %
- 50% pts – remission (Ileocolonic)
- Sulfasalazine Vs Other 5ASA (No data-colonic)

Other 5 ASA

- also effective
- Different mesalamine prepns (No data)

Topical Therapy for distal disease

(mesalamine or corticosteroids)
Not adequately evaluated

Metronidazole Vs Placebo

- more effective for ileocolitis/colitis Vs Ileitis

Metronidazole Vs Sulfasalazine

- Initial response similar
- More patients who failed sulfasalazine responded to metronidazole than *vice versa*.

Ciprofloxacin 1 g daily = Mesalamine 4 g daily

Ciprofloxacin + Metronidazole

- superior results to either agent alone (uncontrolled trials)

Mild–moderate active disease

Esophageal, gastroduodenal, and jejunoileal

Acid Suppressive therapy

relief of symptoms

Pentasa

no clinical trials

Steroids

effective for mod to severe Dz

AZA/6MP

steroids-resistant or steroid-dependent

Mild–moderate active disease

Response to initial therapy- eval within several weeks.

Tt for active disease

continue to the point of symptomatic remission or failure to continue improvement.

Continued symptoms

alt therapy for mild–moderate disease or advanced to treatment for moderate–severe

Moderate–severe disease

Prednisone 40–60 mg/day or budesonide 9 mg daily
(until resolution of symptoms and resumption of weight gain)

Infection or abscess

requires appropriate antibiotic therapy or drainage (percutaneuous or surgical).

Infliximab

effective adjunct or alternative to steroid therapy in patients in whom corticosteroids are contraindicated or ineffective.

Steroids

No appropriate dose-ranging studies

equivalent of prednisone, 0.5–0.75 mg/kg (or 40 mg) daily - approx 50–70% - remission over 8–12 wk

Dose Taper after clinical response

- by 5–10 mg/ week until 20 mg
- by 2.5–5 mg/ week , 20 mg until discontinuation

Steroid dependent / steroid resistant

- (50% of pts treated acutely with steroids)
- AZA/6MP/ Parenteral methotrexate
- Infliximab

Severe–fulminant disease

Hospitalize
Pts with persisting Sx despite oral steroids or infliximab
Pts w systemic toxicity, ?intestinal obstruction, rebound tenderness, cachexia, or ? evidence of abscess

Surgical consultation
Evaluate abdominal mass –CT/USN
Abscesses - percut or surgical drainage.

Once an abscess has been excluded or if pt has been receiving oral steroids, parenteral corticosteroids

No response to parenteral steroids

1. intravenous cyclosporine or tacrolimus
(no controlled or dose-response data)

2. Infliximab
not first line therapy, used primarily in patients refractory to standard therapy

Failure to respond or worsening symptoms
surgical intervention.

Maintenance therapy

Corticosteroids should not be used

AZA / 6MP

after inductive therapy with corticosteroids.

Mesalamine or AZA/6MP

after ileocolonic resections to reduce the likelihood of symptomatic recurrence

5 ASA

No sig maintenance benefits for Crohn's disease after medically induced clinical remissions.

Indications for surgery

Intractable hemorrhage, perforation, Obstruction, abscess (not amenable to percutaneous drainage), or unresponsive fulminant disease.

Most common indications

- Refractory disease despite medical therapy or
- Medication side effects (steroid dependence)

Patients who fail to improve within 7–10 days of intensive inpatient management

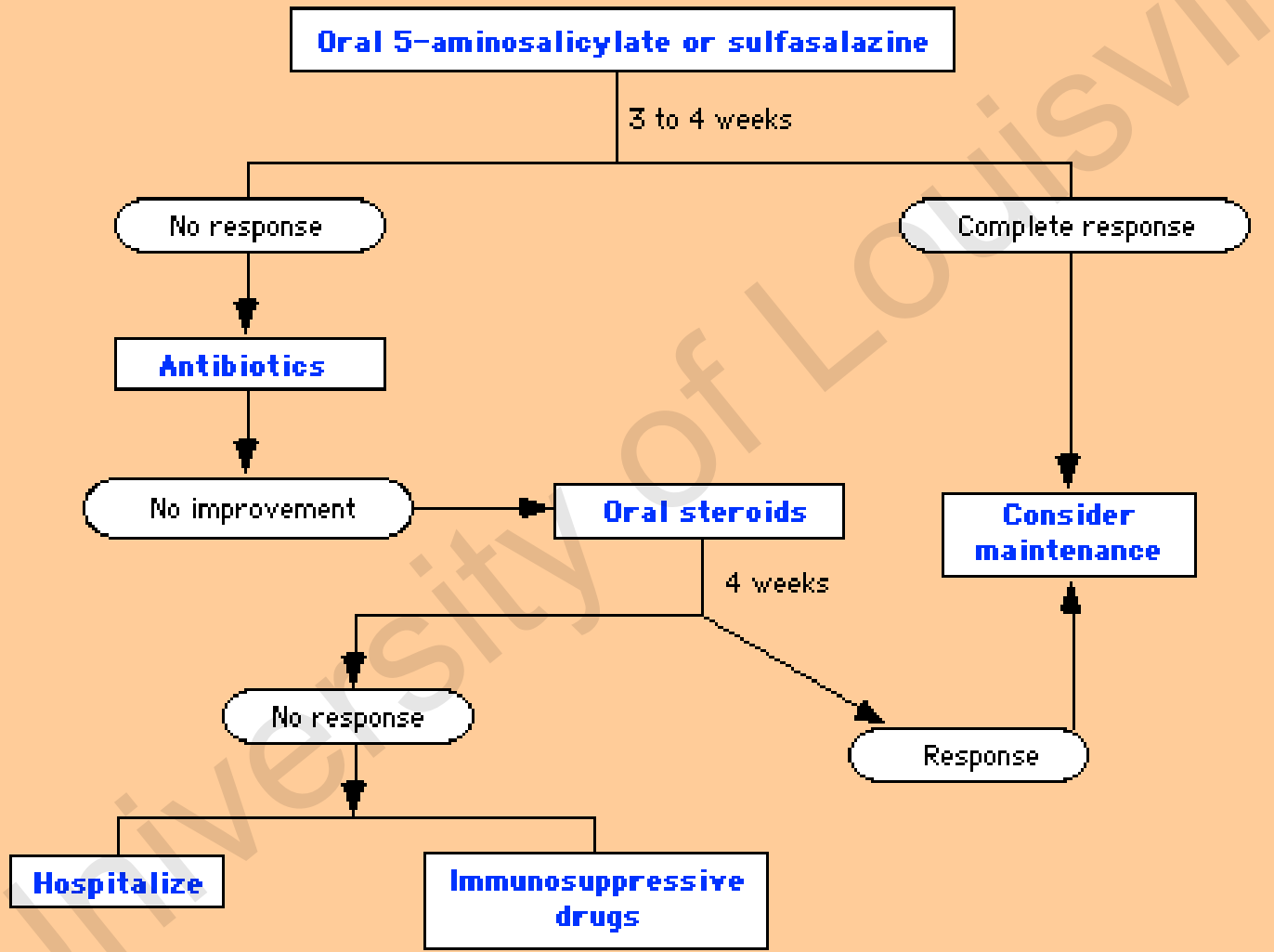
Perianal disease

Acute suppurative Dz - surgery
Nonsuppurative,chronic fistulizing / perianal fissuring
antibiotics, immunosuppressives, or infliximab.

Metronidazole +/- ciprofloxacin
continuous therapy necessary to prevent recurr drainage
(However no trials)

Immunosuppressives
Benefits from short term Cyclosoporine / tacrolimus
(several series but no controlled data)
AZA/6MP- not specifically studied

Overview of the Medical Therapy of Crohn's Disease



Pregnancy and the Inflammatory Bowel Disease Patient

Introduction: Pregnancy & IBD

- Highest age adjusted incidence rates of IBD (15 – 30 yrs) overlap peak reproductive years.
- Improved medical and surgical treatment -pts with more sig illness to consider pregnancy
- Optimal treatment algorithms for IBD patients during pregnancy have not been defined,
- Require obstetricians, gastroenterologists, IBD surgeons.

Goals: Pregnancy and IBD

- Fertility – becoming pregnant.
- Having an uneventful term pregnancy:
  - Avoiding preterm delivery
  - Avoiding severe flare (risk for preterm delivery)
- Use of safe medications to maintain remission in mother
  - during pregnancy.
  - during post-partum and breast feeding

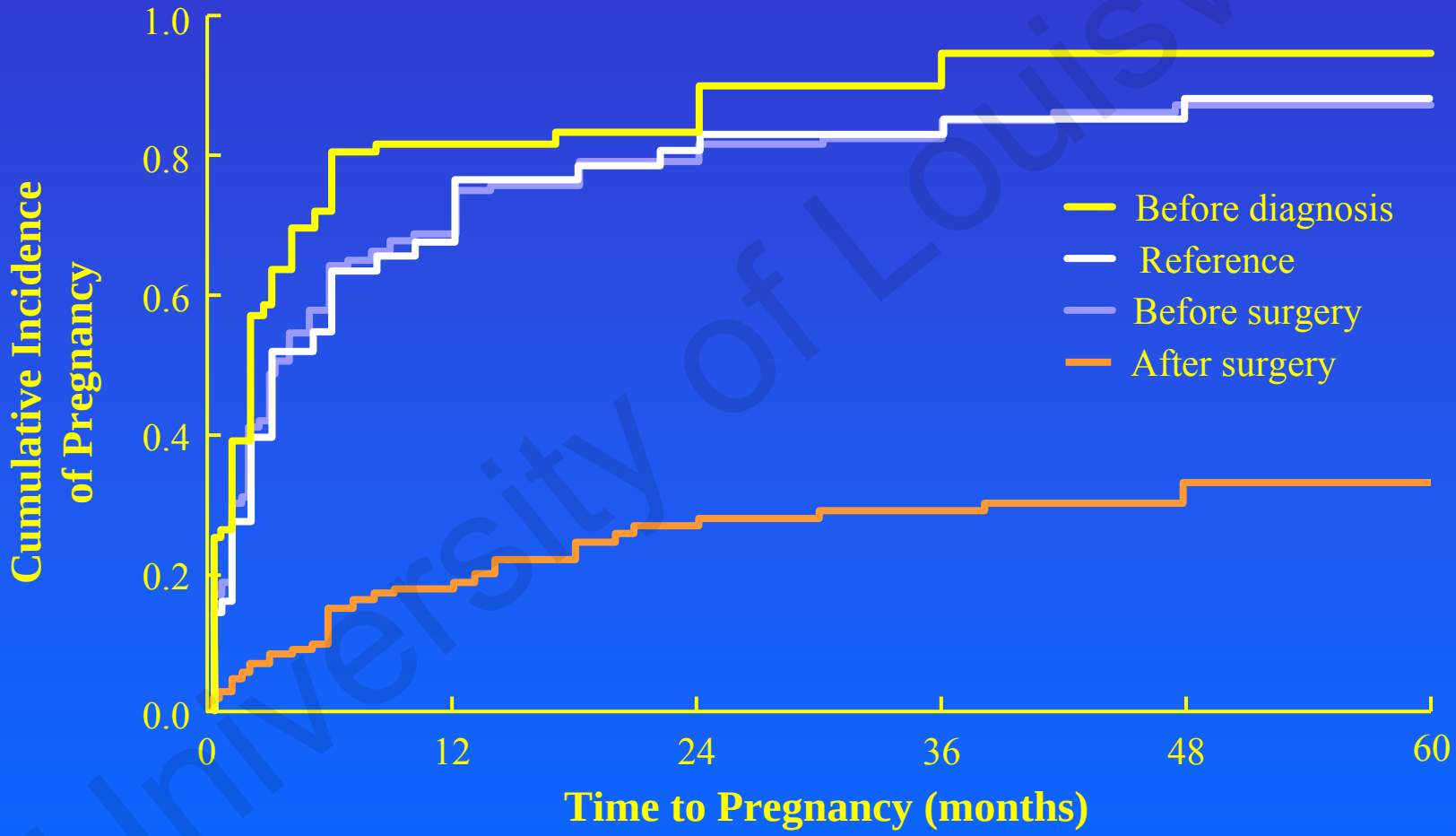
Overview

- Fertility/Fecundity Rates
- Pregnancy Outcomes
- Effects of Medications on Pregnancy
- Special situations - IBD Surgery during pregnancy

Infertility: UC

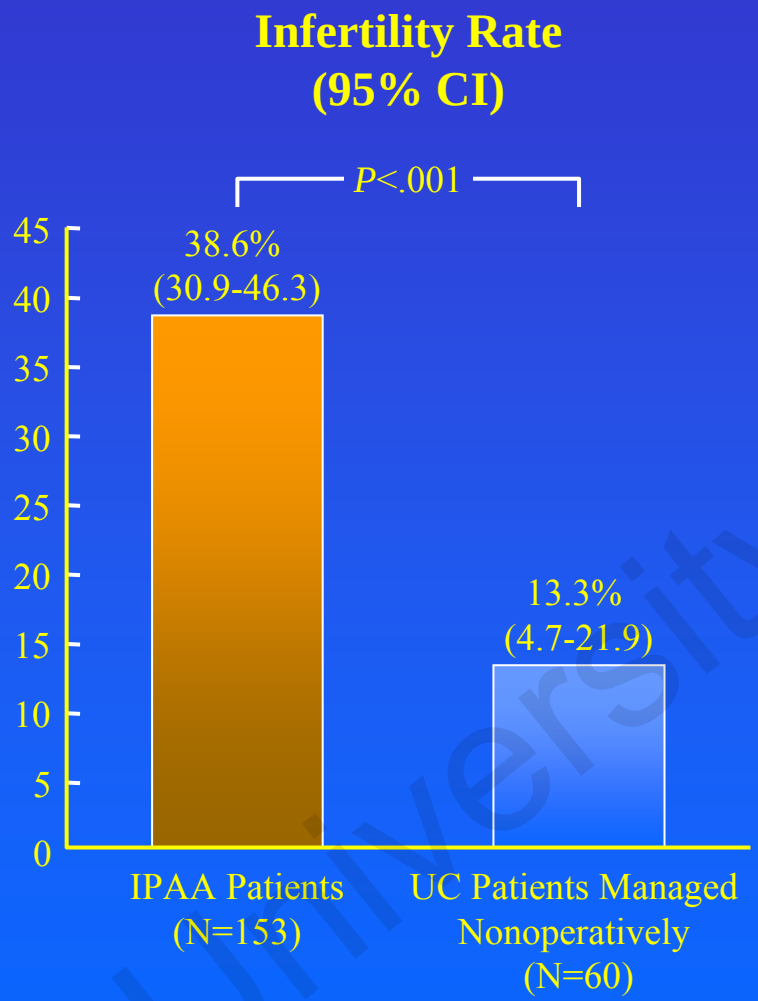
Author	N	UC	Control
Willoughby 1980	147 married Oxford: Ref Ctr	6.8%	Similar
Baird 1990	84 N. Carolina	5% Volntry: 21%	8% 14%
Hudson 1997	138 NE Scotland	15%	14%
Olsen 2002	290 Sweden	FR= 1.01 FR*= 0.20	NS P=<0.0001

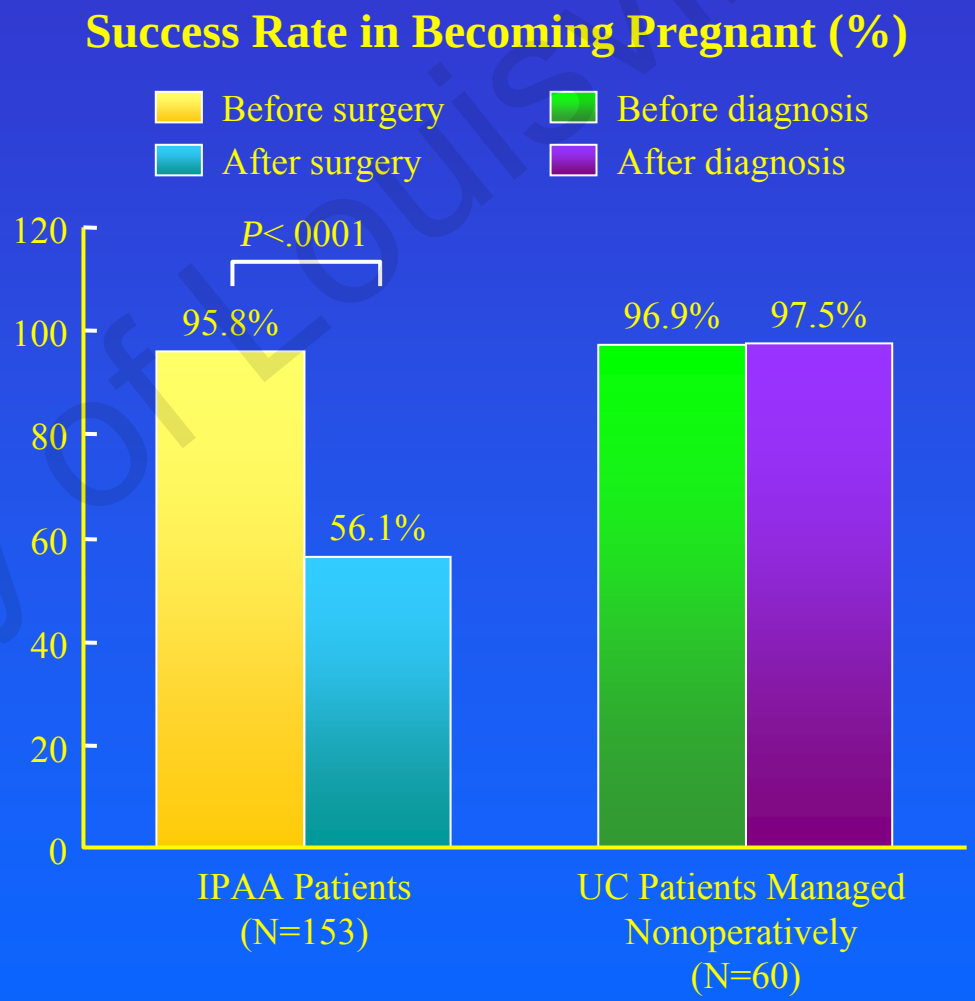
IPAA: Cumulative Incidence of Pregnancy Within 5 Years



Olsen KØ, et al. Gastroenterology. 2002;122:15-19

Female Infertility After IPAA for UC





Johnson P, et al. *Dis Colon Rectum.* 2004;47:1119-1126.

Infertility: Crohn's Disease

Author (yr)	N	Crohn's	Control
Fielding 70	77	32%	
Khosla 84	54 married	12%	10% gen pop
Mayberry 86	275	42% subfertility	28%
Baird 90	177	Involuntary 5% Voluntary 14%	8% 14%
Hudson 97	177	14% Surg. 20% Med 8%	14%

Summary: Female Fertility

- Ulcerative Colitis
  - Similar to the general population prior to colectomy
  - Significantly decreased after IPAA

- Crohn's Disease
  - Studies vary
  - Infertility partly voluntary
    - (dyspareunia, illness, MD advise)
  - Surgery: decreased fertility

IBD pregnancy complications and outcomes (MCW) 1998 - 2004

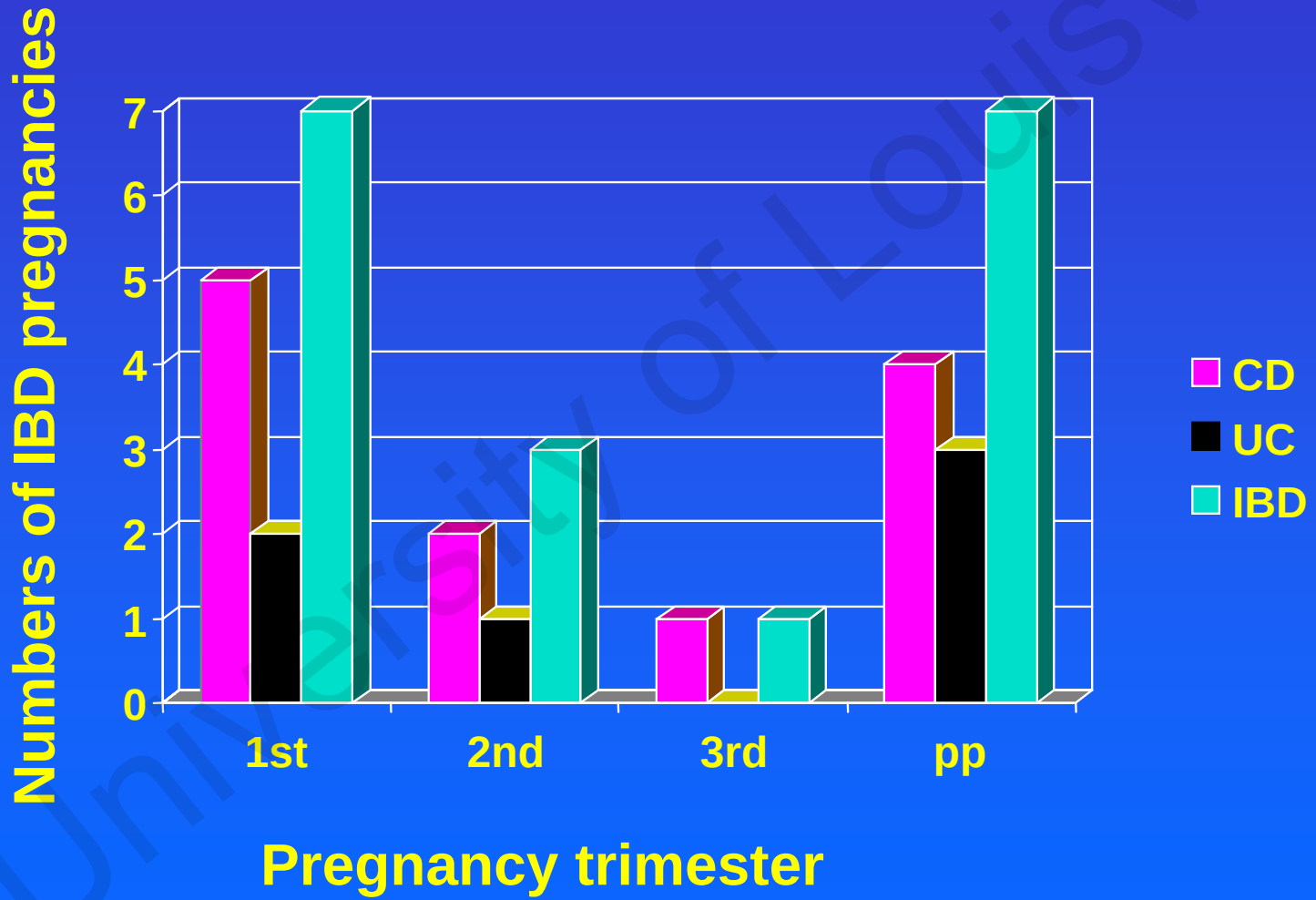
- Preg. in 37 of 416 women (CD 316; UC 110)
- 51 total pregnancies reviewed (CD 81%;UC 19%)
- Mean pregnancy age 28 y/o
- Obstetric and IBD related complications in 57% of pregnancies
- 6 pregnancies required hospitalization (12%)
- Spontaneous abortion in 11.8% (mean age 30.6 years
- Term pregnancy in 70% CD and 80% UC (all children reported healthy)

Beaulieau DB, et al. Gastroenterology 128: A316, 2005.

IBD Flares during pregnancy

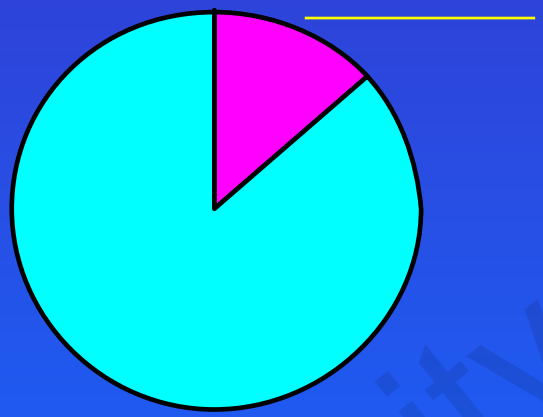
- IBD flare occurred in 21.2% of the IBD pregnancies
- IBD flare occurred most commonly during the first trimester (63.6% of flares)
- IBD maintenance therapy had been discontinued in 43% of patients experiencing first trimester flare.

Timing of IBD flares during pregnancy



Beaulieau DB, *et al.* Gastroenterology 128: A316, 2005.

IBD post-partum flares

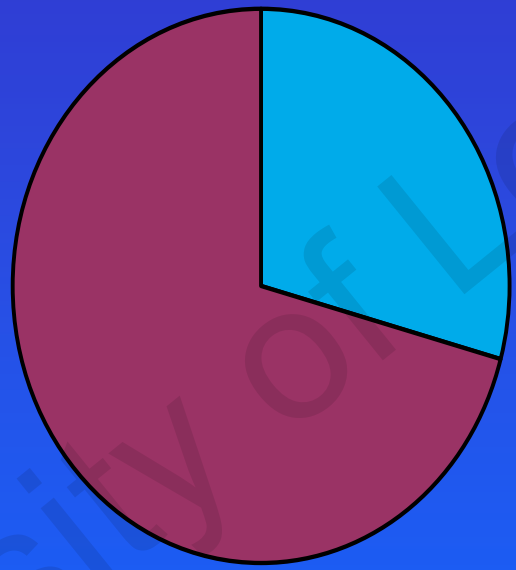


13.7% of IBD patients post-partum flare

- 57% of post partum flares occurred within the 1st month of delivery
- Post-partum flare was associated with drug cessation in 28.6% of patients

IBD obstetric complications

29.3% of IBD patients



- Spontaneous abortions in 11.8%
- Pre-eclampsia in 7.8%
- Gestational diabetes in 2%

Effect of IBD on Birth Outcomes - Sweden, 1991-92

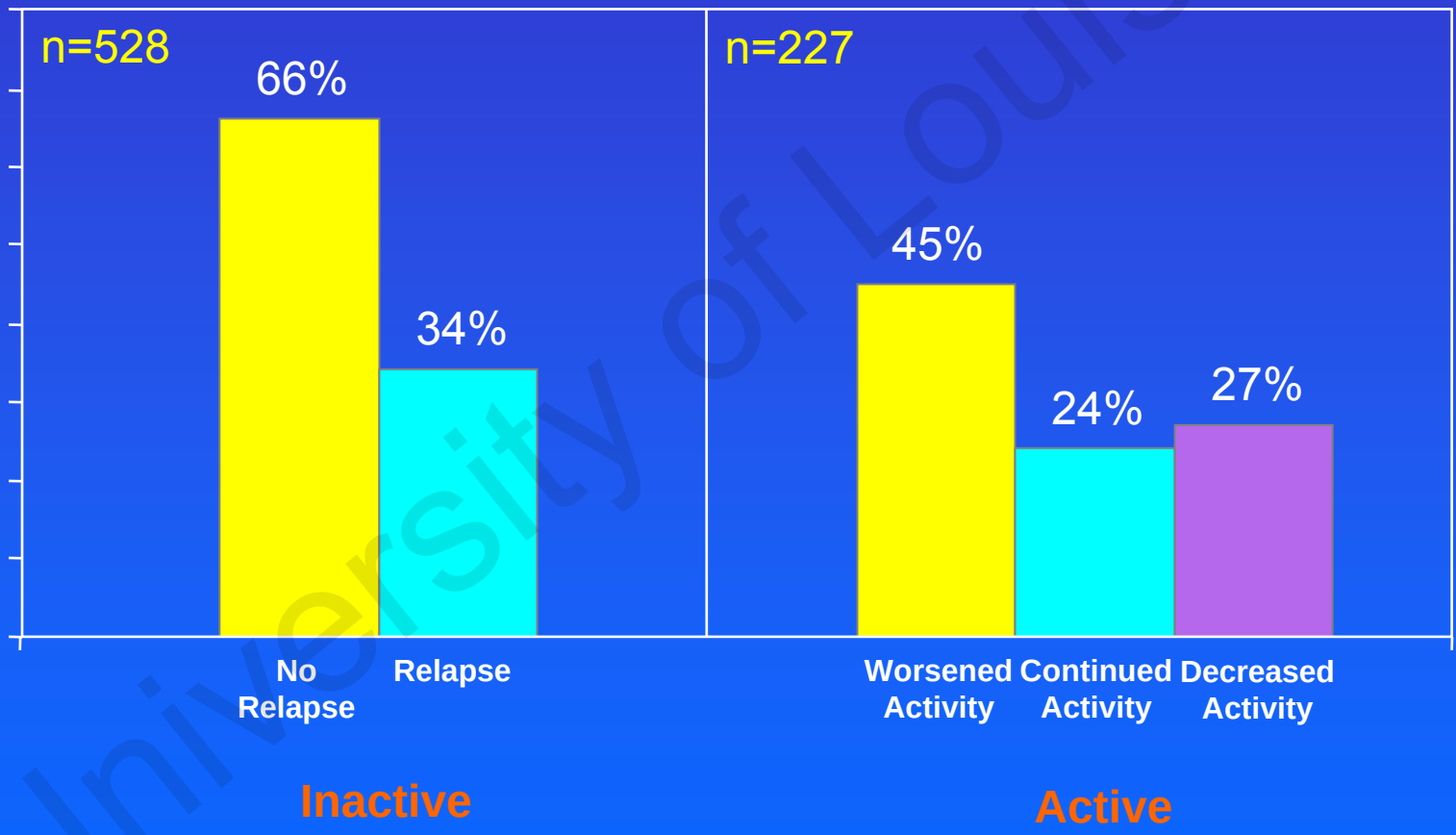
	IBD (n=75)	No IBD (n>239K)	Adjusted OR (95% CI)
Late fetal death	0.5%	0.3%	1.3 (0.6-2.6)
Infant death	0.5%	0.5%	
LBW	1.2%	0.6%	2.2 (1.1-4.2)
Very LBW	4.5%	2.9%	1.6 (1.1-2.2)
Very Preterm	1.9%	1.0%	1.8 (1.1-3.1)
Preterm	6.3%	4.3%	1.5 (1.1-2.0)
SGA	4.0%	2.9%	1.4 (0.97-2.0)
C-section	15%	10%	1.5 (1.2-1.8)

Kornfeld et al, Am J Obstet Gynecol 1997;177:942-6.

Predictors of Poor Outcome

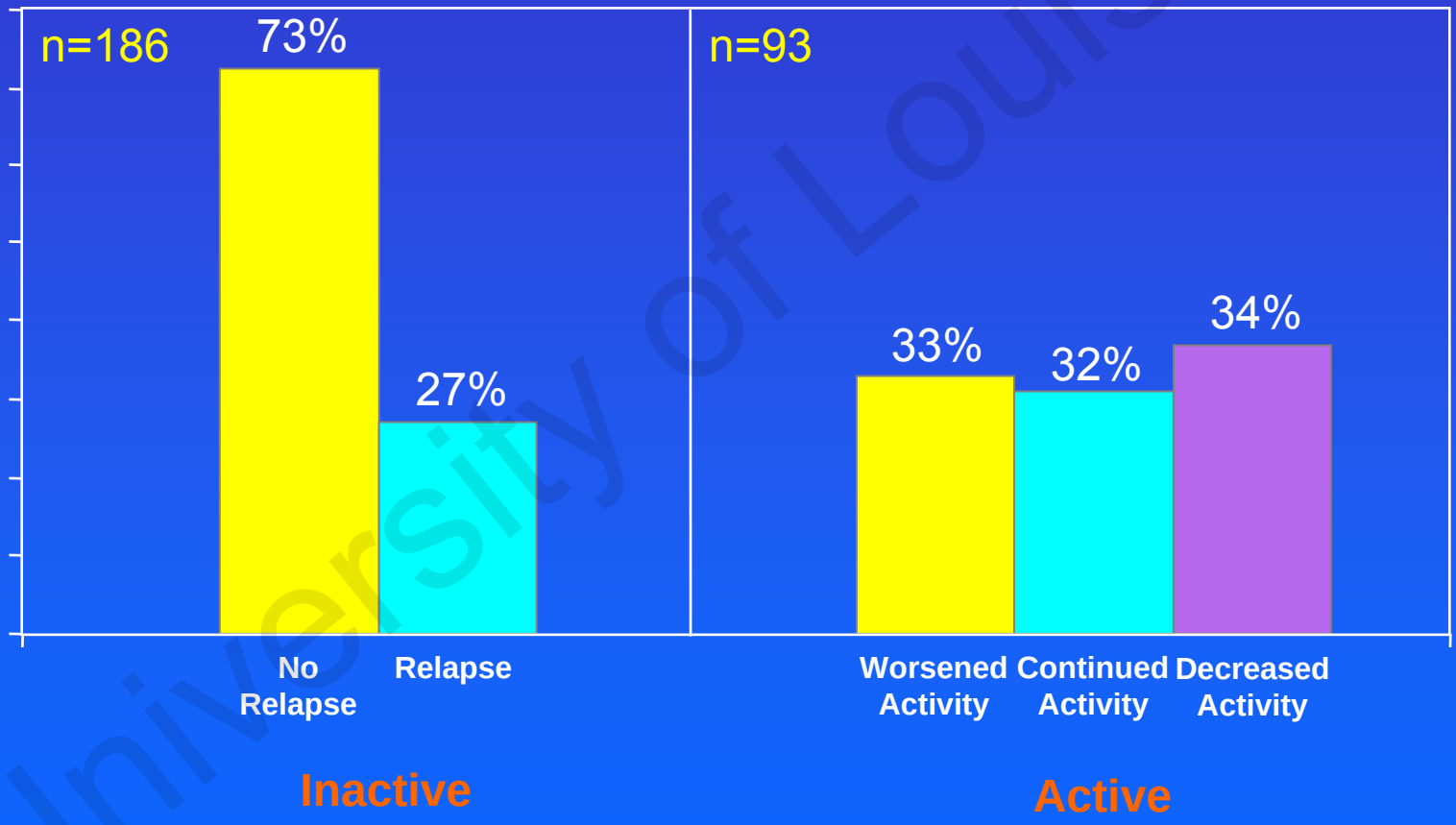
- Active Disease (UC and CD)
  - 50% vs 21% ($p<0.05$) abnormal outcomes
  - Activity at conception => Fetal loss
  - Activity during pregnancy => LBW
  - Independent of medication use

Effect of Pregnancy on UC: Disease Activity at Conception



Miller JP. J R Soc Med. 1986;79:221-5.

Effect of Pregnancy on CD: Disease Activity at Conception



Miller JP. J R Soc Med. 1986;79:221-5.

Medical Therapy in Conception and Pregnancy

Drugs in Pregnancy

- Limited data - Pharmaceutical trials almost never performed in pregnant women.
- PDR medicolegal disclaimer: “use in pregnancy is not recommended unless benefits justify risk to the fetus.”
- Half of all pregnancies are unplanned.
- FDA classification (A, B, C, D, X)
  - Ambiguous
  - Difficult to interpret and use in counseling

Koren G et al. N Engl J Med. 1998;338:1128.

FDA Teratogenicity Classification for Drugs during Pregnancy

- Category A: Controlled studies show no risk
  - No IBD medications in Category A
- Category B: No evidence of risk in humans
- Category C:
  - Animal studies show adverse effect
  - No adequate studies in humans
  - Drug's benefits in pregnant women may be acceptable despite its potential risk
- Category D: Positive Evidence of Risk
- Category X: Contraindicated in Pregnancy

Aminosalicylates

- Category B
  - Only controlled trial

    (Diav-Citrin 1998 gastroenterology)
    - 165 pts. Prospectively followed, controls with smoking/Etoh NOT IBD: Mean daily dose 2 gm
    - No teratogenicity
    - Maternal weight gain significantly lower on 5ASA
    - preterm delivery, LBW
  - Ludvigson (2002) LBW if mother treated with mesalamine or steroids during pregnancy

Aminosalicylates

- Sulfasalazine should be given with folic acid 1 mg BID
  - Folic acid: neural tube defects, CV, urinary tract, cleft palate
  - Case reports of congenital malformation
- Placental and Breast Milk Transfer Occurs
  - Potential of allergic reaction in newborn with watery diarrhea

Corticosteroids

- No evidence of teratogenicity in humans
- Poorer outcomes likely due to worse disease
- Theoretical concern of adrenal suppression in newborn
  - Cross placenta
  - 10-12% of maternal concentration
- Safe in breast feeding

Antibiotics

- Metronidazole/Ciprofloxacin
  - Low risk of teratogenicity
    - Metronidazole: case-control study and meta-analysis
    - Ciprofloxacin: prospective controlled study
  - Cipro- May be toxic to growing cartilage
  - Breast feeding is not advised
  - Minimal benefit in Crohn's and UC
  - No data on long-term safety

Azathioprine/6-MP

- Controversy - Class D label for pregnancy but commonly used in IBD, RA and transplant
- Teratogenicity of 6MP/AZA

  Teratogenic in animals (mice, rabbits, rats)

  No consistent increase in human teratogenicity

Polifka and Friedman (Teratology 65:240-261. 2002)

Human Studies: 6MP/AZA

- Transplantation Experience
  - Frequency of congenital anomalies in renal Tx 0.0-11.8% in 27 clinical series
  - No recurrent pattern of anomalies seen
  - No increase in anomalies (Armenti 1994) in kidney transplant recipients on AZA
  - Immunosuppression is never stopped in setting of organ transplant
- No congenital anomalies in rheumatic disease, SLE

The Safety of 6-Mercaptopurine for Childbearing Patients With Inflammatory Bowel Disease: A Retrospective Cohort Study

Francella et al, Gastroenterology 2003;124:9–17

-485 patients exposed - 6-MP before, or at the time of, conception.

-Compared with IBD patients who had their pregnancies before taking 6-MP.

No statistical difference in conception failures (spontaneous abortion), abortion sec to a birth defect, major congenital malfn., neoplasia, or increased infections among male or female patients taking 6-MP compared with controls (RR 0.85 [0.47–1.55], *P* 0.59).

Norgard (Aliment Pharm Ther 2003)

- Population based prescription registry, Denmark
  - 9 pregnancies (30d before concept/1st trimester)
  - 10 pregnancies (exposed entire pregnancy)
  - Outcomes vs (1) 19,418 pregnancies no drugs (2) any drug (3) 6MP/AZA >3 mos before pregnancy
- 11 pts: 55% IBD, 45% other disease
  - Congenital malform OR = 6.7 (95%CI 1.4-32.4)
  - Mortality OR = 20 (2.5-161.4)
  - Preterm Birth OR = 6.6 (1.7-25.9)
  - LBW OR = 3.8 (0.4-33.3)
- After exclusion of most ill pt (AIH), no statistical significance in OR

AZA/6-MP

- Experience in IBD
  - Alstead (1990): 14 pts: 7 entire pregnancy
    No congenital anomalies
  - Khan (2000): 8 preg/6 pt
    No complications
  - Francella (2003): Retrospective
    79F (24 UC), 76M (27 UC), 325 pregnancies
    No diff. 6MP Vs no 6MP
  - Breastfeeding not recommended

Cyclosporine

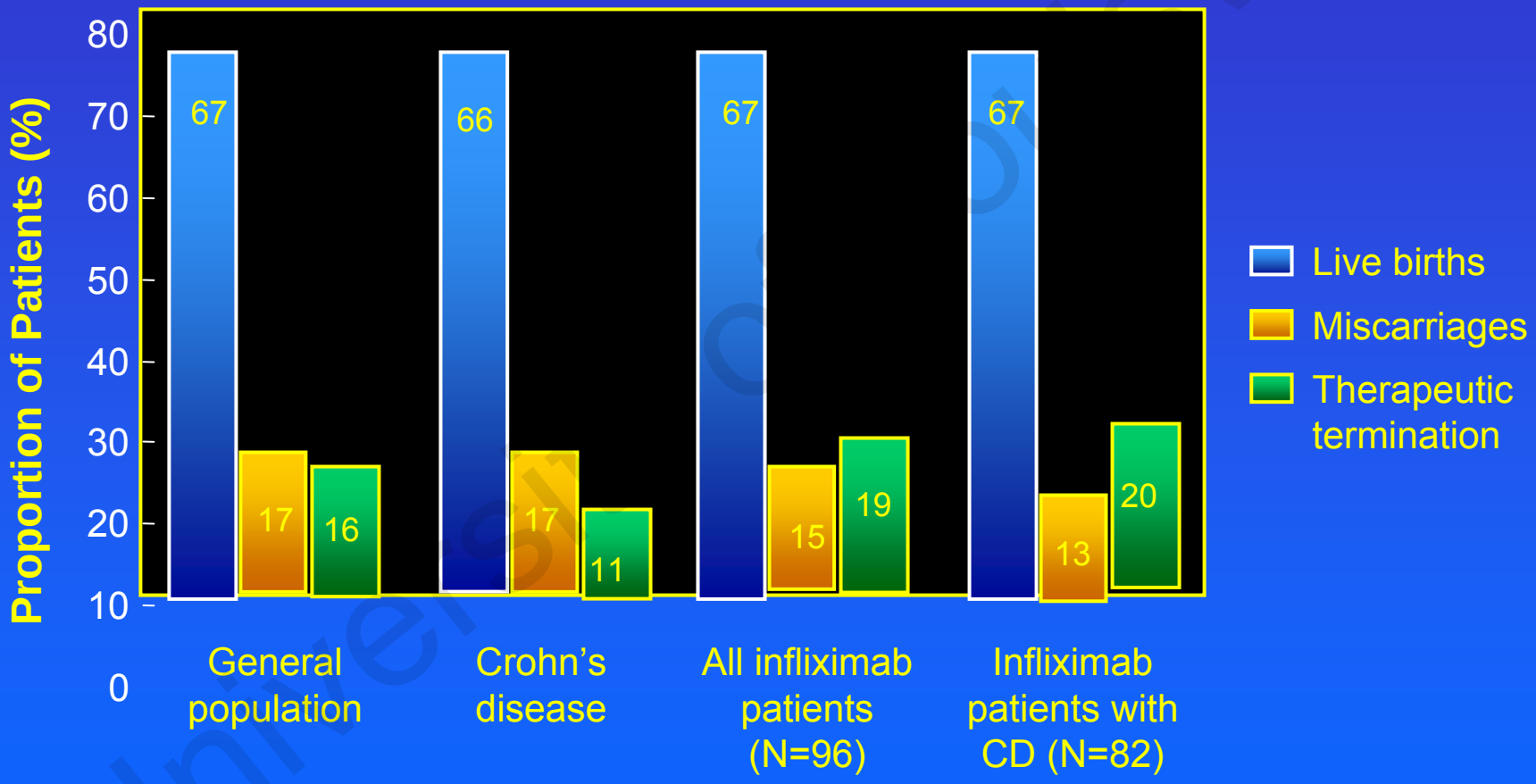
- Teratogenicity
  - Not in animals, probably not in humans
  - One case in humans, administered at 29 weeks.

    Healthy fetus at 34 weeks
  - Used in fulminant colitis, better than emergent colectomy
- Breast feeding not advised
- Reserved for fulminant disease vs colectomy

Infliximab and pregnancy (Category B)

- Katz JA et al. (Am Journal Gastroenterol 2004)
- Infliximab Safety Database
  - 146 identified pregnancies
  - 82 CD, 1 UC, 10 RA, 3 unknown
- Outcome 96 pregnancies, n = 100 births
  - Live birth 64 (67%)
  - Miscarriage 14(15%)
  - Therapeutic termination 18 (19%) (pts. choice)
- Data similar to expected for UC/CD not exposed to Infliximab

Infliximab in Pregnancy: Outcomes of Women Exposed to Infliximab During Pregnancy



Katz JA, et al. Am J Gastroenterol. 2004;99:2385-2392.
Ventura et al. National Center for Health Statistics Vital Health Stat 2000;21:1-59
Hudson et al. Int J Gynaecol Obstet 1997;58:229-237.

Intentional Infliximab in Pregnancy

10 Crohn's disease patients intentionally exposed to infliximab during pregnancy

8 women received maintenance infusions

2 women received initial infusions

10 Live Births

- Congenital malformations (N=0)
- IUGR (N=0)
- SGA (N=0)
- Preterm (N=3)
- LBW (N=1)

8 Caesarean sections: 2 active luminal, 3 perianal disease, 1 preterm

Mahadevan U, et al. *Aliment Pharmacol Ther.* 2005;21:733-738.

Contraindicated Medications

- Methotrexate
  - Known abortifacient
  - Teratogenic (skeletal defects, cleft palate)
  - 3 month “washout” in females and males prior to planned pregnancy
- Thalidomide
  - 20-30% Rate of Birth defects or fetal death
  - limb malformation (phocomelia)