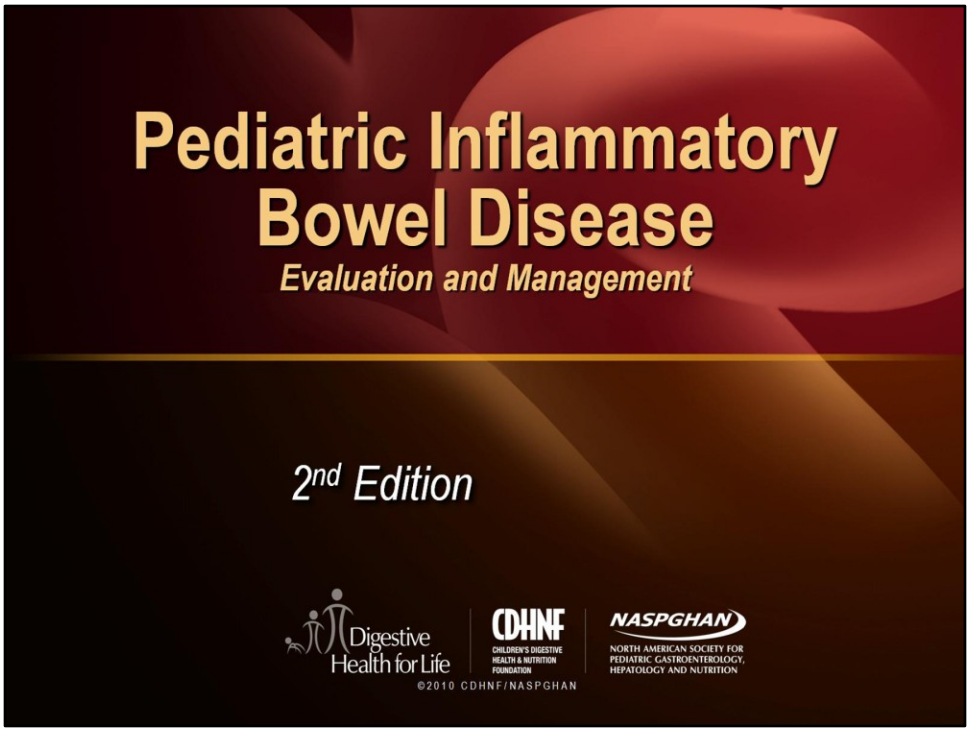
Pediatric Inflammatory Bowel Disease
Evaluation and Management
2nd Edition
Digestive Health for Life
CDHNF
CHILDREN'S DIGESTIVE HEALTH & NUTRITION FOUNDATION
NASPGHAN
NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION
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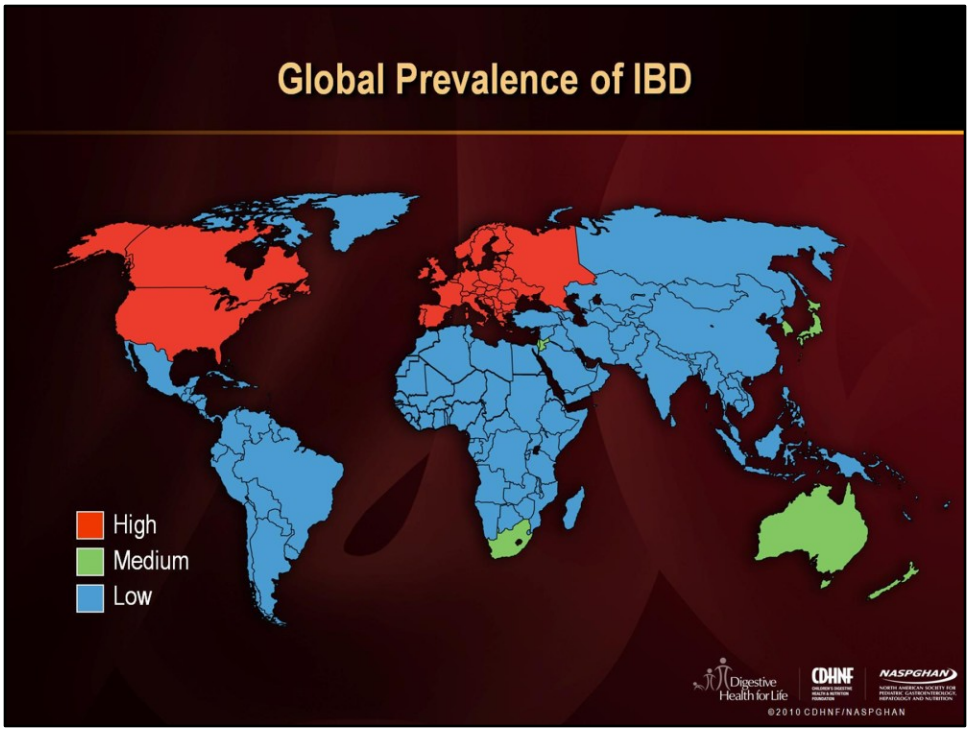
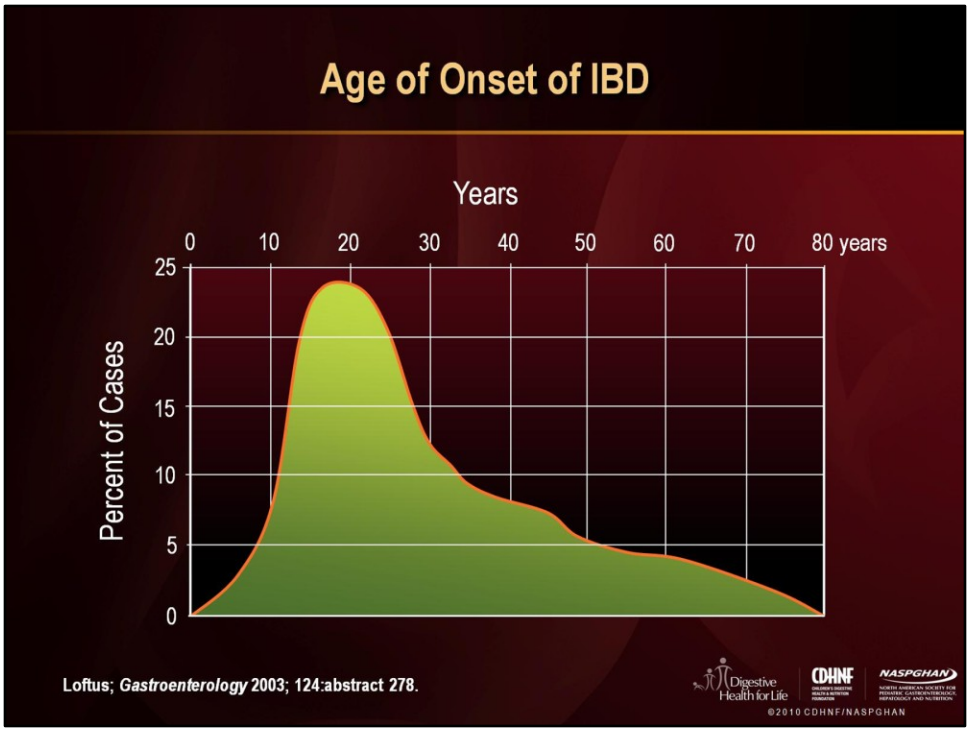
Epidemiology



Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD), is increasing in incidence among children and impinges upon their growth, education and social well-being.
Population-based studies suggest that IBD is unevenly distributed throughout the world with the highest disease rates occurring in western countries.
Epidemiologic surveys have also suggested that IBD incidence rates have changed over the second half of the 20th century with a gradual increase for both Crohn's disease and ulcerative colitis, which appears to be independent of observer bias.
A population-based clinical database of patients with IBD aged <15 years in Ontario, Canada showed
1. an increase in this age Prevalence age- and sex-standardized per 100000 population; from 42.1 (in 1994) to 56.3 (in 2005)
2. Incidence per 100000 increased from 9.5 (in 1994) to 11.4 (in 2005).
3. Statistically significant increases in incidence were noted in 0–4 year olds (5.0%/year, p=0.03) and 5–9 year olds (7.6%/year, p<0.0001), but not in 10–14 or 15–17 year olds

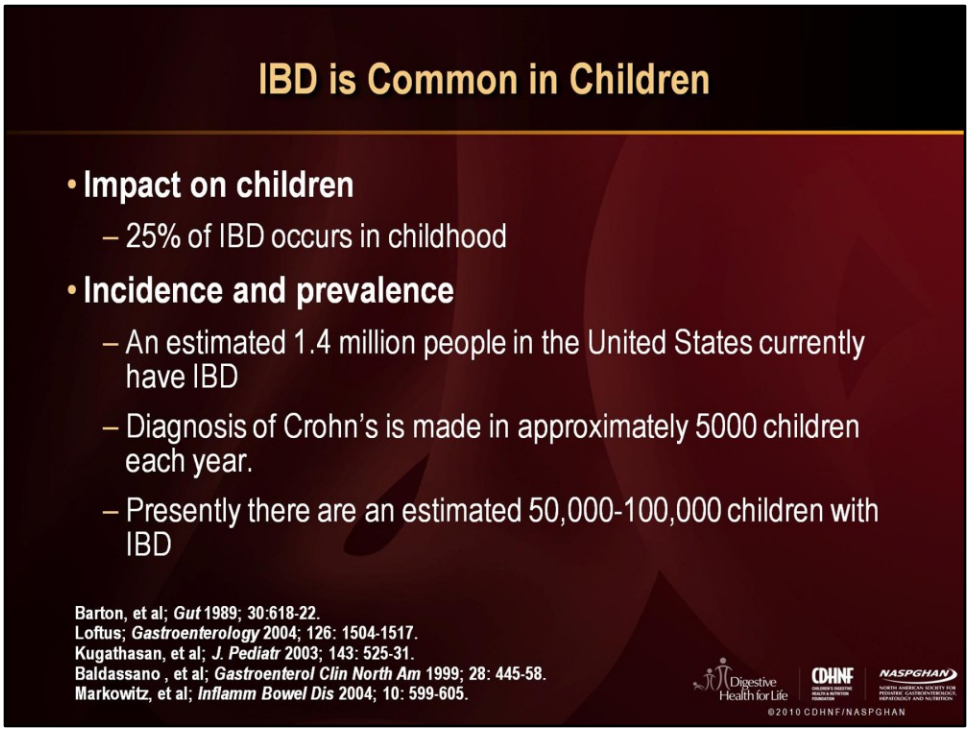
Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data
E I Benchimol1,2,3, A Guttmann1,3,4, A M Griffiths2,4, L Rabeneck1,3,5, D R Mack6, H Brill7, J Howard8, J Guan1, T To1,3,9

Descriptive studies carried out during the latter half of the 20th century reveal that the incidence of IBD varies in different geographical populations.
The highest rates are observed in European and North American populations, with the lowest rates seen among New Zealanders.
Comprehensive data from most parts of Africa, Asia and South America are not available, but emerging data from rapidly developing South Asian countries suggest IBD is also increasingly recognized in those countries.
A study of the 'time trends' in disease incidence has shown that the incidence of CD has increased substantially in most developed countries such as Scotland, Denmark, UK, the USA and Japan.
Lashner BA. Epidemiology of inflammatory bowel disease. Gastroenterol Clin North AM. 1995. Sep. 24(3);467-74. Review



Because high rates of IBD onset occur in childhood and adolescence (peak incidence between 15 to 25 years of age), monitoring the incidence of pediatric IBD may reflect changing trends in IBD demographics. Recent retrospective European studies and one prospective population-based survey from the UK have suggested that the incidence of IBD in children and adolescents has significantly increased over the last 35 years. In addition, data from European pediatric studies also suggest that there has been a change in the patterns of disease, as the incidence of CD has risen above that of UC.

Loftus EV, Gastroenterology. 2003



How common is IBD in the United States? A population-based epidemiological study was completed which evaluated all children in Wisconsin with a new diagnosis of IBD within a two-year period between 2000 and 2001. This found the incidence of IBD to be 7 per 100,000 in children under 18 years of age. The age-specific incidence rates in North America for children 1 to 17 years old are approximately 2 per 100,000 for ulcerative colitis and 4.5 per 100,000 for Crohn's disease (indeterminate colitis in the rest was 0.5 per 100,000). Four percent of pediatric Crohn's disease occurs before the age of five years. Extrapolations of these data suggest that more than 50,000 children and adolescents in North America are suffering from IBD and that there are more than 4,500 new cases of IBD annually. Crohn's disease is twice as common compared with ulcerative colitis in the pediatric age group.

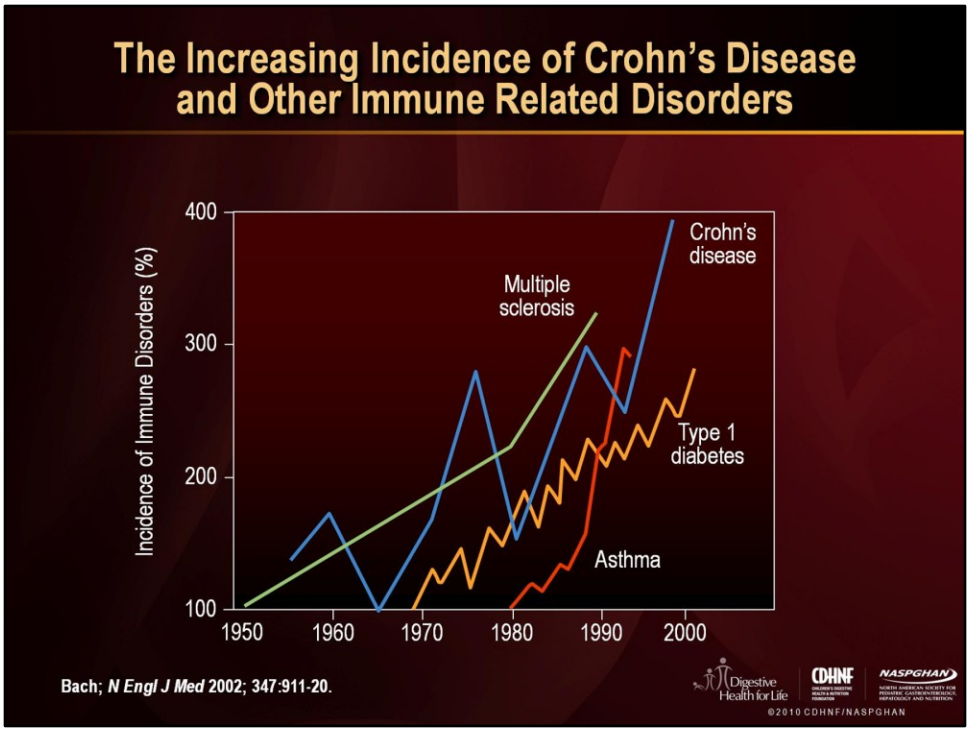
References:

Barton JR, et al. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983; marginal fall in ulcerative colitis, three-fold rise in Crohn's disease. *Gut*. 1989;30(5):618-22

Kugathasan S, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003;143(4):525-31

Baldassano RN, Piccoli DA. Inflammatory bowel disease in pediatric and adolescent patients. *PCNA, Gastroenterol Clin North Am*. 1999;28(2):445-58. Review.

Markowitz JE, Patterns of complementary and alternative medicine use in a population of pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2004;10(5):599-605

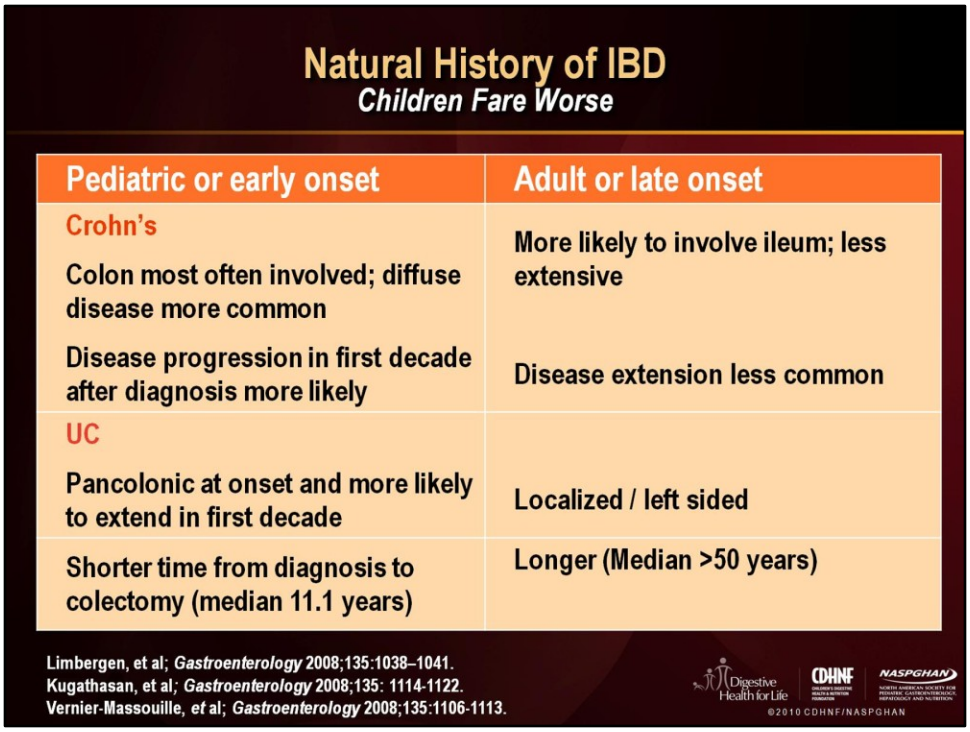


Several studies from Europe have reported an increasing incidence of Crohn's disease and ulcerative colitis. A Scottish cohort of hospitalized pediatric IBD patients noted a three-fold increase in incidence of Crohn's disease from 1968 to 1983, with essentially no change in incidence of ulcerative colitis. Another UK study reported a doubling of incidence of Crohn's disease between years 1983 to 88 and 1989 to 93. The incidence of ulcerative colitis remained stable over the same time period. Similar reports have been published from Scandinavian countries, but data from North America assessing time trends in pediatric IBD is lacking.

Not only is the incidence of IBD increasing, but many other immune-mediated, chronic, inflammatory conditions have been noted to increase during the 50-year period (1950-2000), thus supporting the hygiene hypothesis that while sanitary conditions improve, the immune-mediated diseases increase.

References:

The effect of infections on susceptibility to autoimmune and allergic diseases ***N Engl J Med*****. 2002;347(12):911-20**



Childhood-onset IBD demonstrates unique characteristics in phenotype, severity and family history. A topic of great interest is whether childhood-onset disease is etiologically distinct from adult onset disease—a debate recently catalyzed by the search for susceptibility genes in CD and UC.

Clinical experience in childhood-onset disease suggests that childhood-onset disease may have a more "severe" phenotype. The presenting phenotype of childhood- onset IBD is characterized by extensive anatomic involvement, with strikingly high rates of panenteric CD (small bowel, large bowel, and upper GI tract involvement) as well as extensive UC.

Disease extent is dynamic in childhood-onset disease: Even within 2 years of diagnosis, childhood-onset CD progressed to more extensive anatomic involvement in 1 in 3 patients in Scottish children . Disease behavior rapidly progressed to complications of stricture formation or the development of fistulae. Disease extent in 46% of the few cases of childhood-onset UC with isolated left-sided disease or proctitis at diagnosis also showed extension within the follow-up period.

LIMBERGEN J V et al. Definition of Phenotypic Characteristics of Childhood-Onset Inflammatory Bowel Disease GASTROENTEROLOGY 2008;135:1114–1122

Kugathasan S, Cohen S. Searching for New Clues in Inflammatory Bowel Disease: Tell Tales From

Pediatric IBD Natural History Studies. 2008;135:1038-104

In a French study, Vernier-Massouille et al examined the natural history of pediatric CD in a population-based model in a geographically derived incidence cohort of 404 pediatric-onset cases. 29% of children with CD were found to have complicated disease, defined as perforating and/or stricturing disease at diagnosis and almost two thirds of children with CD had complicated disease behavior at the 7-year follow-up. Based on a large amount of adult IBD literature, the general belief is that the disease extension or change of location is relatively rare during follow-up in CD. In the French cohort, a surprising 31% had disease location extending to areas other than those present at the time of initial diagnosis. Those with stricturing behavior at diagnosis had a 2.5-fold greater risk for surgery and any exposure to corticosteroid had a 3-fold greater risk for surgery. The authors conclude that pediatric CD is

characterized by a severe, extensive phenotype, and a greater risk for disease extension by location and surgery despite increasing use of immunomodulators.

Vernier-Massouille et al N**atural history of pediatric Crohn's disease: A population based cohort study. Gastroenterology 2008;135:1106-1113**

Recent data from the North American Pediatric IBD Consortium Registry are consistent with above findings. 600 pediatric CD patients at diagnosis: 61.5% of children had small bowel and colon involvement (compared with 50.5% in Van Limbergen study). **Gupta N, Bostrom AG, Kirschner BS, et al. Gender differences in presentation and course of disease in pediatric patients with Crohn's disease. Pediatrics 2007;120:e1418–e1425.)**

Baldassano et al have described a cohort of 142 children with CD: 86% had involvement of the small bowel and colon (this group included involvement of UGI tract). **Baldassano RN, Bradfield JP, Monos DS, et al. Association of the T300A non-synonymous variant of the ATG16L1 gene with susceptibility to paediatric Crohn's disease. Gut 2007;56:1171–1173.**

Cucchiara et al showed in an Italian cohort of pediatric CD patients with 1 year of follow-up (*n* 200) that 58% had ileocolonic CD. However not all these studies have followed the same classification system. **Cucchiara S, Latiano A, Palmieri O, et al; on behalf of the Italian Society of Pediatric Gastroenterology and Nutrition. Polymorphisms of tumor necrosis factor-[alpha] but not MDR1 influence response to medical therapy in pediatric-onset inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2007;44:171–179.**

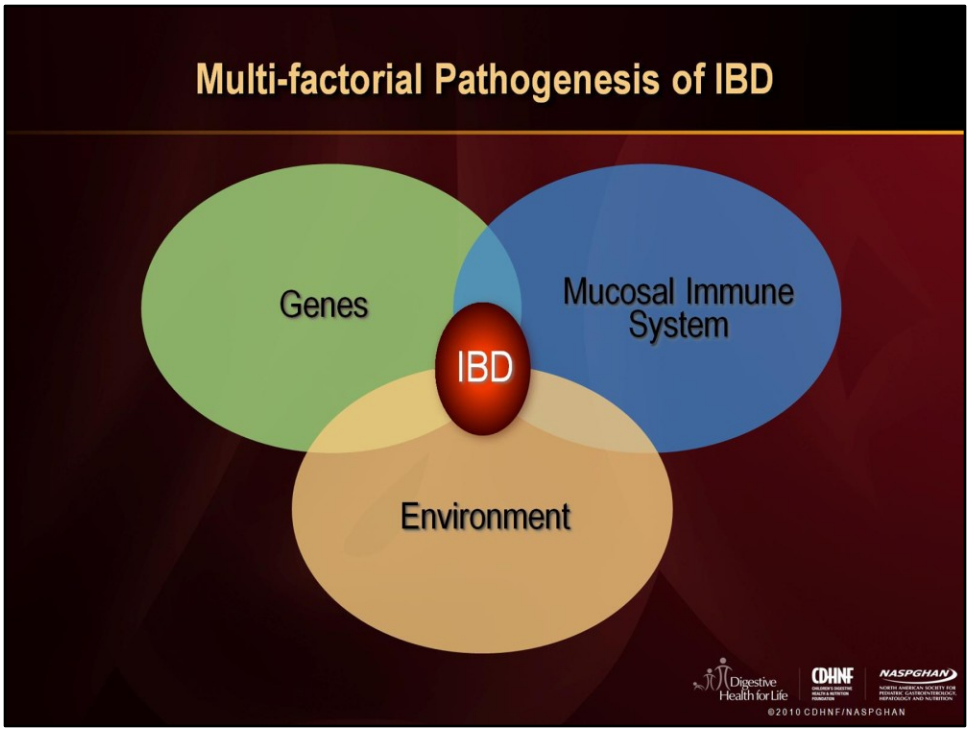
All three studies given below suggest that younger children with CD have more colonic disease:

1. The CD cohort in van Limbergen study children 8 years old at the time of diagnosis had significantly less involvement of the ileum and more isolated colonic disease than children 8 years at diagnosis. **JOHAN VAN LIMBERGEN Definition of Phenotypic Characteristics of Childhood-Onset Inflammatory Bowel Disease GASTROENTEROLOGY 2008;135:1114–1122**

2. In a large study of nearly 1400 North American early-onset patients, Heyman et al demonstrated by multifactorial analysis that a colonic predominant phenotype exists in IBD diagnosed under the age of 8 years. **Heyman MB, Kirschner BS, Gold BD, et al. Children with early onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. J Pediatr 2005;146:35–40.**

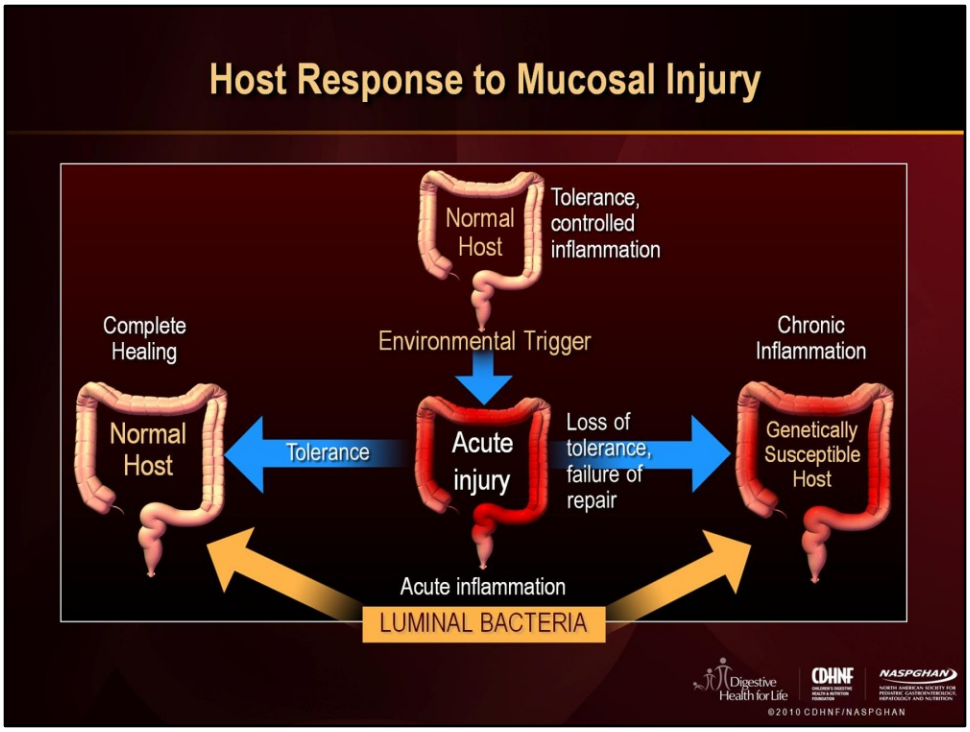
3. Paul et al studied 413 pediatric IBD patients and also demonstrated a greater tendency for very young patients to present with colonic disease. **Paul TM, Birnbaum AM, Pal DKP, et al. Distinct phenotype of early childhood inflammatory bowel disease. J Clin Gastroenterol 2006;40:583–586.**


Pathogenesis
and Immunology



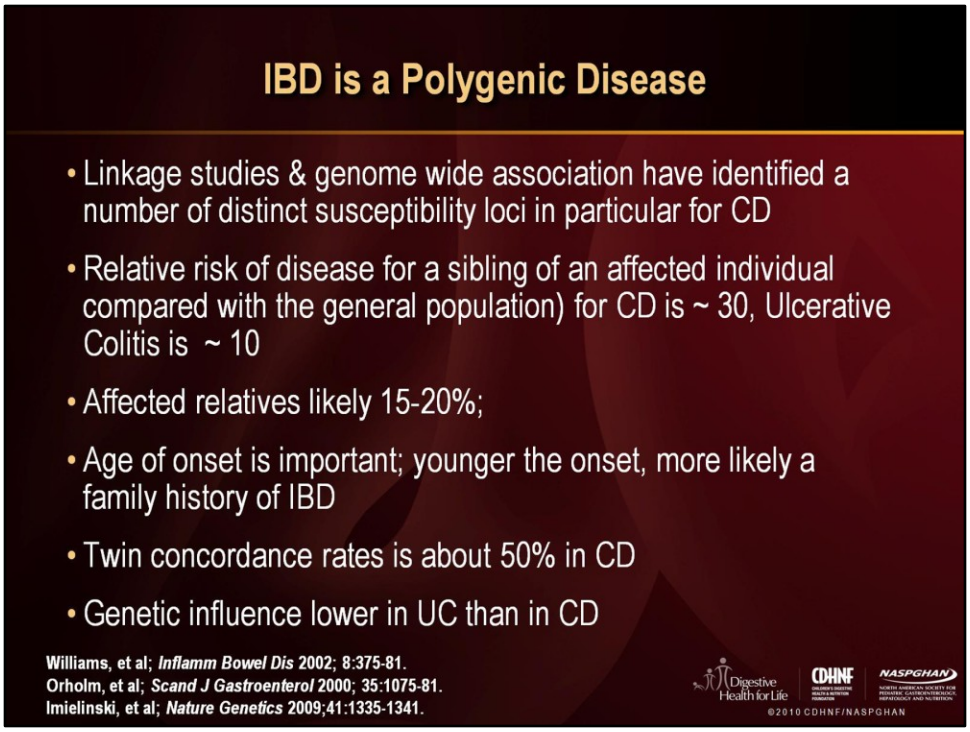
It has been speculated that genes and the environment play a central role in the development of IBD. As with most common disorders, both nature (genes) and nurture (environment) are responsible, not just one versus the other. Because IBD is a disease of chronic gut inflammation, we must first ask what starts the inflammation and then ask what keeps it going? Most IBD researchers believe that something in the environment triggers inflammation in individuals whose genetic profile makes them susceptible to IBD. Once inflammation begins, the genetic influence plays a large role in maintaining (or not maintaining) the inflammatory reaction. It is likely that IBD has several different, as yet unnamed, subtypes. These subtypes would each have a different genetic and environmental profile, probably modulated by bacterial flora in the gut, but would all cause approximately the same symptoms. Only further genetic and environmental studies from both an epidemiological and microbiological perspective will be able to clarify this.

Several susceptibility genes have been identified for IBD, with two of them now well established for Crohn's Disease. It is believed that IBD develops when a genetically susceptible host is exposed to a series of environmental triggers. In a normal host, these environmental triggers would lead to self-limited activation of the mucosal immune system. However, when combined with specific IBD genes, these environmental triggers lead to a chronic activation of the mucosal immune system, which we recognize clinically as Crohn's disease or ulcerative colitis.



The gut is exposed to numerous dietary and bacterial antigens each day and normally exists in a state of controlled inflammation known as tolerance. Environmental triggers such as infections or NSAIDs will lead to an increase in gut inflammation. In a normal host, the tolerance and repair mechanisms in the gut are then activated, restoring the intestine to its baseline state. In a genetically susceptible host, a failure of these tolerance and repair mechanisms leads to chronic activation of the mucosal immune system and ongoing injury.


Genetics



The current belief is that IBD is a polygenic disease with a pattern of complex genetic traits The genetic influence of Crohn's disease is greater than that of ulcerative colitis, although in both disorders there is a 15 to 20% likelihood of a patient having an affected relative, usually a first or second degree relative. There is evidence that pediatric onset IBD patients have a greater likelihood of having a family history of IBD. Familial patterns of disease location or phenotype (fistulizing vs. stenotic disease) exist in Crohn's disease. However, inheritance does not follow simple Mendelian genetics. The research on genetic susceptibility of inflammatory bowel diseases (IBD) has been tremendous and over 13 chromosomal regions have been identified by genome-wide linkage scanning. Many of these genes are involved in mucosal function, particularly mucosal barrier function.

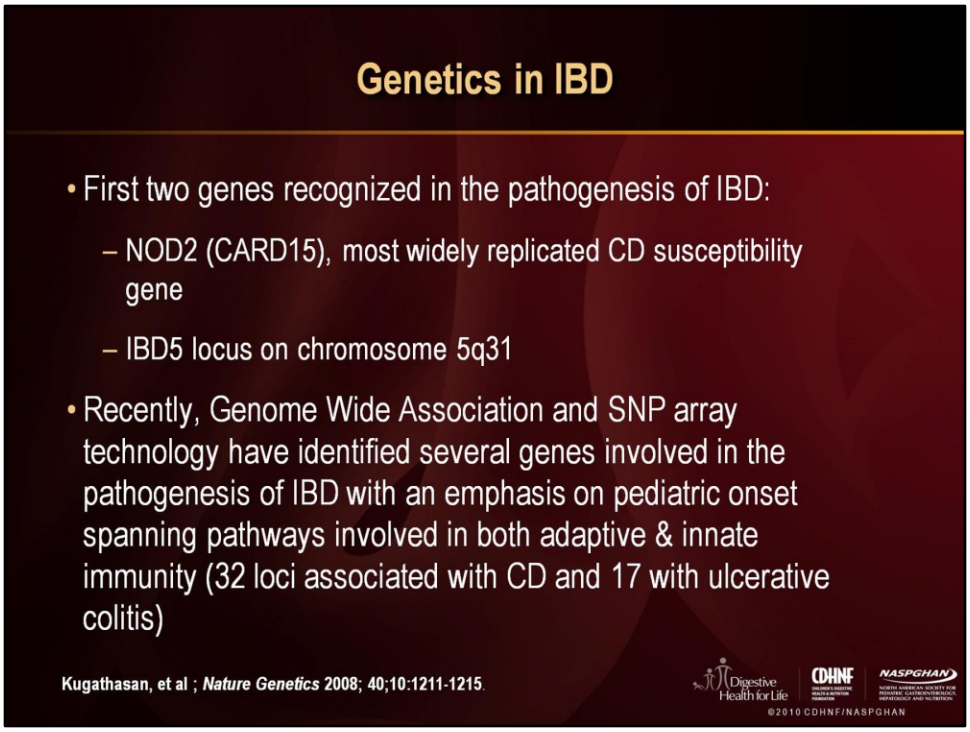
***Williams CN,Kocher K, Lander ES, Daly MJ, Rioux JD* Using a genome-wide scan and meta-analysis to identify a novel IBD locus and confirm previously identified IBD loci . *Inflamm Bowel Dis.* 2002 Nov;8(6):375-81.**

Orholm M, Binder V, Sorensen TI, Rasmussen LP, Kyvik KO. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. Scand J Gastroenterol. 2000 Oct;35(10):1075-81.

Incidence, family, twin and phenotype concordance studies suggest that IBD is highly heritable, albeit complex, spurring an ongoing search for genetic factors that confer susceptibility to this disease2,3. Genome-wide association studies (GWASs) applying high-density SNP array technology have greatly expanded the number of genetic factors implicated in IBD pathogenesis to include 32 loci associated with Crohn's disease and 17 associated with ulcerative colitis, spanning pathways involved in adaptive (*IL23R*, *IL10*, *IL12B*, *STAT3*) and innate (*CARD15*, *ATG16L1*, *IRGM*) immunity.

Early-onset IBD, has unique characteristics of phenotype, severity and familiality, features that provide support for the search for loci that may be specific to early-onset disease. In addition, because early-onset IBD has a stronger familial component than the adult disease, studies targeting this subgroup potentially provide additional power to identify genes that contribute modest effects.

Common variants at five new loci associated with early-onset inflammatory bowel disease. Imielinski M, Baldassano RN Griffiths AM et a;l. Nature Genetics volume 41 | number 12 | 2009; 1339.



The major breakthrough in understanding the pathogenesis pf Crohn's disease occurred in 2001 with identification of the first susceptibility gene NOD2/CARD15. The NOD2/CARD15 gene is undoubtedly replicated most widely and most understood at present.

-This gene recognizes -intracellular lipopolysaccharide (endotoxin) from gram negative bacteria and transducer signals activating NFκB and initiating apoptosis.

-is involved in the recognition of bacterial peptidoglycan-derived muramyl dipeptide (MDP)

-stimulates secretion of antimicrobial peptides including alpha-defensins (also called cryptdins) to protect the host from invasion.

Three SNPs within the NOD2/CARD15 mutations (R702W, G908R and 1007fsinsC) are established independent risk factors for Crohn's disease in Caucasians.

Ethnic variations

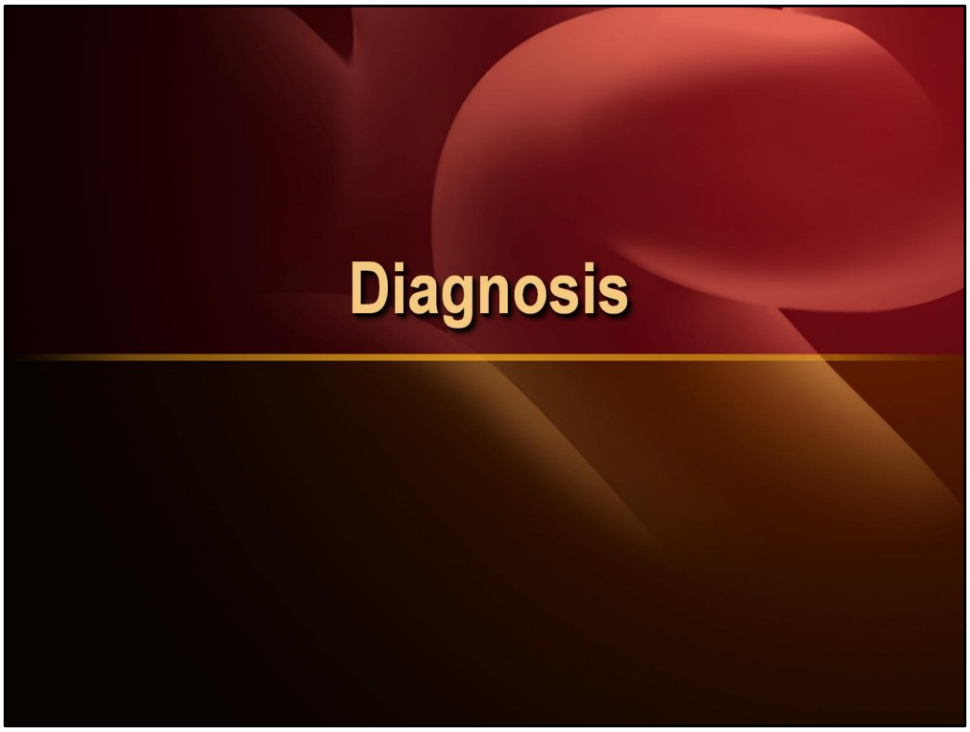
NOD2/CARD15 mutations are absent, or very rare, in Asians (Japanese, Chinese and Korean), Arabs, Africans and African Americans. Even among Caucasian Crohn's disease patients, a great amount of genetic heterogeneity exists.

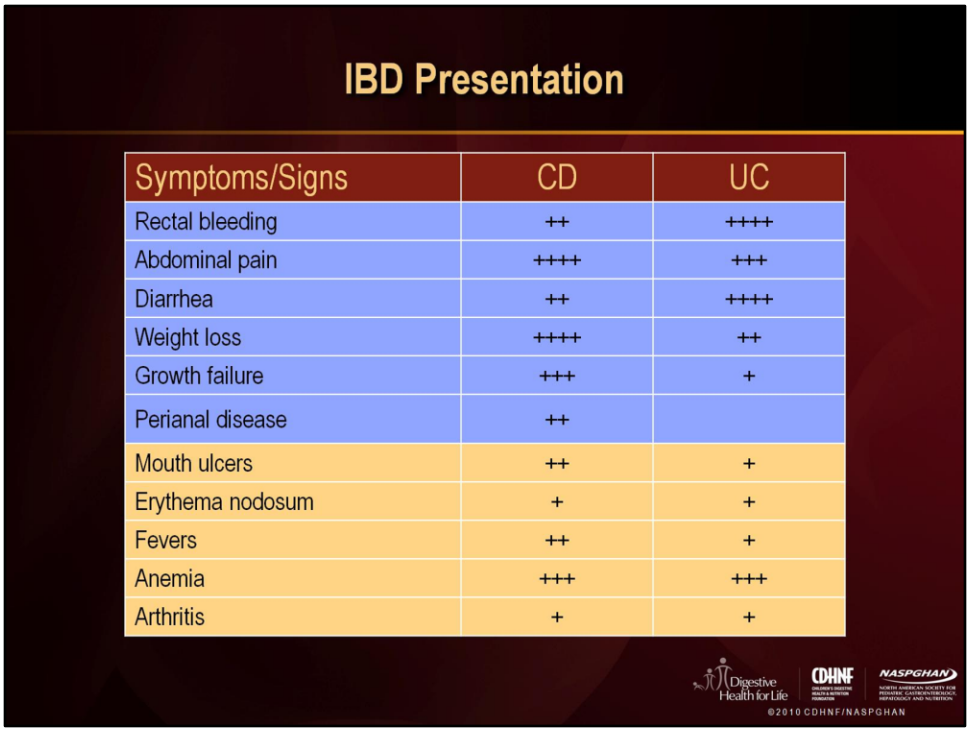
The NOD2/CARD15-dependent population-attributable risk is mild to modest among Northern European populations (Irish, Norwegians, Scots, Finns) as compared with populations residing in the lower latitudes (Germans and Italians). Individuals with one of the three major disease-associated alleles have a 2 to 4-fold increased risk for developing Crohn's disease, whereas homozygous or compound heterozygous carriers have an up to 40-fold increase in genotype-relative risk.

Despite their strong association with Crohn's disease, genetic alterations of the NOD2/CARD15 gene are neither sufficient nor necessary for the development of Crohn's disease. This is based on the observation that 1 to 5% of the general Caucasian population is homozygous, and 10 to 20% is heterozygous for Crohn's disease associated mutations while up to 70% of Crohn's disease patients do not have NOD2/CARD15 alleles mutated. Furthermore, NOD2/CARD15-deficient mice do not develop intestinal inflammation spontaneously.

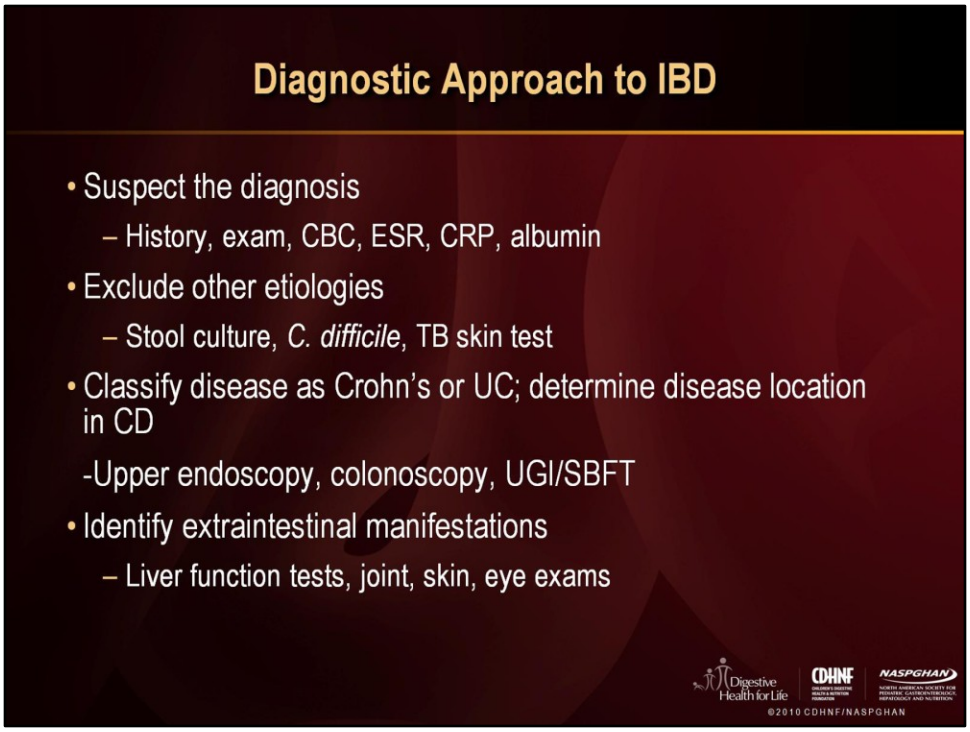
References:

Hugot JP et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001;411: 599-603. Ogura Y et al. A frame shift mutation in NOD2 associated with Crohn's disease. *Nature* 2001;411:603-6. Ahmad T. Armuzzi A, Bunce M et al. The molecular classification of the clinical manifestations of Crohn's disease. *Gastroenterology* 2002;122:854-66. Chamaillard M, Jacob R, Desreumaux P, et al. Advances and perspectives in the genetics of inflammatory bowel diseases. Clin Gastroenterol Hepatol 2006;4(2):143-51.

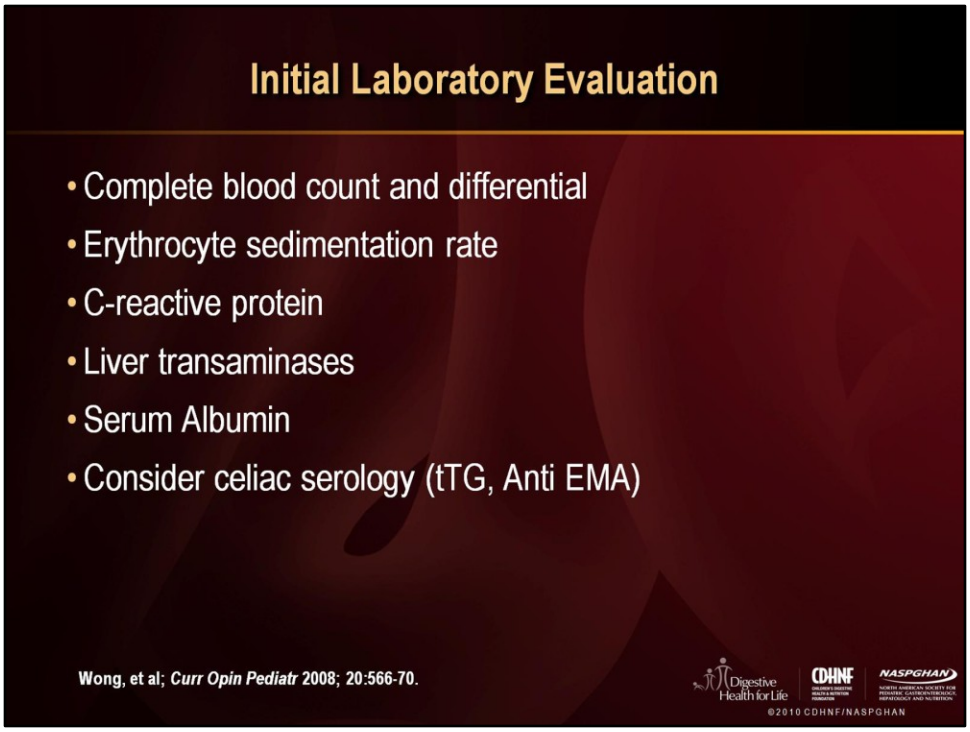

Diagnosis



IBD involving the colon (whether ulcerative colitis or Crohn's disease) most commonly presents with diarrhea and rectal bleeding. In contrast, Crohn's disease involving the terminal ileum and/or cecum tends to present more subtly, with abdominal pain, weight loss, fatigue, and fever. Perianal fistulae and infections are seen in Crohn's disease, but not ulcerative colitis. Extraintestinal manifestations (e.g. erythema nodosum, arthritis) are seen in both CD and UC, but are a presenting feature less than 15% of the time.

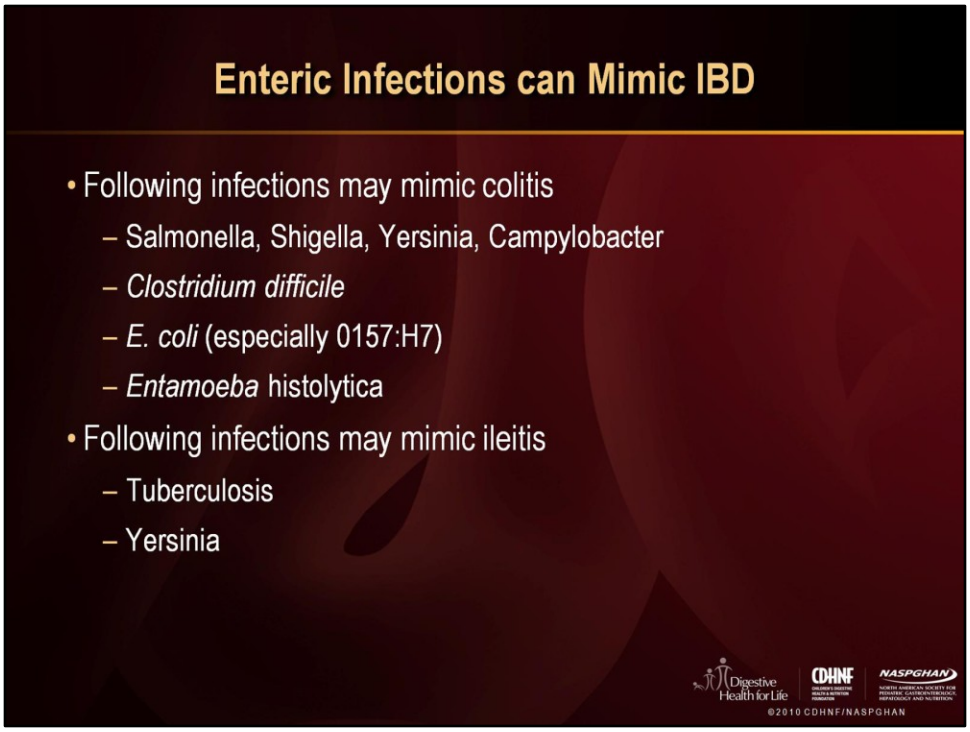


The principles of diagnosing IBD remain the same. First, the clinician must suspect the diagnosis based on the history and examination. Second, other causes of bowel inflammation must be excluded. Third, the physician must perform radiography and endoscopy to classify the disease as either Crohn's disease or ulcerative colitis. Fourth, the physician must assess the extent and severity of the disease, and accurately define the disease location. Finally, the physician must carefully evaluate for extraintestinal manifestations, including arthritis and liver disease.

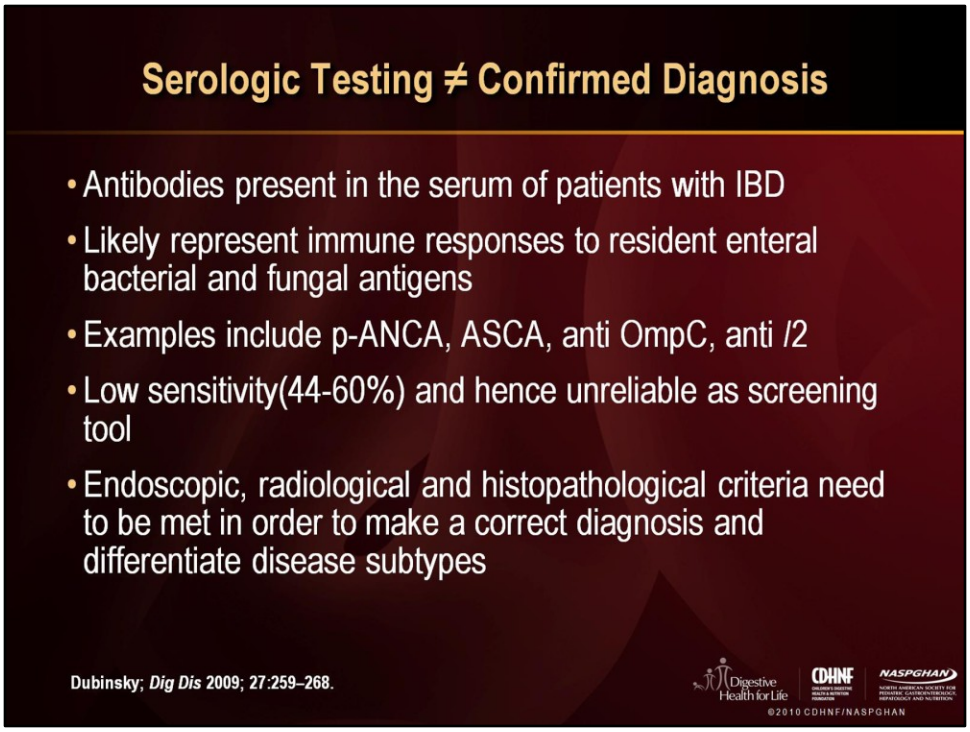


Diagnosing inflammatory bowel disease (IBD) is straightforward when alarm symptoms are present, such as bloody diarrhea and weight loss. Appropriate use of noninvasive tests can help identify which patients should undergo further investigation. Primary care physicians should continue to rely on routine laboratory tests and clinical suspicion to decide which patients with abdominal pain to refer to a gastroenterologist.

Wong A, Bass D. Laboratory evaluation of inflammatory bowel disease. Curr Opin Pediatr. 2008 Oct;20:566-70



It is important to exclude enteric infections, especially in patients who present with bloody diarrhea. For patients with colitis, infection with enteric pathogens (Salmonella, Shigella, Yersinia, Campylobacter, E. coli, ameba, and Clostridium difficile) should be assessed. For patients with ileitis, tuberculosis and yersinia should be excluded. At times, vasculitides (including Henoch-Schonlein purpura) can present with diarrhea and abdominal pain.



The ideal noninvasive diagnostic test is both highly sensitive and specific. Moreover, it should be as good as the gold standard. To date, no such test has been developed; however, advances in testing strategies and the addition of novel markers have helped the characteristics of available tests.

Numerous studies have examined the diagnostic value of ASCA and pANCA in particular, in IBD and non-IBD patients. Peeters et al. found that positivity for both markers was significantly lower in healthy and non-IBD controls.

For differentiating IBD from control ASCA sensitivity = 60% (243/407), specificity= 91% (345/378, PPV= 88% (243/276),, and NPV = 68% (345/509 for differentiating IBD from controls were:

For pANCA+: Sensitivity = 50% (73/147), specificity = 95% (605/638),PPV= 69% (73/106), and NPV= 89% (605/679);

ASCA+/pANCA–: Sensitivity= 56% (229/407), specificity= 94% (355/378), PPV= 91% (229/252), and NPV =67% (355/533);

pANCA+/ASCA–: Sensitivity = 44% (65/147), specificity = 97% (620/638), PPV= 78% (65/83), andNPV = 88% (620/702).

This study concluded that the specificity of serological markers for IBD is high, but low sensitivity making them less useful as diagnostic tests. And the combination of these tests is probably more powerful as a tool to differentiate IBD from non-IBD.

What Is the Role of Serological Markers in IBD? Pediatric and Adult Data. Marla Dubinsky Dig Dis 2009;27:259–268

Additional reading:

Peeters M, Joossens S, Vermeire S, et al: Diagnostic value of anti- *Saccharomyces cerevisiae* and antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease. Am J Gastroenterol 2001; 96: 730–734.

A meta-analysis was performed to examine the test characteristics of ASCA and pANCA [31] . Sensitivity, specificity, and likelihood ratios (LR+,

LR–) were calculated for different test combinations for CD, UC, and for IBD compared with controls. A total of 60 studies comprising 3,841 UC and 4,019 CD patients were included.

The ASCA+ with pANCA– test offered the best sensitivity for CD (54.6%) with 92.8% specificity.

Sensitivity and specificity of pANCA+ tests for UC were 55.3 and 88.5%, respectively (AUC of 0.82; LR+ = 4.5, LR– = 0.5).

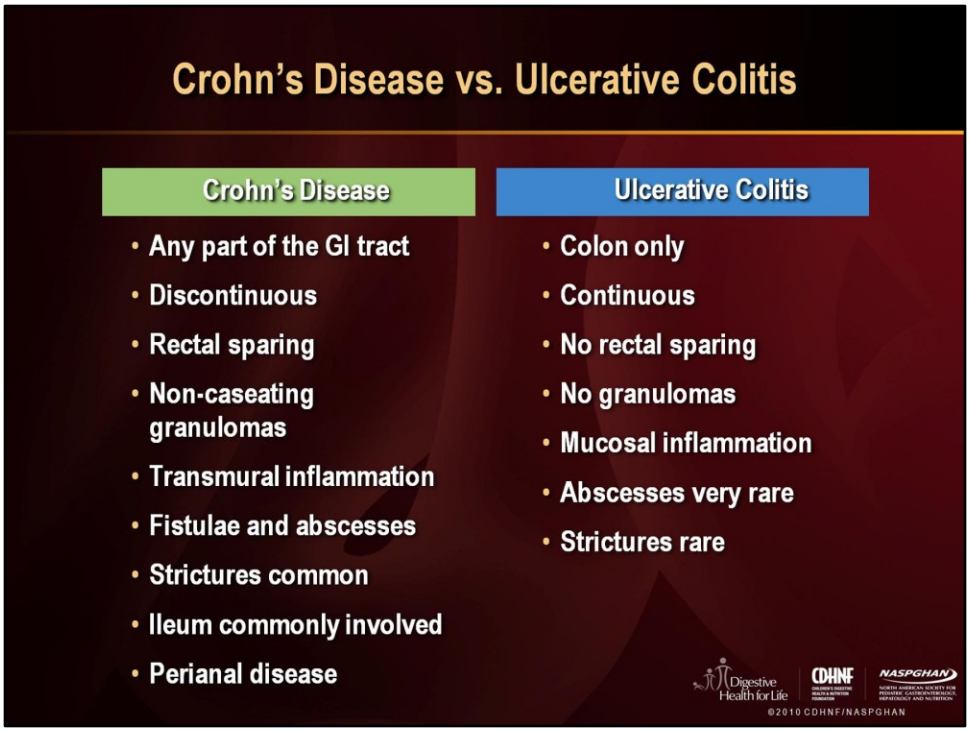
Sensitivity and specificity were improved to 70.3% and 93.4% in a pediatric subgroup when combined with an ASCA-negative test.

Meta-regression analysis showed decreased diagnostic precision of ASCA for isolated colonic CD (RDOR = 0.3).

This study concluded that ASCA and pANCA testing are specific but not sensitive for CD and UC. It may be particularly useful for differentiating between CD and UC in the pediatric population.

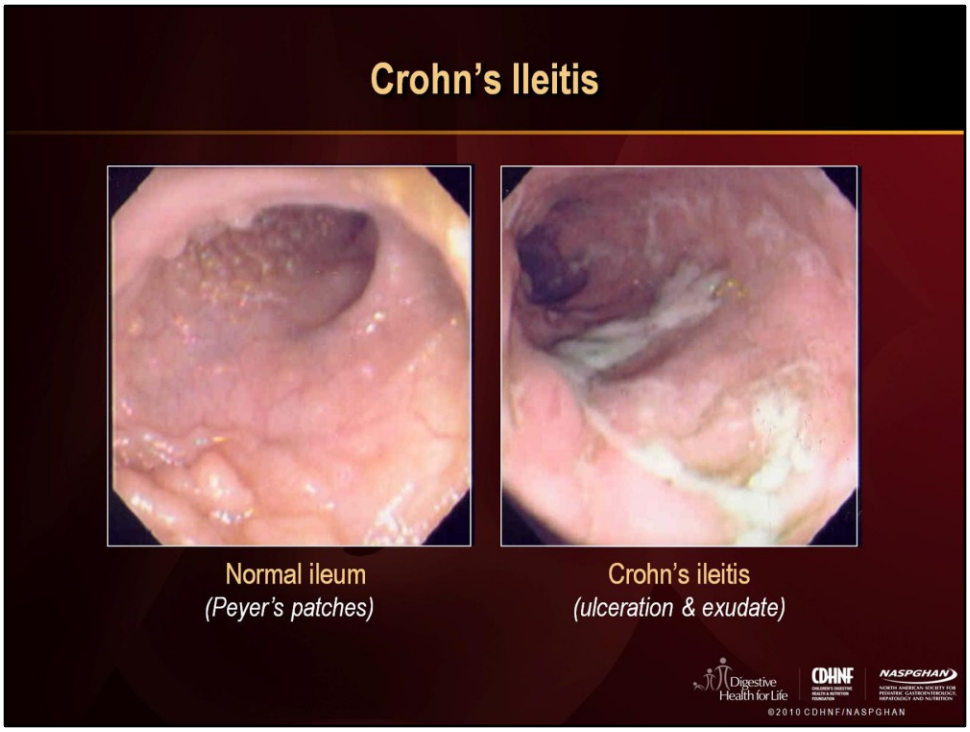
Reese GE, Constantinides VA, Simillis C, Darzi AW, Orchard TR, Fazio VW, Tekkis PP: Diagnostic precision of anti-*Saccharomyces cerevisiae* antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. Am J Gastroenterol 2006; 101: 2410–2422

Areas of discussion:
Differentiating IBD from non-IBD
Differentiating UC from Crohn's
Predicting disease behavior
?response to therapy

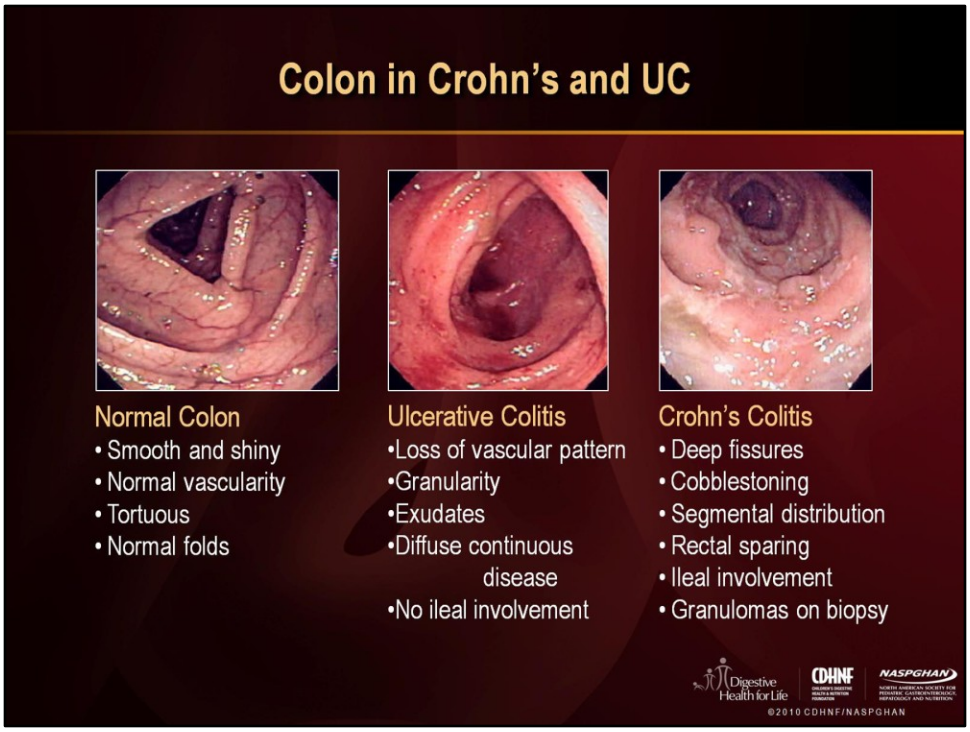


The definitive diagnosis of IBD is established by a combination of radiography, endoscopy, and histology. Differentiating Crohn's disease from ulcerative colitis can be difficult, especially if the IBD is limited to the colon. The diagnosis of Crohn's disease can be made definitively if there is clear small bowel inflammation (not simply "backwash ileitis"), discontinuous colitis, perianal disease, or granuloma identified on biopsy. Over time, the natural history of the two diseases differs. Patients with Crohn's disease will frequently develop complications such as strictures, abdominal abscesses, or perianal fistulae, whereas patients with ulcerative colitis continue to have bloody diarrhea as their principal manifestation.

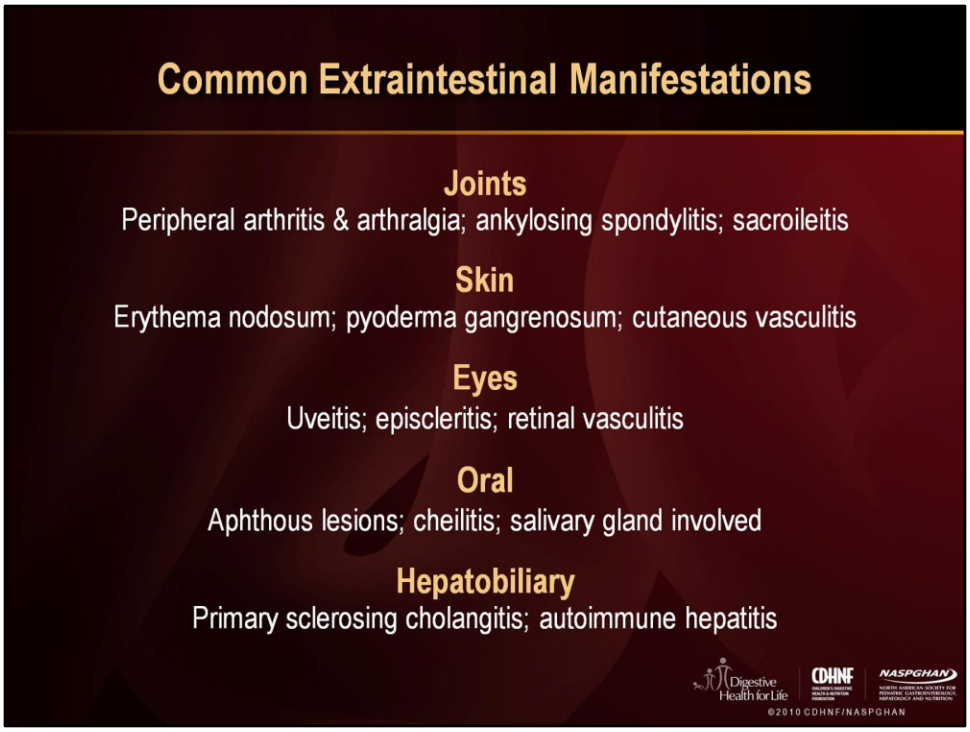
Crohn's of the terminal ileum is often first identified on upper GI with small bowel radiograph, which shows ileal stenosis and separation of bowel loops.



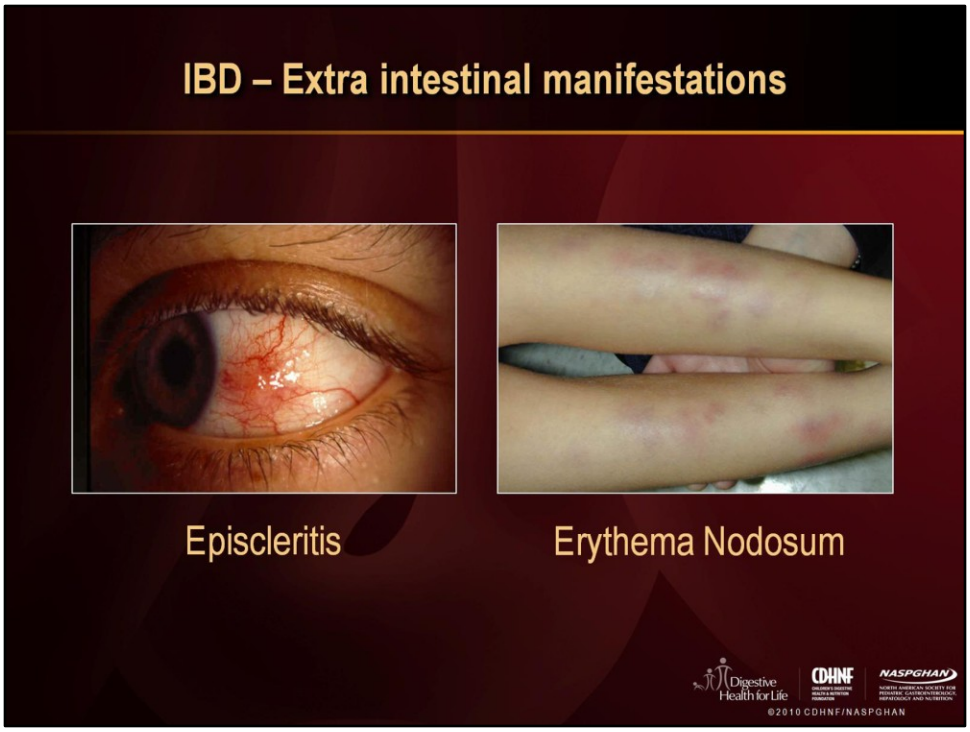
Ileitis can also be assessed by endoscopy. The normal ileum may show Peyer's patches and nodularity, but the ileum affected by Crohn's disease will demonstrate stenosis, linear ulceration, and mucopurulent exudate.



The normal colon is shiny, has triangular folds in the transverse colon, no bleeding, and a normal vascular pattern.



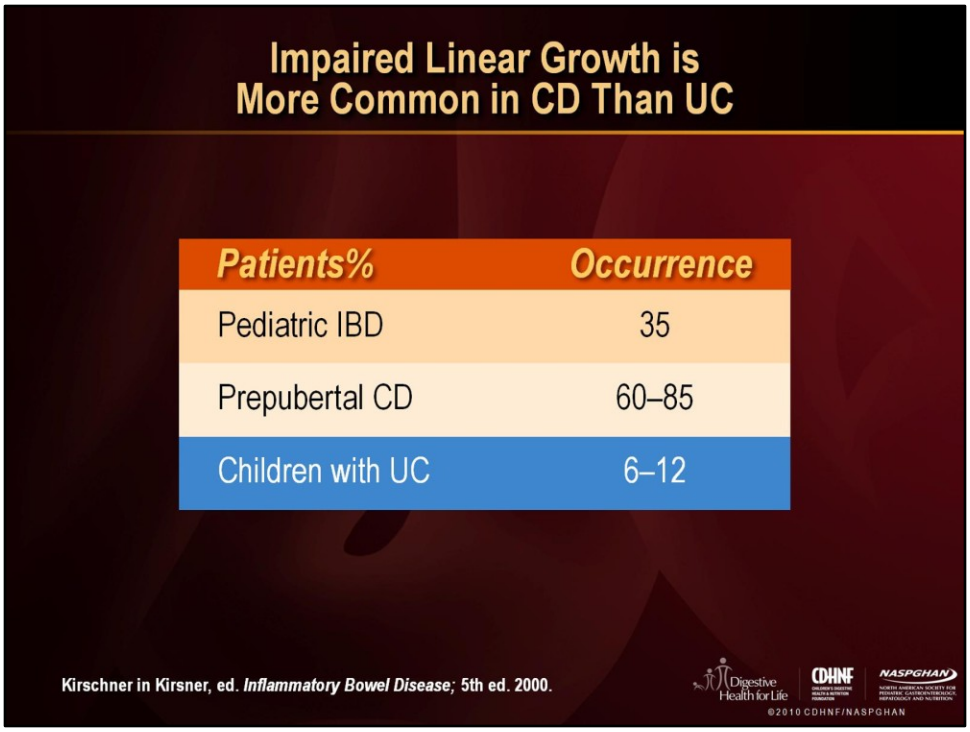
Once an IBD diagnosis has been established, the clinician should evaluate for extraintestinal manifestations of the disease.



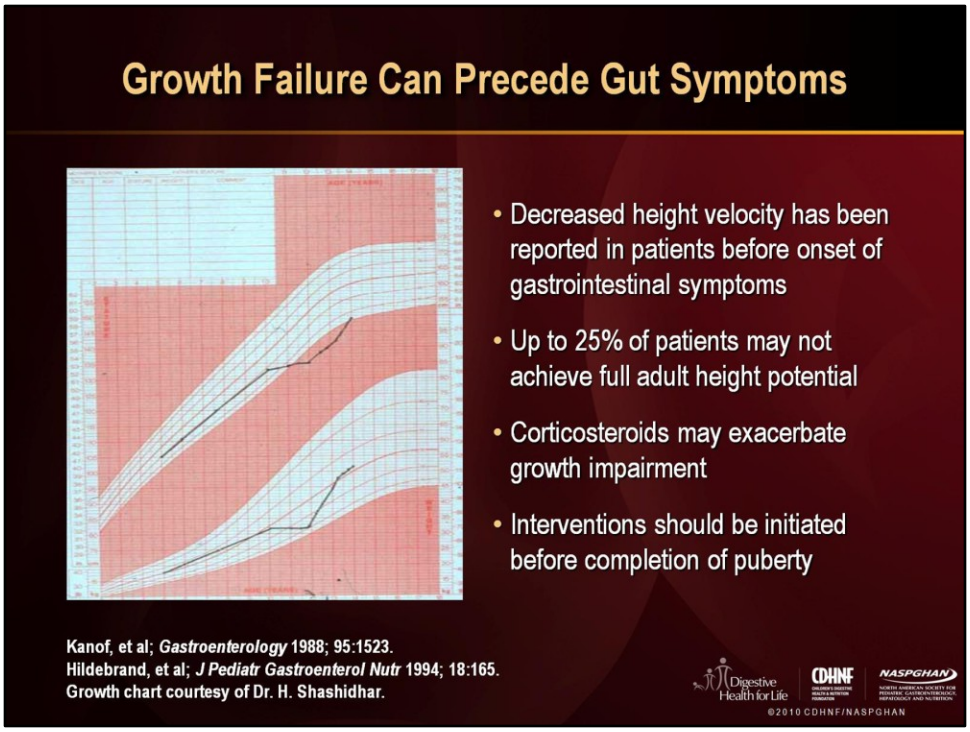
Patients with IBD may also develop ocular inflammation (uveitis and episcleritis), which should not be mistaken for conjunctivitis.

Erythema nodosum is also shown.


Growth Failure



Growth failure is a common problem in children and adolescents with Crohn's disease. Height velocity is the most sensitive parameter by which to recognize impaired linear growth. Please see next slide for more notes.



Growth failure is a common problem in children and adolescents with Crohn's disease. Height velocity is the most sensitive parameter by which to recognize impaired linear growth.

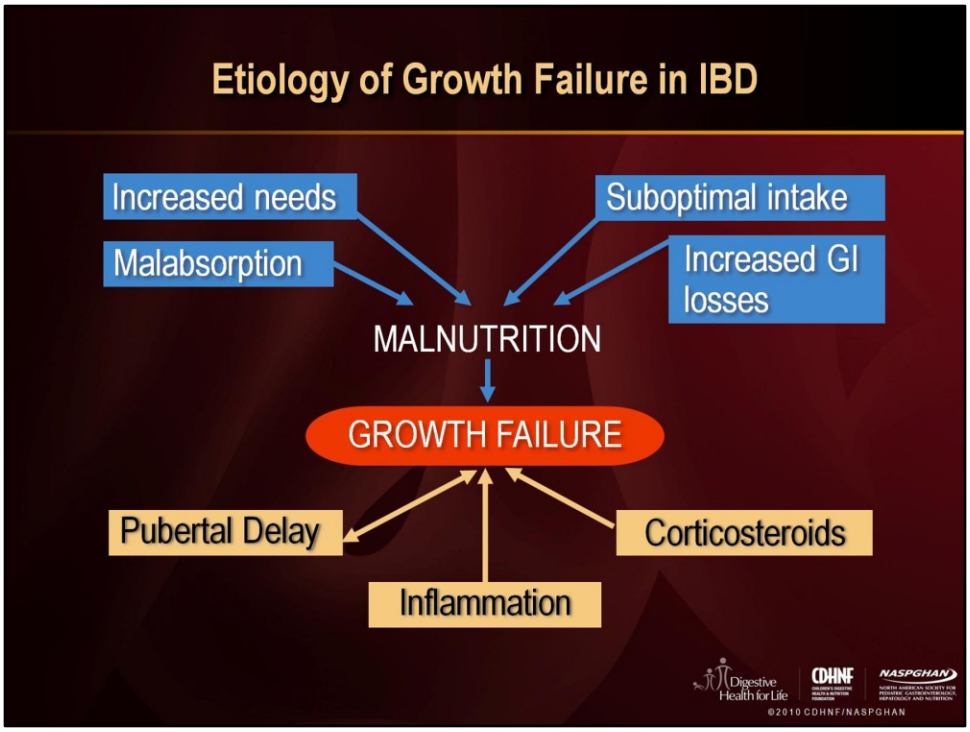
Decreased height velocity is seen in 46% of patients before symptom onset and 42% of patients after symptom onset. A third of children may have substantial height deficits at presentation. The onset of growth failure may also be insidious, starting years before the manifestations of other symptoms of Crohn's disease. Additionally, growth failure may be the only presenting symptom in certain patients with IBD.

Studies have shown that up to 25% of patients with Crohn's disease may not achieve full adult height potential. Medications, specifically corticosteroids, may exacerbate this problem. Timely identification of growth failure is critical, as interventions and referral to endocrinology should be made prior to the attainment of puberty. Quality of life is an increasingly important outcome measure. Growth failure, resulting in short stature, may have devastating psychological consequences, particularly for adolescents.

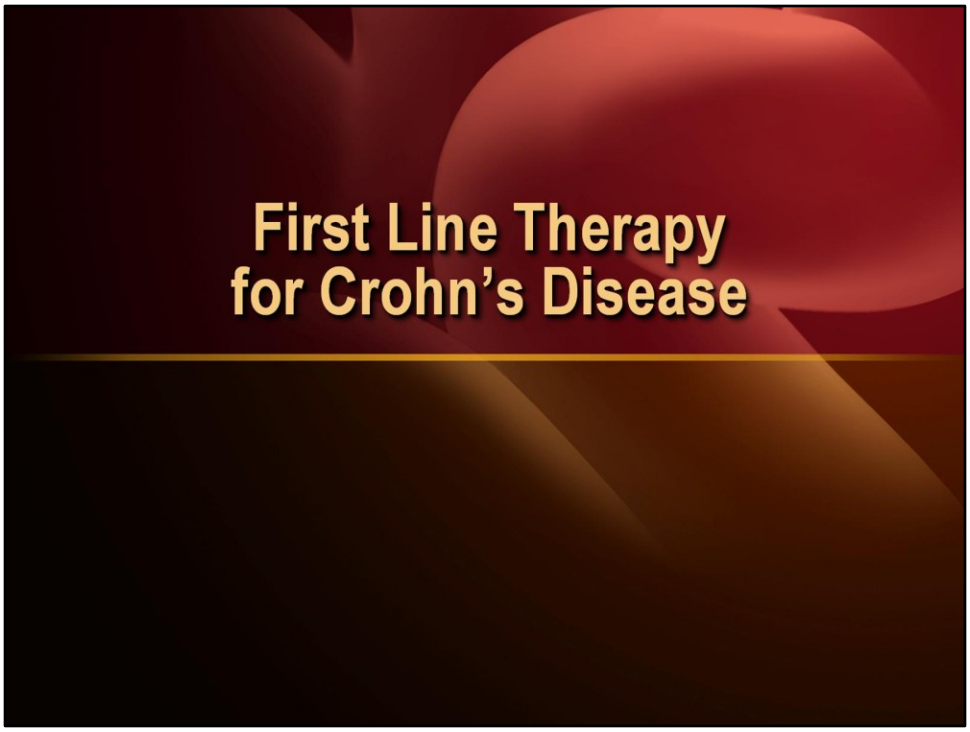
References:

Kanof ME et al, Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology, 95:1523, 1988

Hildebrand H et al, Longitudinal growth in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 18:165, 1994

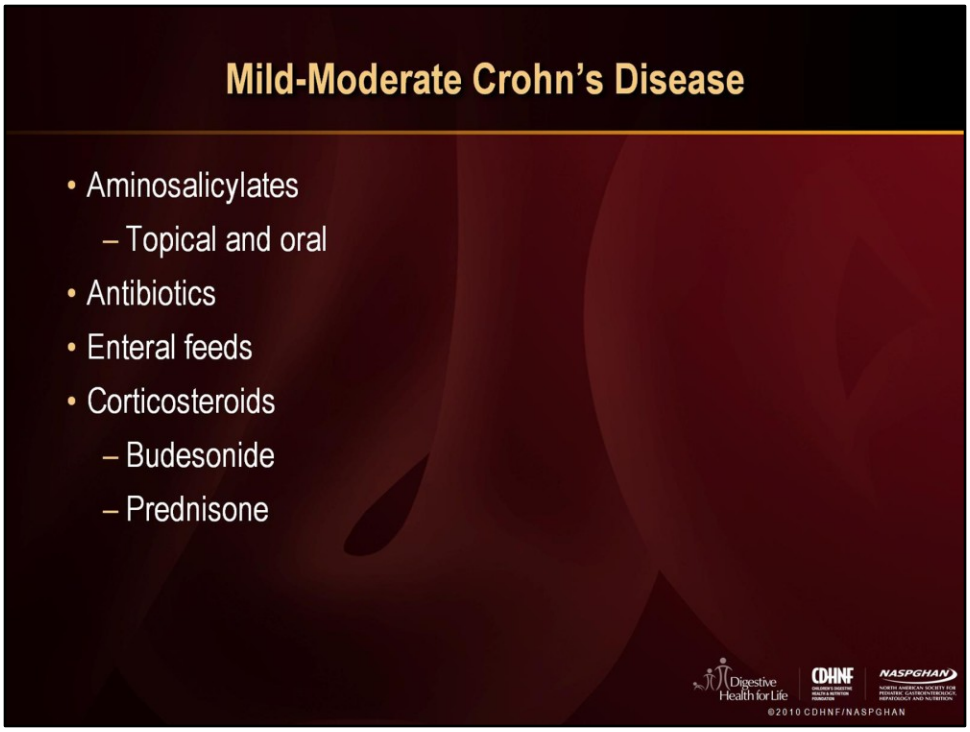


Poor linear growth is a common sequela of pediatric IBD and is roughly twice as common in Crohn's disease as it is in ulcerative colitis. The pathogenesis of growth failure in IBD is mutlifactorial. Malabsorption, increased caloric needs, suboptimal intake due to anorexia, and gastrointestinal losses all contribute to malnutrition, which directly affects growth. However, delayed puberty, corticosteroids, and proinflammatory cytokines such as TNFα and interleukin 6 are also responsible for growth failure in this patient population. Weight loss may precede decreases in height velocity.


First Line Therapy
for Crohn's Disease

When planning therapy for Crohn's disease, or any other chronic condition, it is important to have specific therapeutic goals that are directed toward the patient's physical, as well as psychosocial, well-being. Short-term goals should include the relief of immediate symptoms such as pain and diarrhea. Long-term therapeutic goals include changing the natural history of the disease by minimizing long-term complications such as growth failure, the need for hospitalization or surgery. Ultimately, the patient's quality of life is improved by achieving therapeutic goals with treatments that have minimum side effects. Improving the simplicity of the therapeutic regimen also improves quality of life while maximizing adherence. Attention to emotional and family implications of chronic illness is an integral part of the long-term care of the pediatric patient with Crohn's disease.

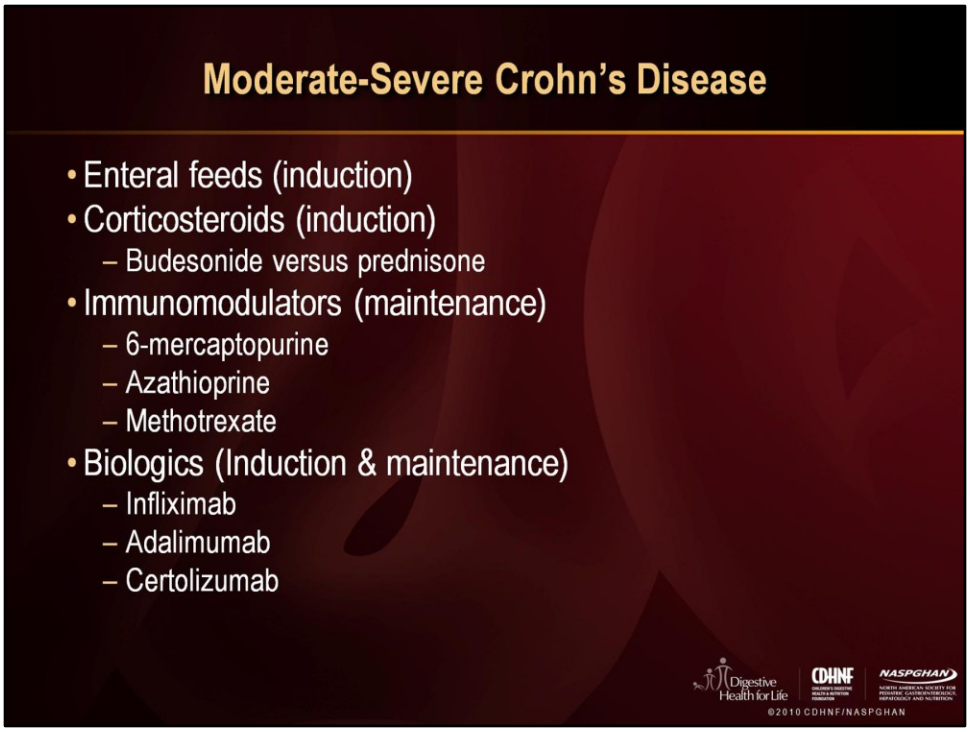
While the current goals of therapy remain defined in clinical terms, future directions could include additional indicators of efficacy such as mucosal healing. Ultimately, the finding of a biomarker(s) that is predictive of clinical course would be an extremely helpful factor in planning and maintaining effective therapy.



IBD clinical activity can be globally divided into mild, moderate and severe categories. Induction therapy is used to bring about remission of clinical activity and maintenance therapy should successfully maintain such a remission.

With mild-to-moderate levels of disease activity, there are various groups of interventions that have been shown to be effective at both inducing and maintaining remission. These include the aminosalicylates, antibiotic therapy, corticosteroids and enteral nutrition.

Some therapies such as aminosalicylates and corticosteroids can be delivered either orally or rectally and the location of disease activity should be kept in mind when deciding on the route of administration.



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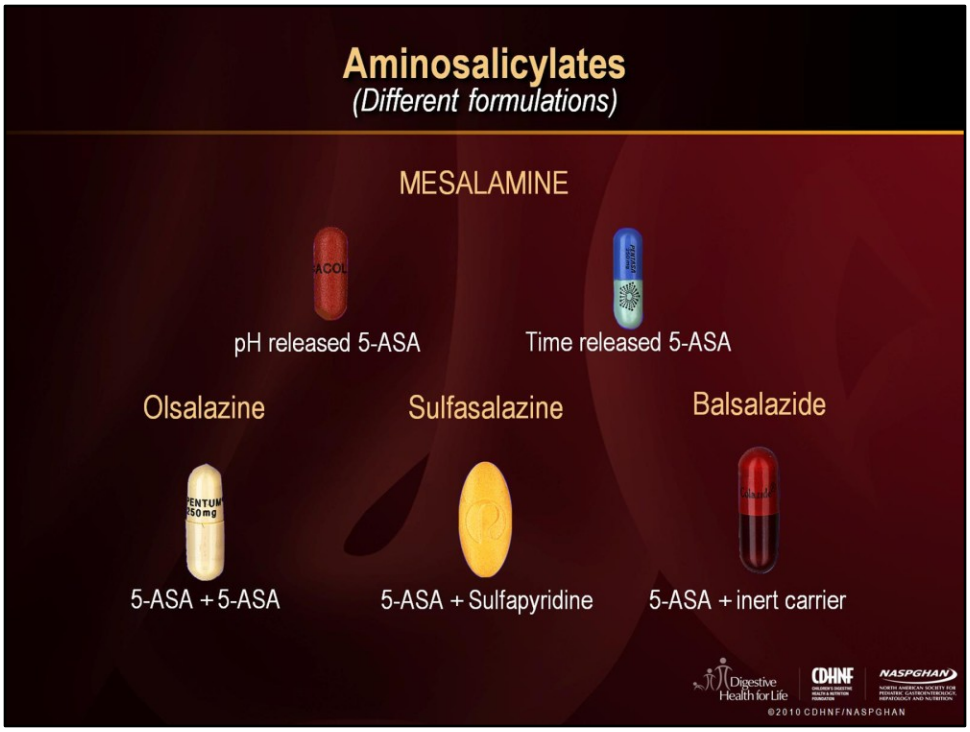
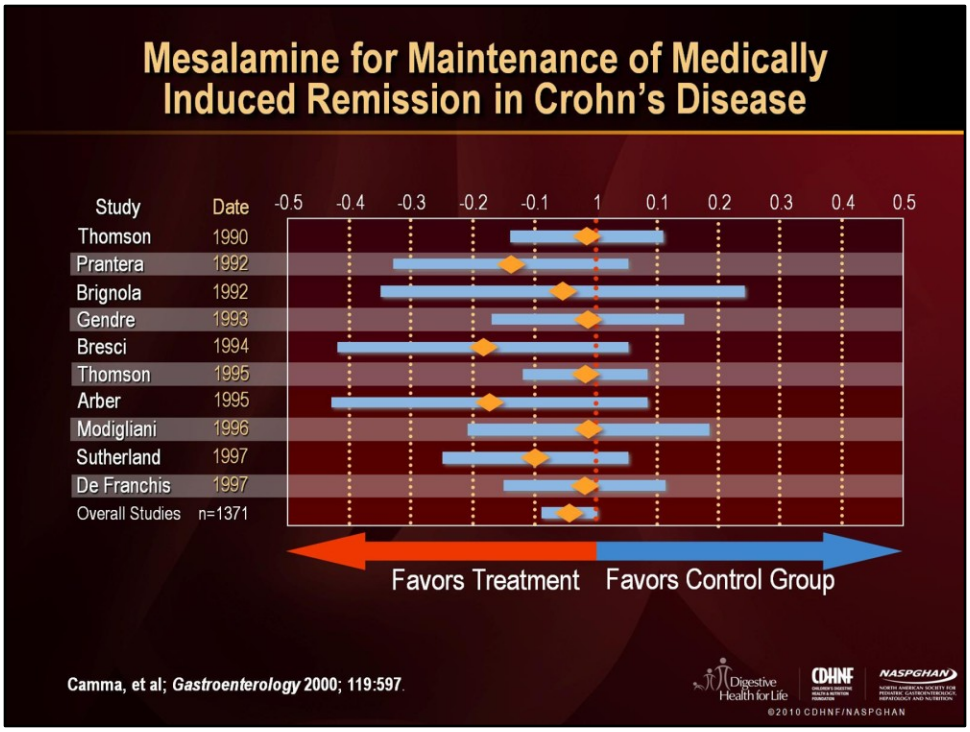


Aminosalicylic acid is a locally active, anti-inflammatory agent. In addition to oral delivery systems, this agent is commercially available as rectal suppositories and enemas, as well.

There are several oral preparations of aminosalicylic acid. Each of these employs a different delivery mechanism to protect the active drug from intra-gastric degradation with release of the active agent at varying levels throughout the gastrointestinal tract.

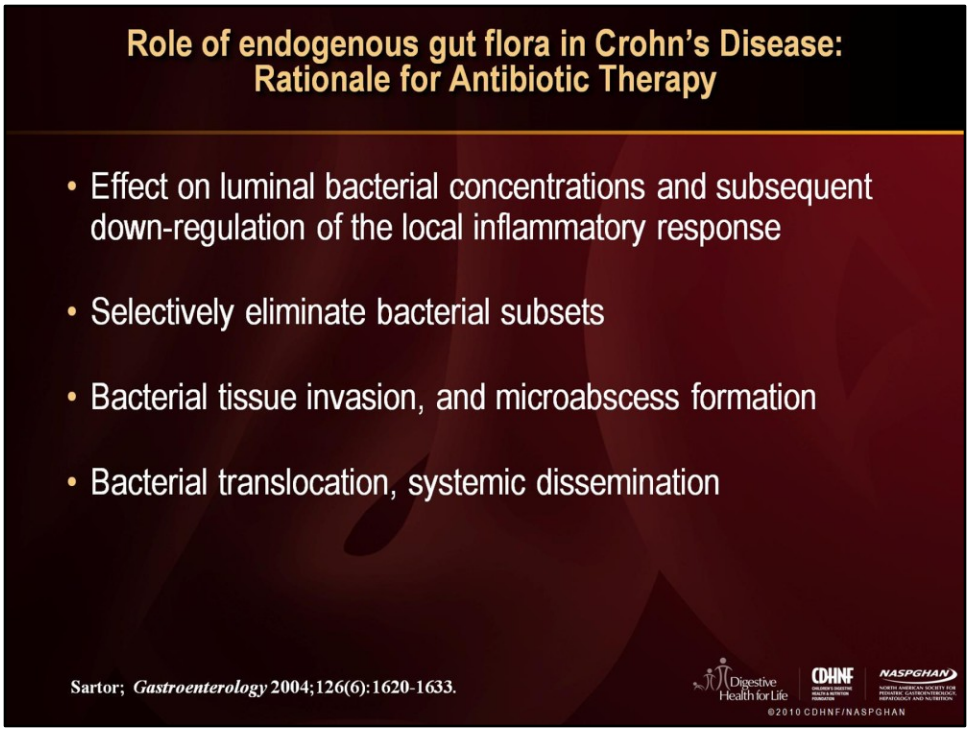


The use of aminosalicylates to maintain remission has also been an area of intense interest and varying results. Again, various sites of original disease activity, drug delivery systems and doses used has resulted in an array of findings.

Camma performed a meta-analysis of controlled trials that looked at the use of aminosalicylates to maintain remission in patients who had undergone medical induction (as opposed to surgical resection). The findings of this meta-analysis were weakly positive in favor of treatment with aminosalicylates over control for Crohn's maintenance therapy.

References:

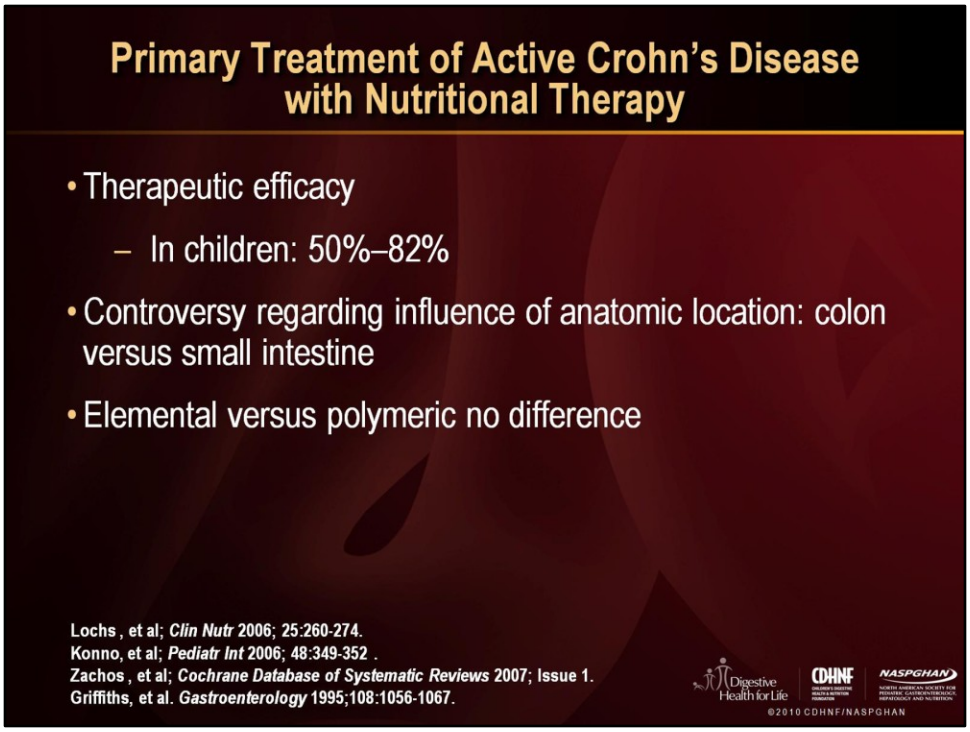
Camma C, Cottone M. Mesalamine and relapse prevention in Crohn's disease. *Gastroenterology* 2000;119:597



The endogenous gastrointestinal bacterial flora play an important role in the pathogenesis of Crohn's disease. Evidence for this includes studies that demonstrate that animal models of Crohn's are not effective when performed in germ-free species. Additional evidence comes from the understanding that NOD2/CARD-15, the gene recently associated with Crohn's disease, is involved in local bacterial handling.

Antibiotics have shown efficacy in treating active Crohn's Disease, especially when there is colonic or perianal involvement. Fistulizing disease and post-operative recurrence have also been shown to be influenced by antibiotic therapy.

There are several potential explanations for the efficacy of antibiotics in Crohn's Disease. Treatment of a specific pathogen does not seem to be the answer. Rather, influences on the endogenous flora with subsequent down-regulation of the local inflammatory response seem to be the likely explanations.



Enteral feedings as a therapy for Crohn's disease have been discussed since the 1970s when it was noticed that preoperative patients on such feedings, while awaiting surgery, showed clinical improvement. Such therapy is likely more common in Europe than the United States.

In 2006, both the European Society for Clinical Nutrition and Metabolism (ESPEN) and The Working Group of the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition each independently published guidelines recommending that enteral nutrition be considered as the first line therapy in children with CD.

Lochs H, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Schutz T, van GW, van GA, Valentini L, Lubke H, Bischoff S, Engelmann N, Thul P. ESPEN Guidelines on Enteral Nutrition: Gastroenterology. Clin Nutr 2006;25:260-274.

Konno M, Kobayashi A, Tomomasa T, Kaneko H, Toyoda S, Nakazato Y, Nezu R, Maisawa S, Miki K. Guidelines for the treatment of Crohn's disease in children. Pediatr Int 2006;48:349-352

Prospective trials have included small numbers of patients and are confounded by the inability to blind this therapy versus corticosteroids. Therefore, meta-analysis techniques have been employed to look at this topic.

Griffiths, et al. in their meta analysis showed that enteral nutrition is a possible therapy for the treatment of Crohn's disease. Subsequent authors have pointed out that this may be best early in the disease course. The disease site may play a role in response with small bowel disease showing better response. The possibility that this can be an adjunctive therapy and that it may not preclude other oral nutrition also remain points of debate.

References:

Griffiths et al. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. Gastroenterology 1995;108:1056-1067

Mary Zachos et al conducted a systematic meta analysis of all randomized and quasi-randomized controlled trials involving patients with active Crohn's disease defined by a clinical disease activity index and studies evaluating the administration of one type of enteral nutrition to one group of patients and another type of enteral nutrition or conventional corticosteroids to the other group were selected for review.

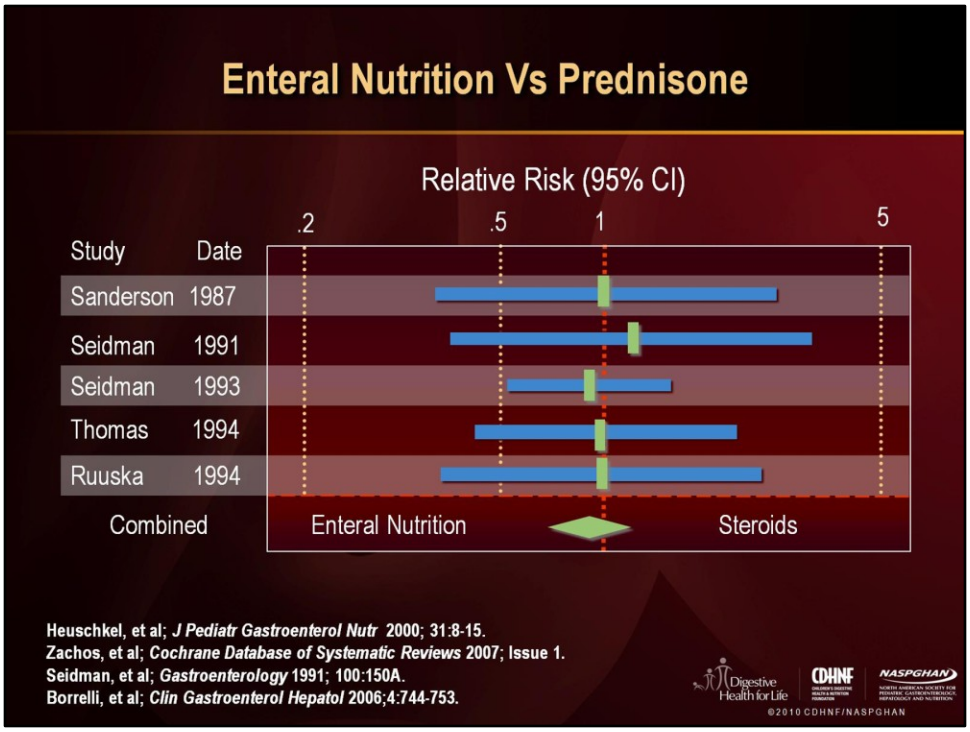
Conclusions

1.Corticosteroid therapy is more effective than enteral nutrition for inducing remission of active Crohn's disease as was found in previous systematic reviews.

2. Protein composition does not influence the effectiveness of EN in the treatment of active CD. A non significant trend favouring very low fat and/or very low long chain triglyceride content exists but larger trials are required to explore the significance of this

finding.

Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. ***Cochrane Database of Systematic Reviews*** **2007, Issue 1.**



Steroid usage in children has been associated with adverse side effects, particularly with delayed growth and pubertal development.

Heuschkel et al studied identifying randomized clinical trials comparing exclusive enteral nutrition with corticosteroids. Studies were assessed for heterogeneity and relative risks for remission induction with enteral nutrition were obtained.

The study found that in five randomized clinical trials comprising 147 patients, enteral nutrition was as effective as corticosteroids at inducing a remission (RR = 0.95 [95% confidence interval 0.67, 1.34]).

Addition of two further nonrandomized trials did not significantly alter the result.

The study also determined statistically a minimum of 10 further studies, equal in size and outcome to the largest reported pediatric trial to date (n = 68, RR = 0.84), would be required to demonstrate a significant benefit of steroid therapy over enteral nutrition. There is no difference in efficacy between enteral nutrition and corticosteroid therapy in the treatment of acute Crohn's disease in children. Improved growth and development, without the side effects of steroid therapy, make enteral nutrition a better choice for first-line therapy in children with active Crohn's disease.

Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children.J Pediatr Gastroenterol Nutr. 2000 Jul;31(1):8-15.

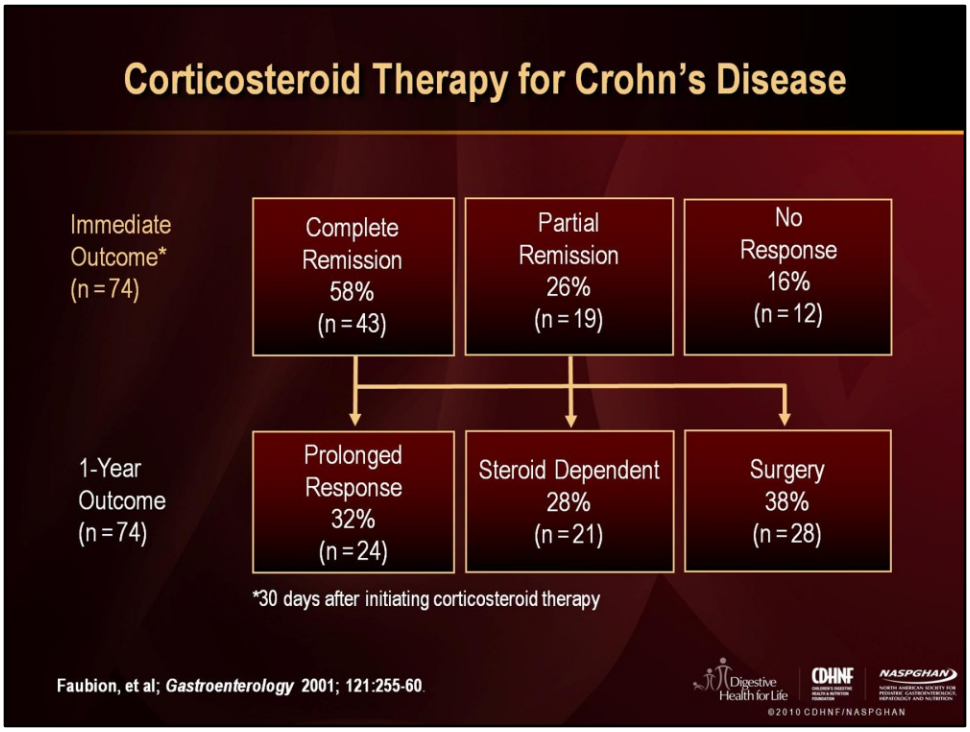
Mary Zachos meta analysis (see notes from the previous slide) also showed that corticosteroid therapy is more effective than enteral nutrition for inducing remission of active Crohn's disease as was found in previous systematic reviews in adults. However, many pediatric trials were excluded from this analysis owing to methodological weakness. The authors mention that a previous abstract (See below: Seidman et al) and one pediatric trial(see below: Borrelli et al both favor EEN over corticosteroids. These results, along with the meta analysis above by Heuschkel et al suggest the effects may be more beneficial in children.

Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2007, Issue 1.

Seidman E, Turgeon J, Bouthillier L, Morin CL. Elemental diet versus prednisone as initial therapy in Crohns disease: early and long-term results. Gastroenterology 1991;100:150A.

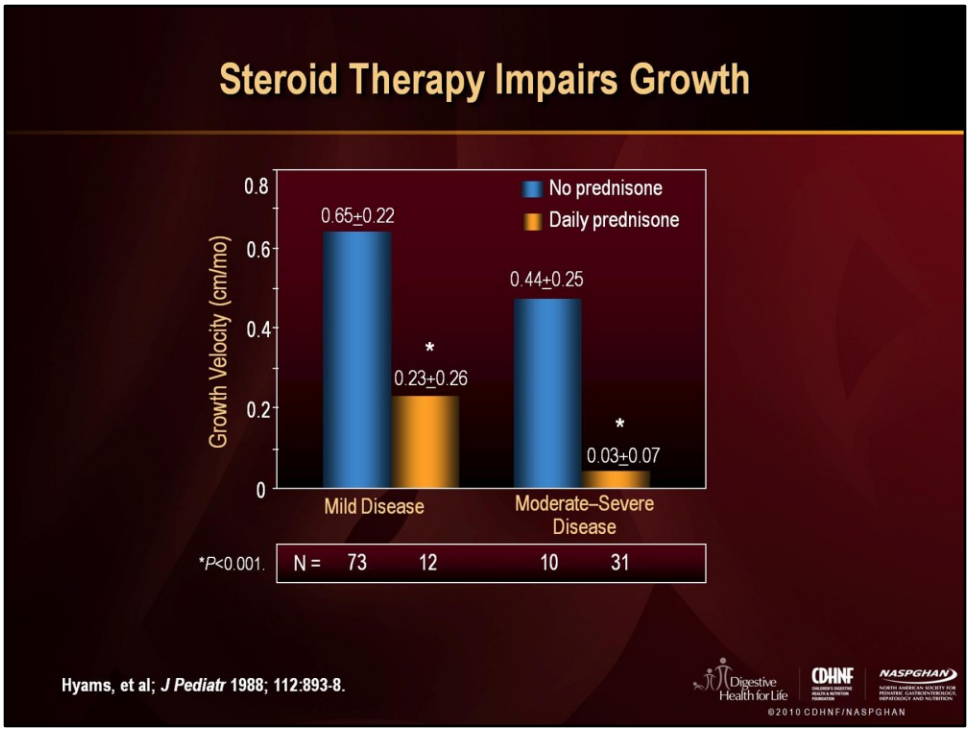
Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, Russo PM, Cucchiara S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol 2006;4:744-753.

Corticosteroids have long been recognized to affect Crohn's disease activity. By being both anti-inflammatory as well as immunomodulatory, corticosteroids were one of the first therapies used to fight Crohn's disease. This slide highlights several critical principles with regard to the optimal use of corticosteroid therapy. While corticosteroids have been shown to be an effective induction agent, they have not been shown to be capable of maintaining remission in Crohn's disease. This lack of efficacy and numerous potential side effects from chronic administration preclude corticosteroids from being considered as a maintenance agent. When used, corticosteroids should be dosed at an effective level to induce remission and serve as a bridge to an effective maintenance agent. Lack of efficacy, especially in the absence of any cosmetic side effect, may be due to issues of absorption that can be addressed by changing to a short course of parenteral administration.



The inadequacy of long-term corticosteroid treatment was demonstrated by the population based study performed by Faubion, et al. This study showed that the majority of patients had a favorable short-term response to corticosteroids by one month. However, more than a third required surgery by one year and only 32% had a prolonged response to corticosteroids when they were assessed at one year after being diagnosed with Crohn's Disease and treated with steroids. This data demonstrates that while corticosteroids may have a desirable immediate effect on Crohn's Disease activity, such therapy does not have a favorable affect on the natural history of the disease.

The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study.
:255-60.



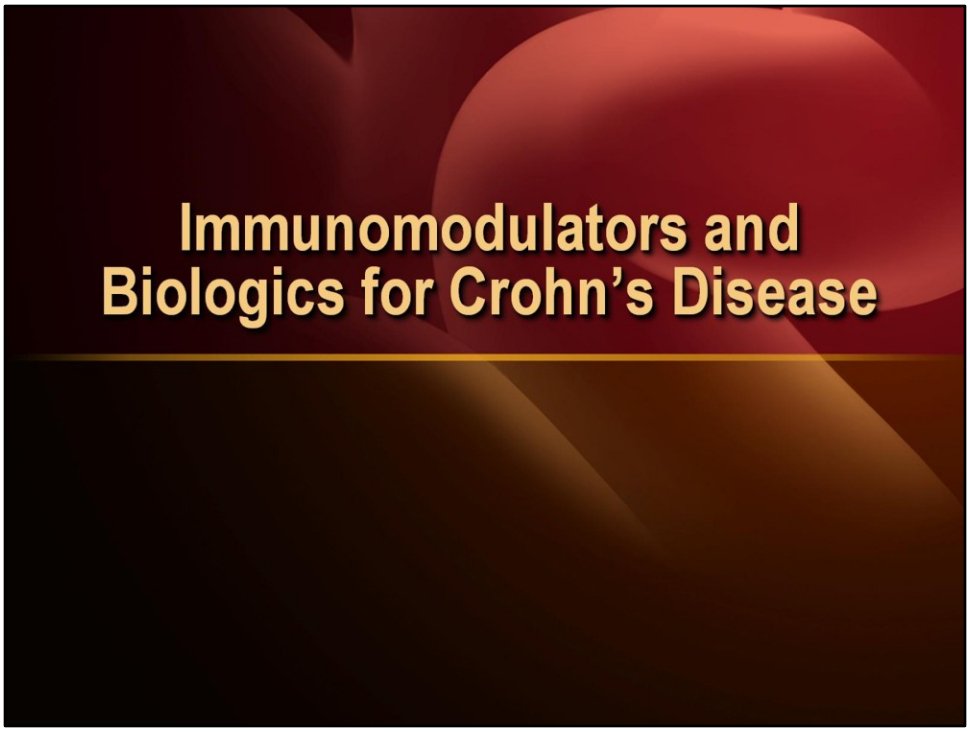
The cosmetic and metabolic side effects of corticosteroids are legion and can be quite severe.

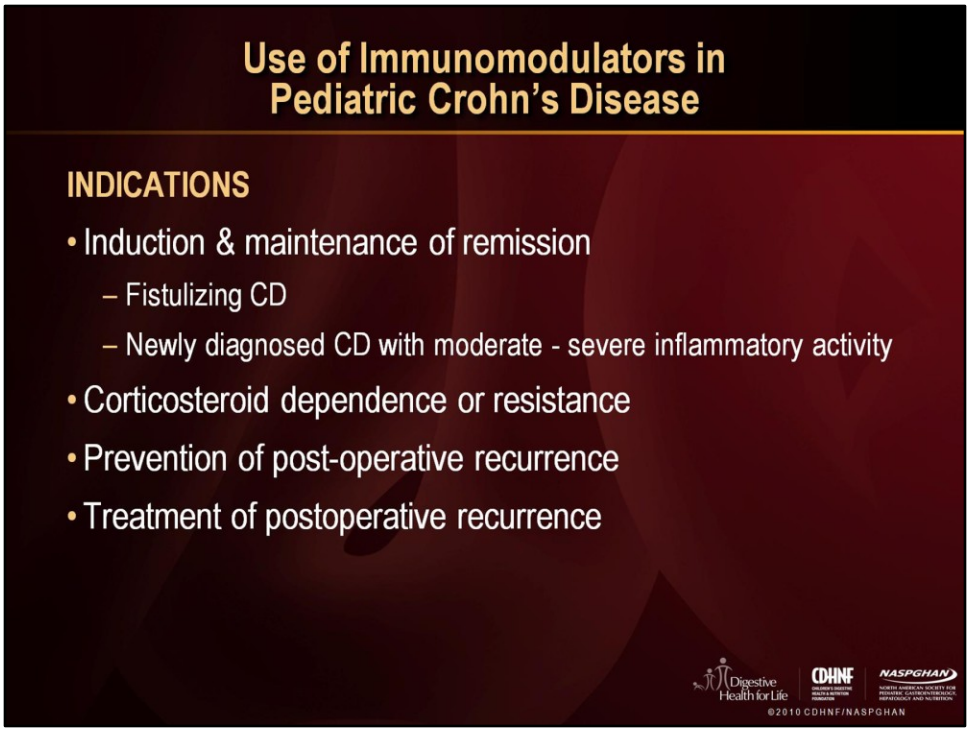
The potentially profound affect that corticosteroids can have on bone physiology is being increasingly appreciated. In pediatrics, this can take the unique form of an adverse affect on linear growth.

This study from Hyams, et al. performed almost 20 years ago documented the adverse effect chronic corticosteroid therapy can have on linear growth in patients with pediatric IBD at all levels of clinical activity.

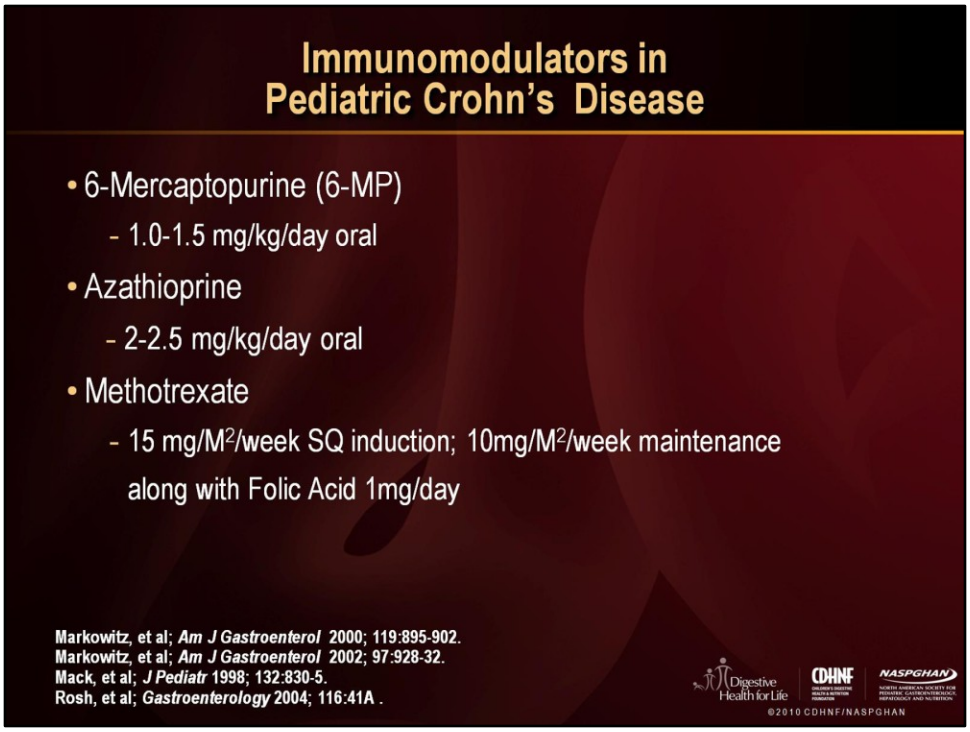
References:

Relationship of type I procollagen to corticosteroid therapy in children with inflammatory bowel disease. (6):893-8


Immunomodulators and
Biologics for Crohn's Disease



Measurement of thiopurine methyltransferase (TPMT), a genetically controlled enzyme active in 6-MP/AZA metabolism, may identify some patients at risk for drug-induced neutropenia . Although the US Food and Drug Administration suggests that TPMT genotype or enzyme activity be assessed before commencing thiopurine therapy to avoid potential adverse events, prospective studies evaluating dose optimization based on measurements of TPMT are lacking . For patients with normal TPMT genotype or enzyme activity, doses of about 1.0 to 1.5 mg · kg-1 · day-1 of 6-MP and about 2.0 to 3.0 mg · kg-1 · day-1 of AZA have been recommended. Once therapy is initiated, thiopurine metabolite monitoring (eg, measuring thioguanine levels) may be useful when determining medical noncompliance, monitoring toxicity, or optimizing dose, but this approach continues to be a source of debate, and the feasibility of obtaining these types of tests can vary significantly among health providers, institutions, and countries ."



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6-mercaptopurine/azathioprine

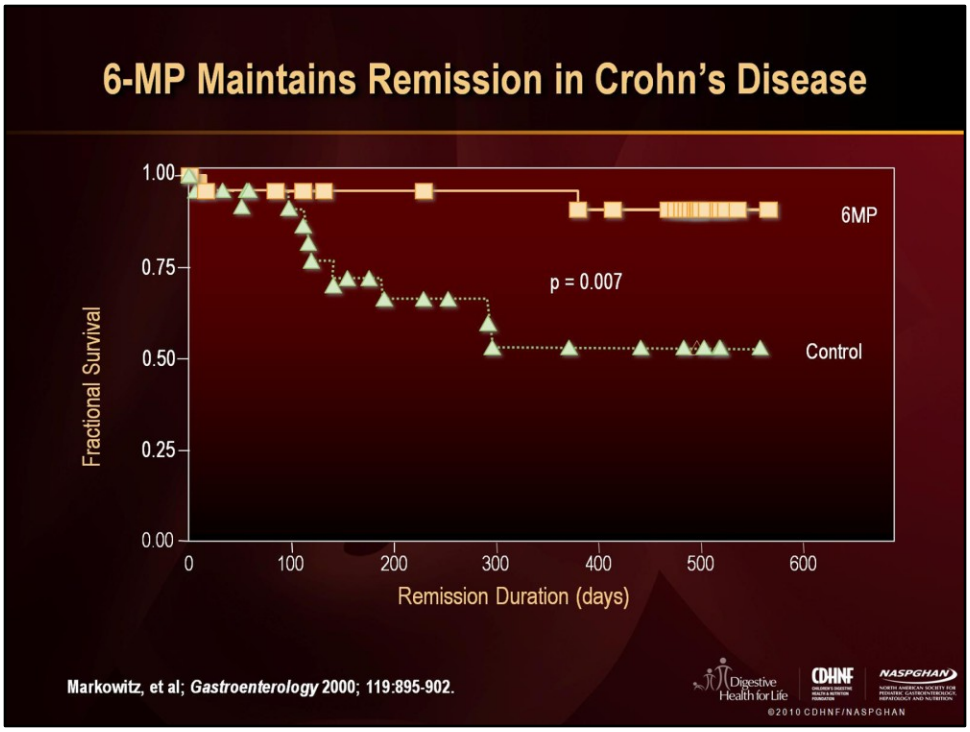
Markowitz J, Grancher K, Kohn N, Lesser M, Daum F, and the 6MP Collaborative Group. A multicenter trial of 6-mercaptopurine and prednisone in newly diagnosed children with Crohn's disease. *Gastroenterol*. 2000;119:895-902

Markowitz J, Grancher K, Kohn N, Daum F. Immunomodulatory therapy for pediatric inflammatory bowel disease: changing patterns of use 1990 - 2000. *Am J Gastroenterol* 2002;97:928-932

Methotrexate

Mack DR, Young R, Kaufman SS, Ramey L, Vanderhoof JA. Methotrexate in patients with Crohn's disease after 6-mercaptopurine. *J Pediatr* 1998;132:830-5.

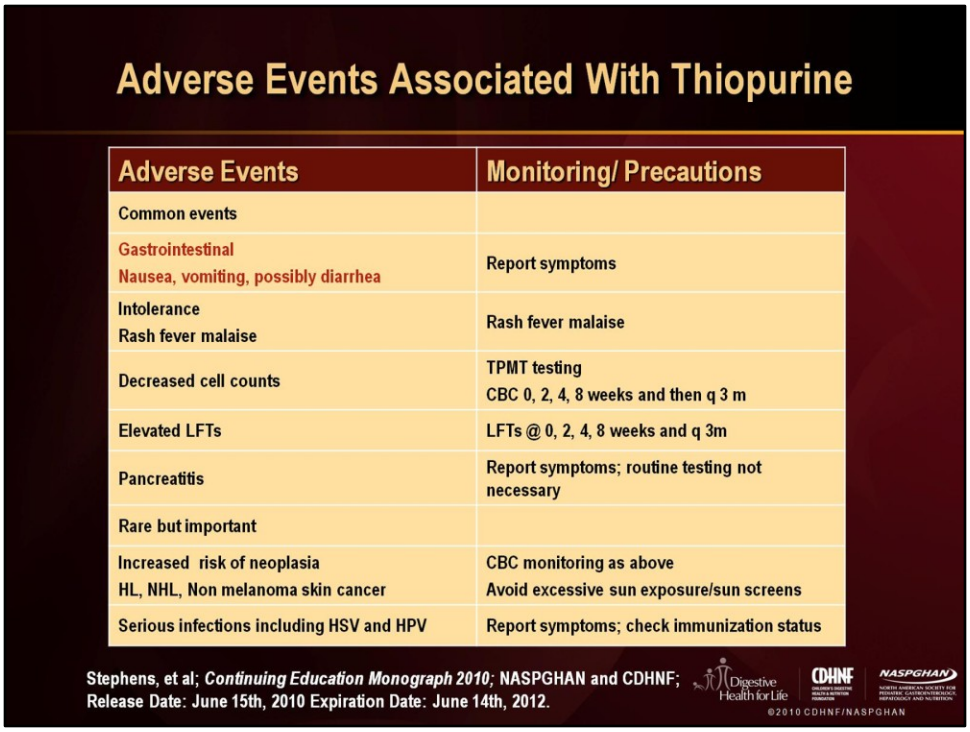
Rosh JR, Youssef NN, Schuckalo S, Punati J, Fehling B, Mones RL. Methotrexate as rescue therapy in pediatric Crohn's disease. *Gastroenterology* 2004;116:41A (abstract)



In this multicenter, double-blind, placebo-controlled clinical trial studied 55 newly diagnosed children with Crohn's disease (ages 13 2 yrs the 6-MP group maintained remission significantly better over 18 months with significantly less corticosteroid exposure.

References:

Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology.* 2000 Oct;119(4):895-902.



Stephens M and Rosh J :Optimizing therapeutic safety in children and young adults with IBD. A continuing education monograph series by NASPGHAN and CDHNF, Jointly sponsored by NASPGHAN, CDHNF, and TCL Institute, LLC.

Release Date: June 15th, 2010 Expiration Date: June 14th, 2012.

Additional reading:

1. Drugs@FDA Web site. Available at http://www.accessdata Accessed April 26, 2010..fda. gov/scripts/cder/drugsatfda/index.cfm. Accessed April 26, 2010.

2. Diefenbach KA, Breuer CK. Pediatric inflammatory bowel disease. *World J Gastroenterol.* 2006;12:3204-3212.

3. Bousvaros A. Advances in the monitoring and therapy of pediatric inflammatory bowel disease. Slides presented at: DDW Annual Meeting 2008. Available at http://www.ddw.org/user-assets/ doccuments/PDF/01_program/Sp570_Bousvaros.pdf

4. Bermejo F, Lopez-Sanroman A, Taxonera C, et al. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. *Aliment Pharmacol Ther.* 2008;28:623-628.

5. Azathioprine package insert. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 26, 2010.

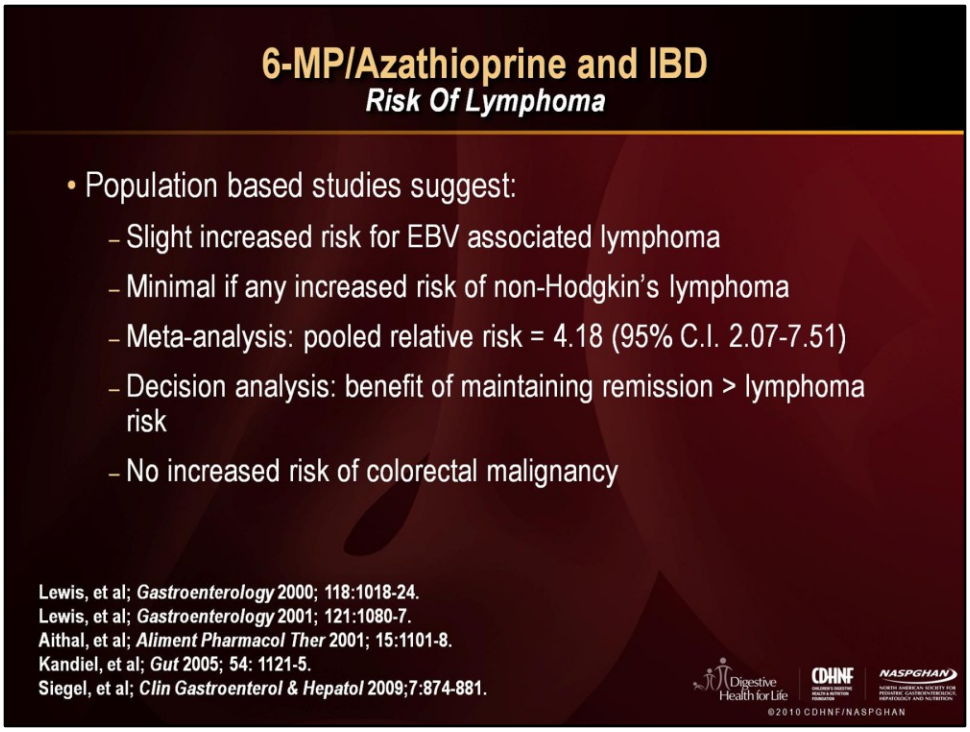
6. 6-mercaptopurine package insert. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 26, 2010

The side effect profile of 6-MP and azathioprine can be divided into 2 main groups: allergic/non-dose dependent and those dose dependent.

The allergic type reactions often happen within the first 2 weeks of starting the medication. Often patients have a recurrence of these reactions when rechallenged. Pancreatitis is a contraindication for rechallenge.

The most concerning side effect of these medications is bone marrow or myelosuppression and increased risk of neoplasia. This myelosuppression is dose dependent and the white count often recovers by lowering the dose or stopping the medication. Viral infections can cause significant leukopenia and should be considered in patients on

these therapies.



Whether the risk of lymphoma in patients with Crohn's disease treated with 6-MP or azathioprine is increased compared to those who do not receive these immunomodulators remains unclear. No data specific to children treated with these agents has been reported. Reports including adult patients with both Crohn's disease and ulcerative colitis, including a recent meta-analysis of six studies, suggest that treatment with 6-MP and azathioprine is associated with an approximate four-fold increased risk of lymphoma, although whether the increased risk is due to treatment with these agents or the severity of the disease, or both, remains unknown.

There are no published data demonstrating an increased risk of colorectal or small bowel carcinomas in patients treated with 6-MP orazathioprine.

Cory Siegel evaluated twenty-six studies involving 8905 patients and 21,178 patient years from different databases including Medline,

of follow-up were included. Among anti-TNF treated subjects, 13 cases of NHL were reported (6.1 per 10,000 patient years).

The majority of these patients had previous immunomodulator exposure.

The following rates are from this study(Standardized Incidence Ratio)

Baseline or "expected" rate of NHL in the SEER database (1.9 per 10,000 patient-years),

Anti-TNF treated subjects had a significantly elevated risk (SIR, 3.23; 95% confidence interval, 1.5– 6.9)

When compared with the NHL rate in CD patients treated with immunomodulators alone (4 per 10,000 patient-years), the SIR was 1.7 (95% confidence interval, 0.5–7.1)

Siegel et al. Risk of Lymphoma Associated With Combination Anti–Tumor Necrosis Factor and Immunomodulator Therapy for the Treatment of Crohn's Disease: A Meta-Analysis Clin Gastroenterol & Hepatol 2009;7:874–881

References:

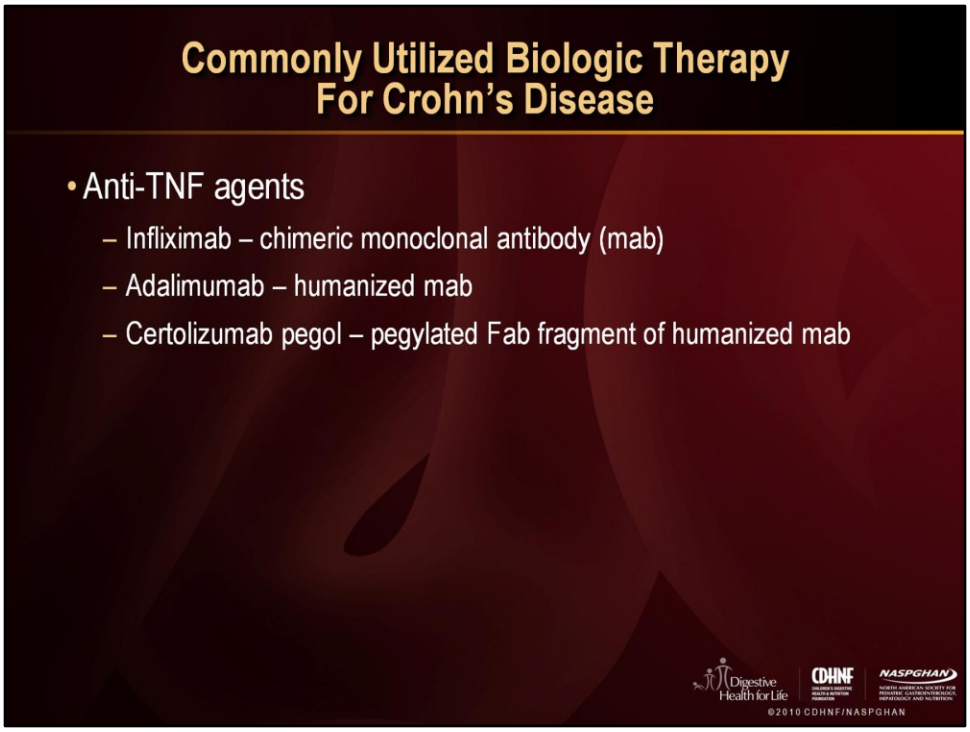
Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. *Gastroenterology.* 2000.

Lewis JD, Bilker WB, Brensinger C, Deren JJ, Vaughn DJ, Strom BL. Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology.* 2001 Nov;121(5):1080-7.

Aithal GP, Mansfield JC. Review article: the risk of lymphoma associated with inflammatory bowel disease and immunosuppressive treatment. *Aliment Pharmacol Ther*. 2001 Aug;15(8):1101-8.

Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel

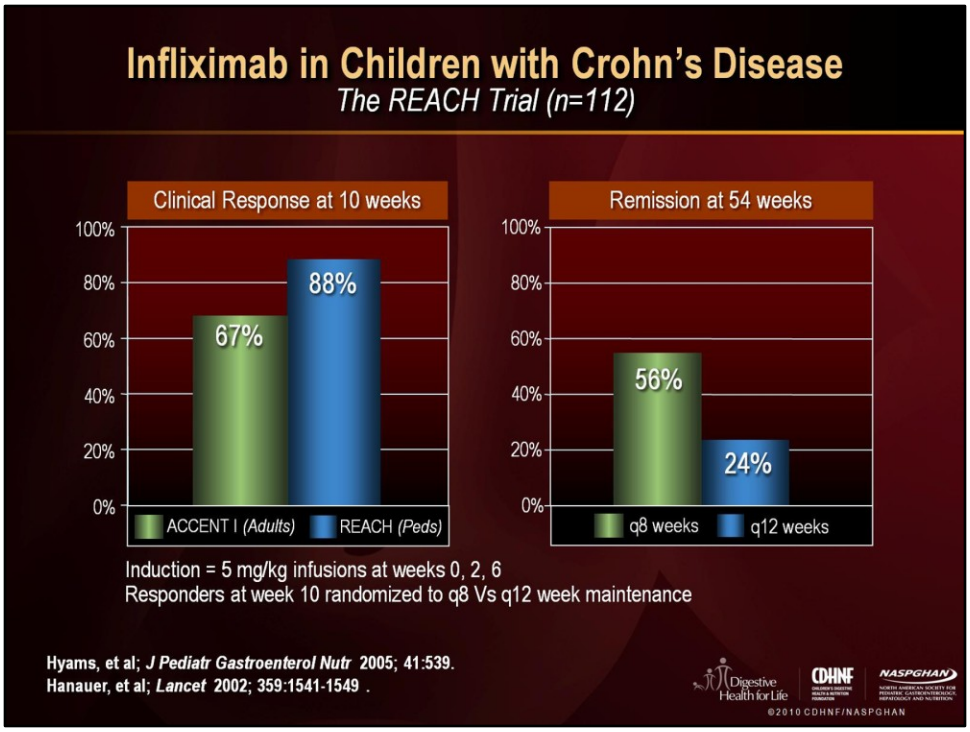
disease patients treated with azathioprine and 6-mercaptopurine. *Gut*. 2005 Aug;54(8):1121-5.



FDA approval for use in adults with Crohn's: Infliximab(1998), adalimumab(2007) & certolizumab(2008) .

Infliximab (2006) has been approved by Food and Drug Association for the treatment of Crohn's disease in children .

Certolizumab study is under way to gain FDA approval for pediatric Crohn's disease

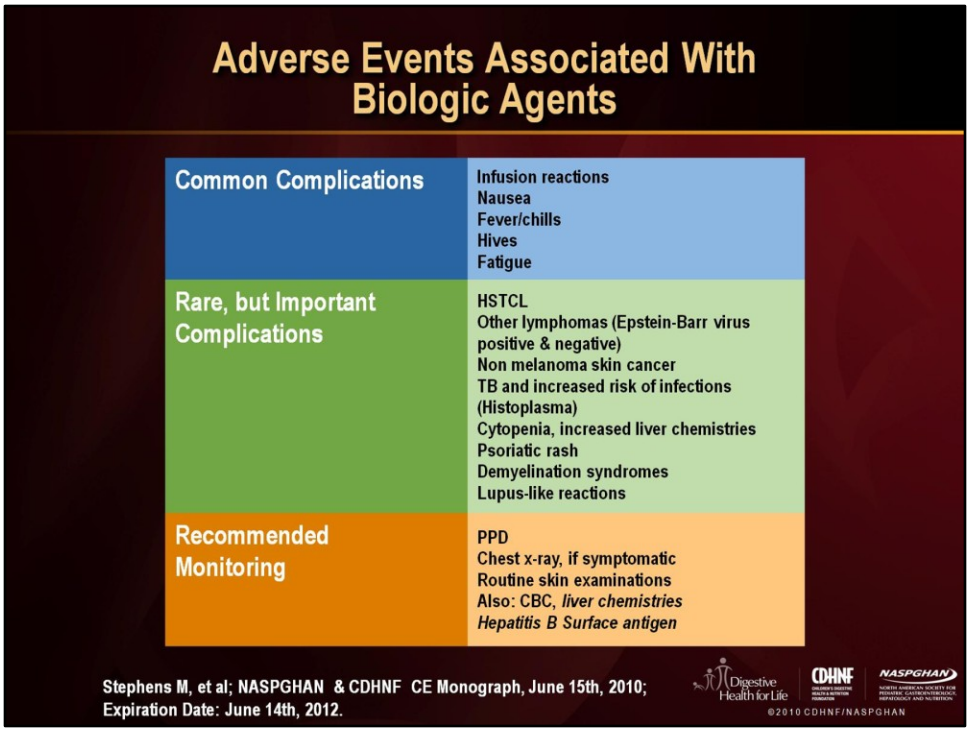


The REACH trial was an open label, multi-center trial in children with moderate-to-severe Crohn's disease despite treatment with an immunomodulator. All children received 5 mg/kg induction at 0, 2, and 6 weeks. Here is the clinical response at 10 weeks compared to historical adult controls as seen in the ACCENT I trial. REACH trial responders at 10 weeks were randomized to every 8 versus every 12 week maintenance with response/remission determined at 54 weeks.

References:

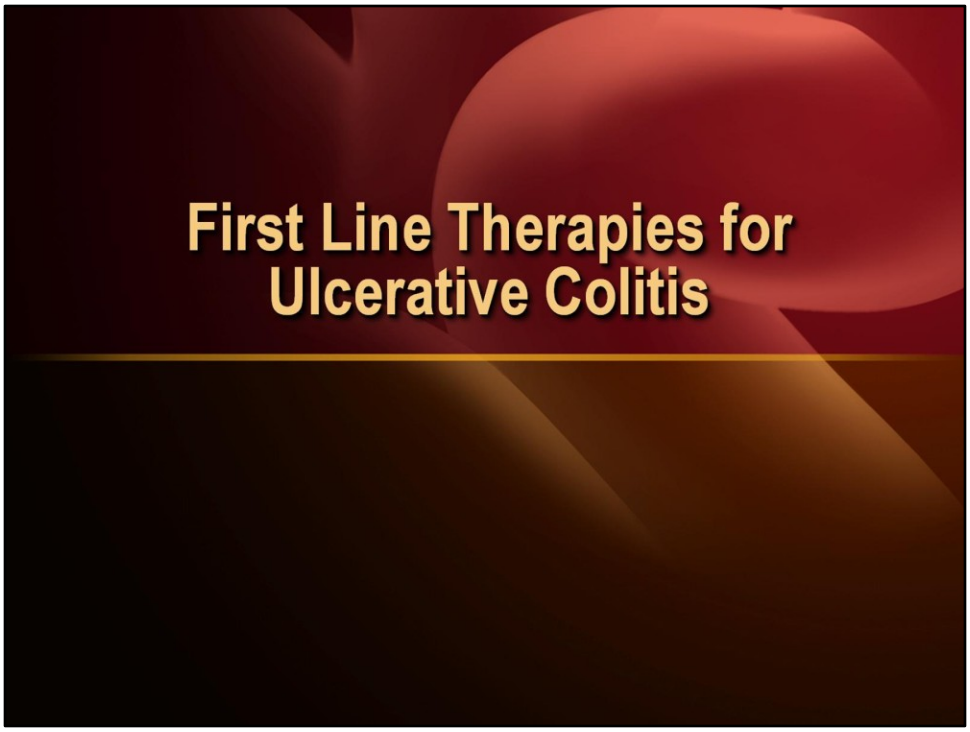
Hyams J, Crandall W, Kugathasan S, et al A Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Infliximab in Pediatric Patients with Moderate-To-Severe Crohn's Disease. *J Pediatr Gastroenterol Nutr* 2005;41:539 (abstract)

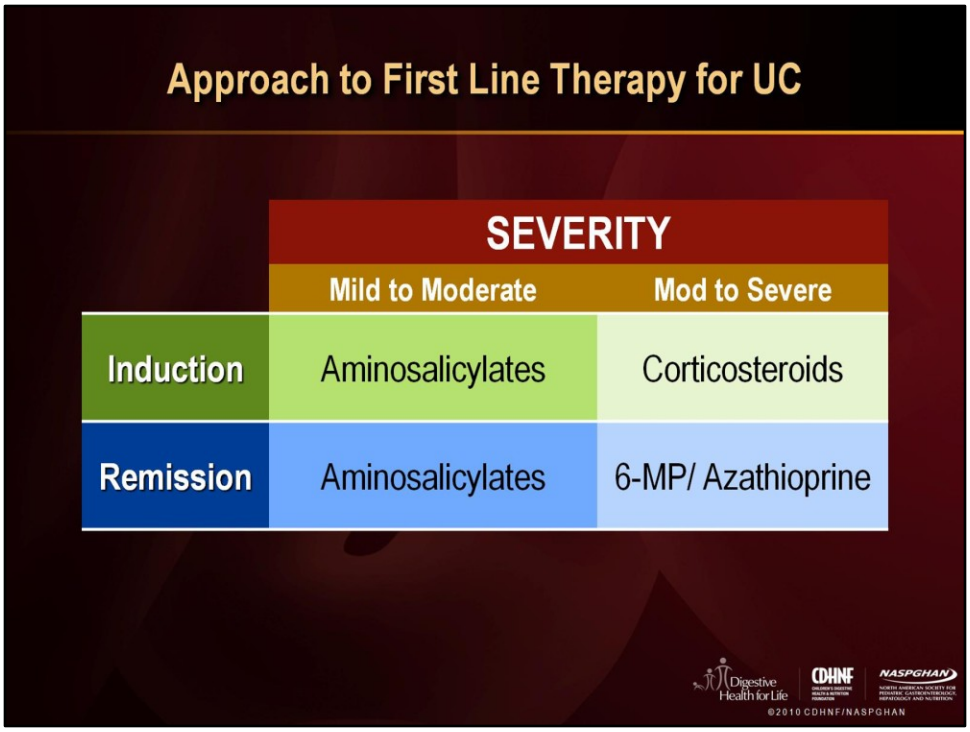
Hanauer Sb, Feagan Bg, Lichtenstein Gr *et al.*: Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* (2002) 359:1541-1549.



Stephens M and Rosh J :Optimizing therapeutic safety in children and young adults with IBD. A continuing education monograph series by NASPGHAN and CDHNF, Jointly sponsored by NASPGHAN, CDHNF, and TCL Institute, LLC.

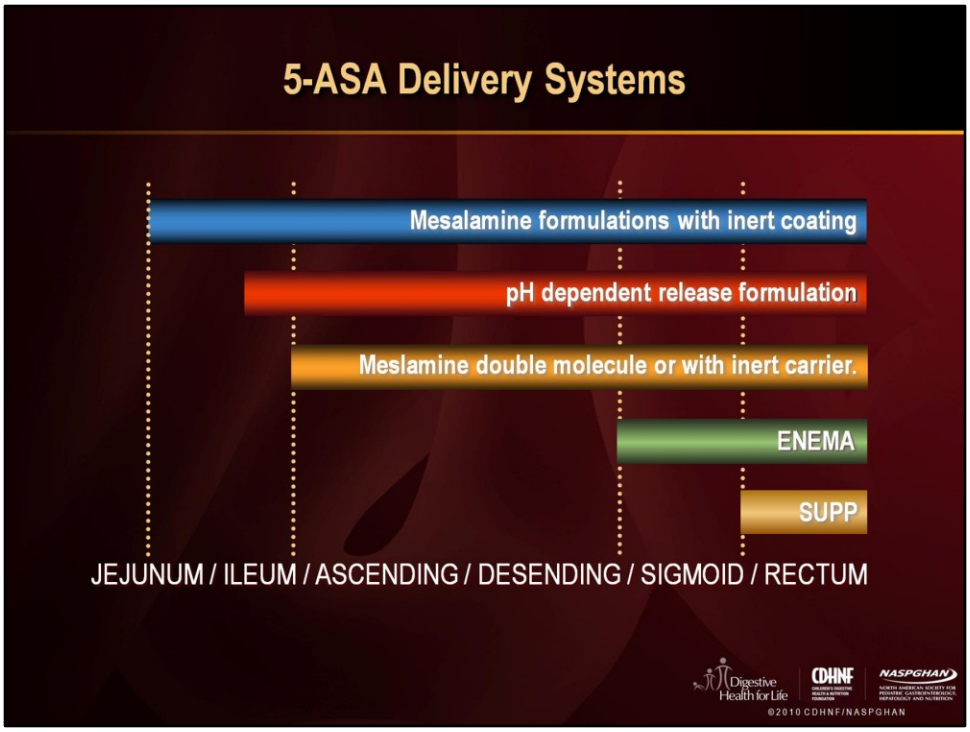
Release Date: June 15th, 2010 Expiration Date: June 14th, 2012.


First Line Therapies for
Ulcerative Colitis

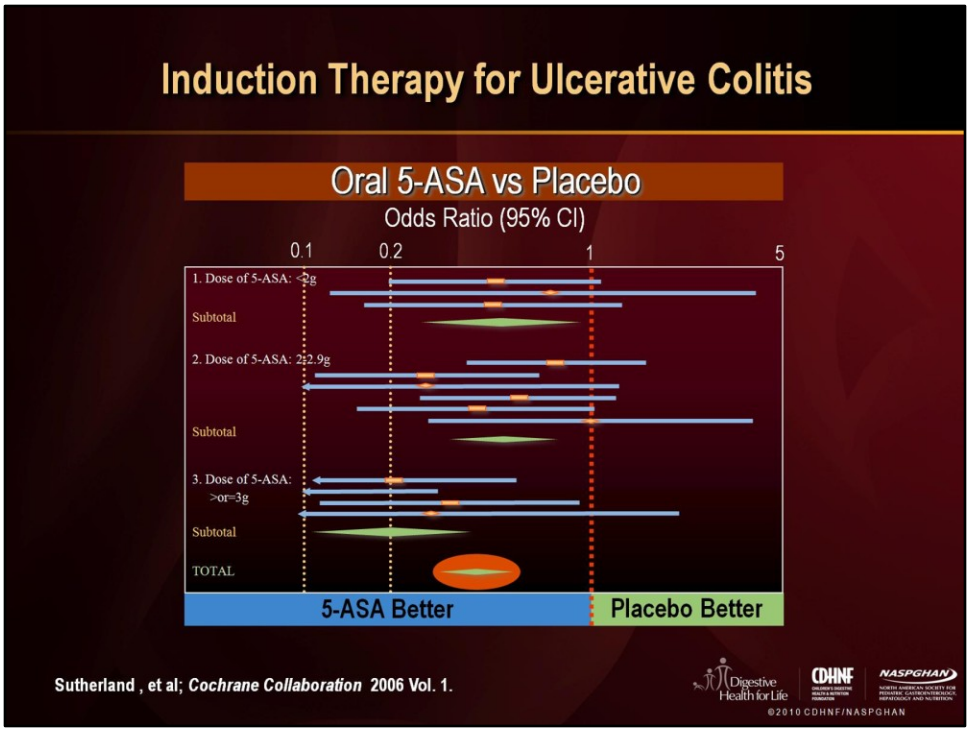


This slide shows severity assessed according to previously discussed slides. It introduces a difference between using steroids as inducing agents and 6-MP/Azathioprine as maintenance agents.

Therapy should be tailored based on individual response: Children who respond to induction therapy with corticosteroids often are able to maintain remission with aminosalicylates.

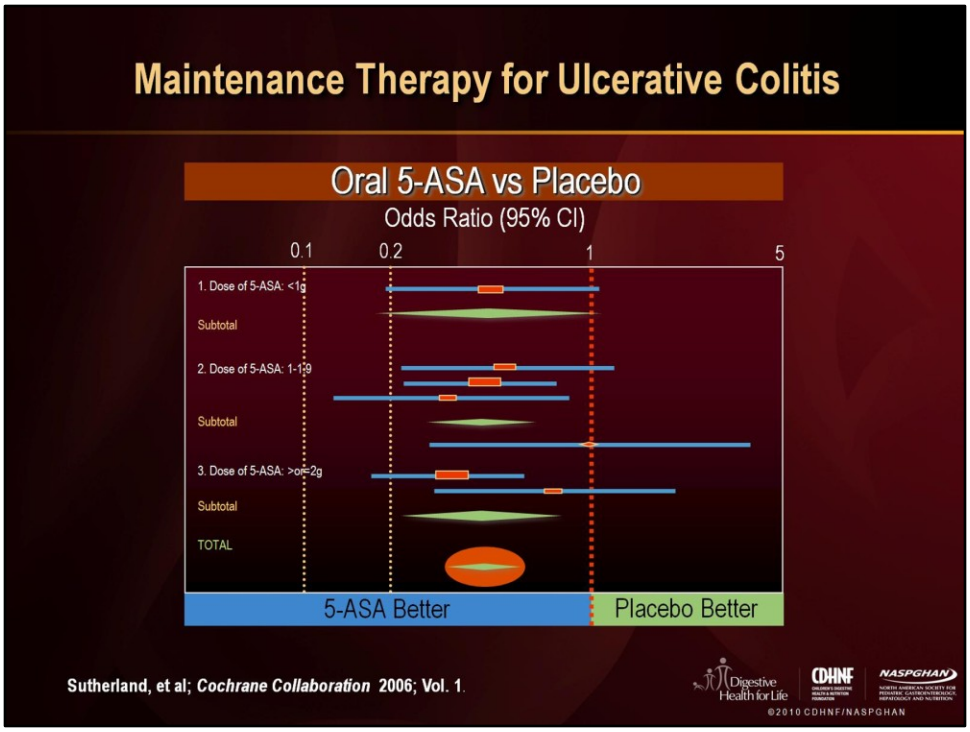


This slide graphically shows the site of release of the active drug for the various forms of aminosalicylates that are commercially available in the United States. Note that while all cover the colon, only the mesalamine preparations offer true drug release in the small intestine, which is a frequent site of activity in Crohn's disease.

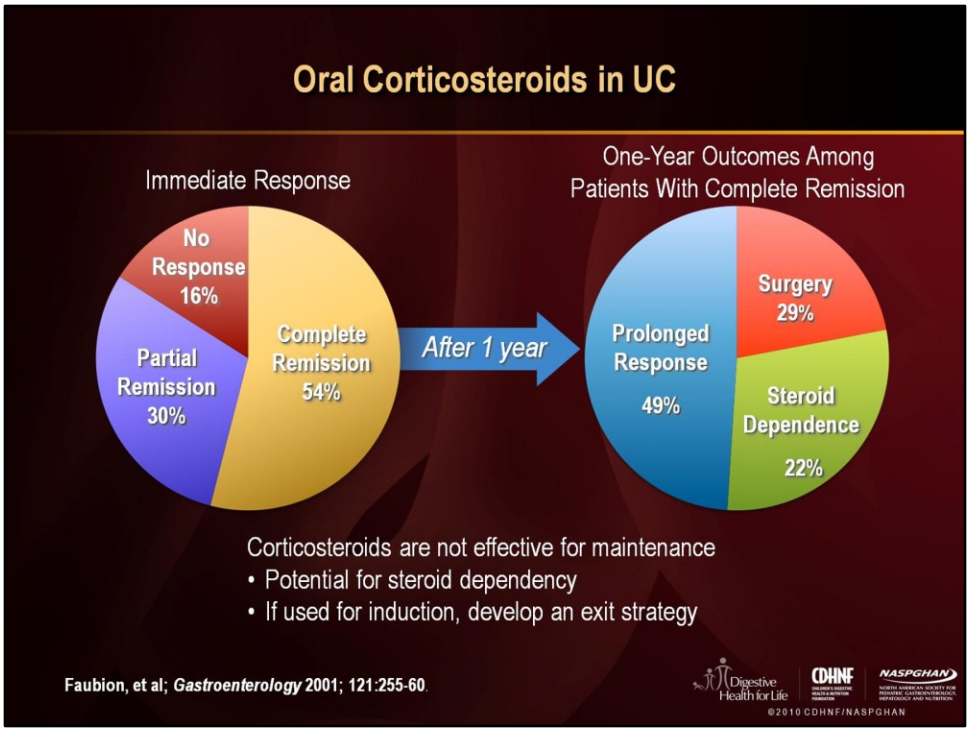


A meta-analysis of all randomized studies comparing oral 5-ASA to placebo as part of the Cochrane collaboration show conclusively that 5-ASA therapy is beneficial in inducing remission in ulcerative colitis. Most studies are in patients with mild-to-moderately active UC."

References:



Considering maintenance therapies, we again see the effectiveness of 5-ASA compared to placebo.

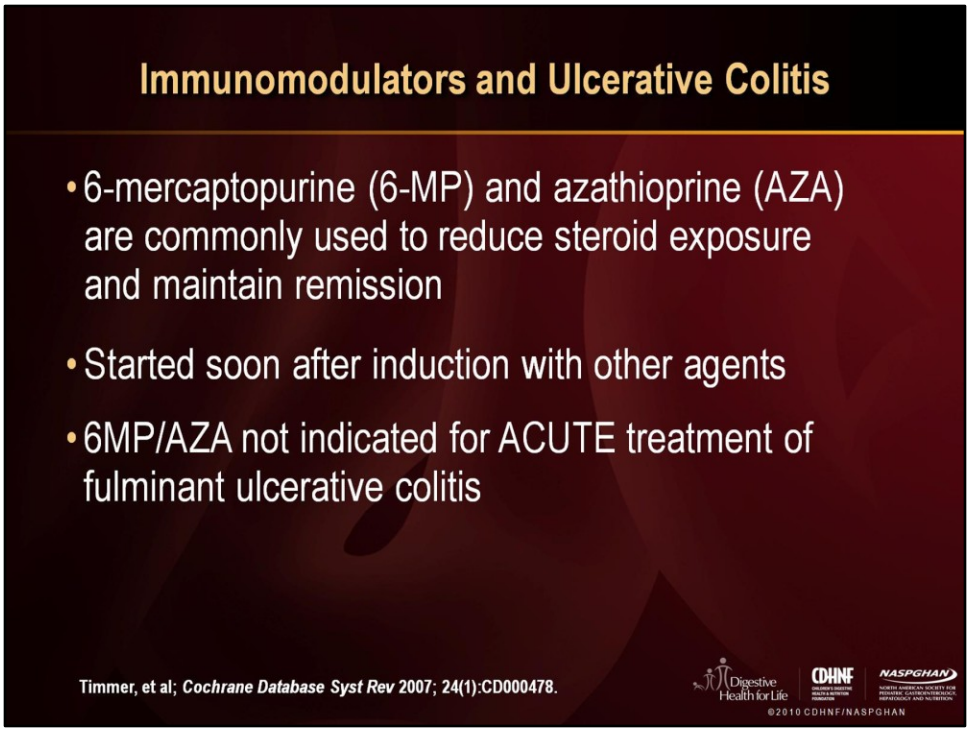


Sixty-three patients with ulcerative colitis given corticosteroids for induction of remission were followed over a one-year period. Patients received mesalamine or sulfasalazine for maintenance. Of the 54% who achieved complete remission, only 49% were still in remission after 1 year, while 22% were steroid-dependent and 29% required surgery. The study underlines the importance of an exit strategy once corticosteroid therapy is initiated, as patients do not stay in remission off steroids without additional medications and some, in fact, are steroid dependent.

Reference:

Faubion WA, Loftus EV, Harmsen WS, et. al. The Natural History of Corticosteroid Therapy for Inflammatory Bowel Disease: A Population-Based Study. *Gastroenterology*. 2001; 121: 255-260.

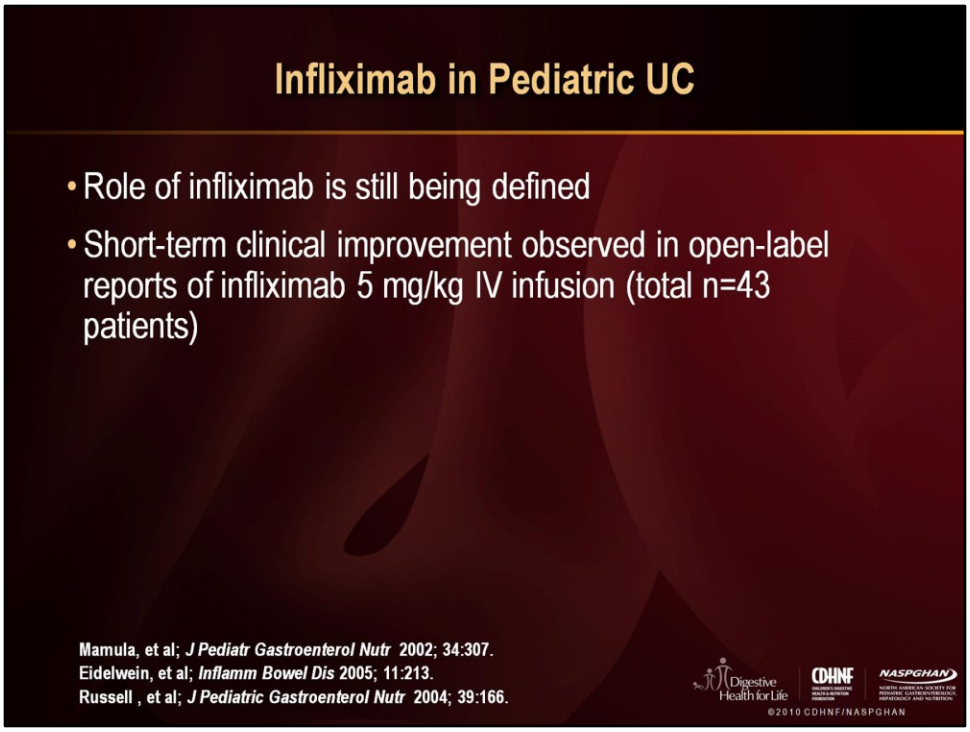
Immunomodulators and Biologics for Ulcerative Colitis



Cochrane database review in 2007 showed that azathioprine may be an effective maintenance therapy for adult patients who have failed or cannot tolerate mesalazine or sulfasalazine and for patients who require repeated courses of steroids. The studies showed that azathioprine was better than placebo for maintenance treatment (i.e. preventing the disease from coming back once the patient has responded to treatment). **Fifty-six per cent of patients treated with azathioprine were disease free after one year of treatment compared to 35% of patients** who received placebo. It also concluded More research is needed to evaluate superiority over standard maintenance therapy, especially in the light of a potential for adverse events from azathioprine.

This has to be tempered with the knowledge that in children the disease tends to be more severe or more extensive; early therapy may alter the natural history of the disease although data is still not available for this stratagem. (please see notes on IBD natural history)

Timmer A, McDonald JW, Macdonald JK Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD000478



Although now approved for the treatment of refractory ulcerative colitis in adults, the exact parameters for using infliximab to treat UC are still being defined. In open label studies, infliximab has been demonstrated to be effective at inducing remission in patients with moderate to severe UC.

Mamula, et al. published the first pediatric experience with infliximab for UC in 2002, demonstrating a high response rate and steroid sparing effect.

References:

Infliximab as a novel therapy for pediatric ulcerative colitis.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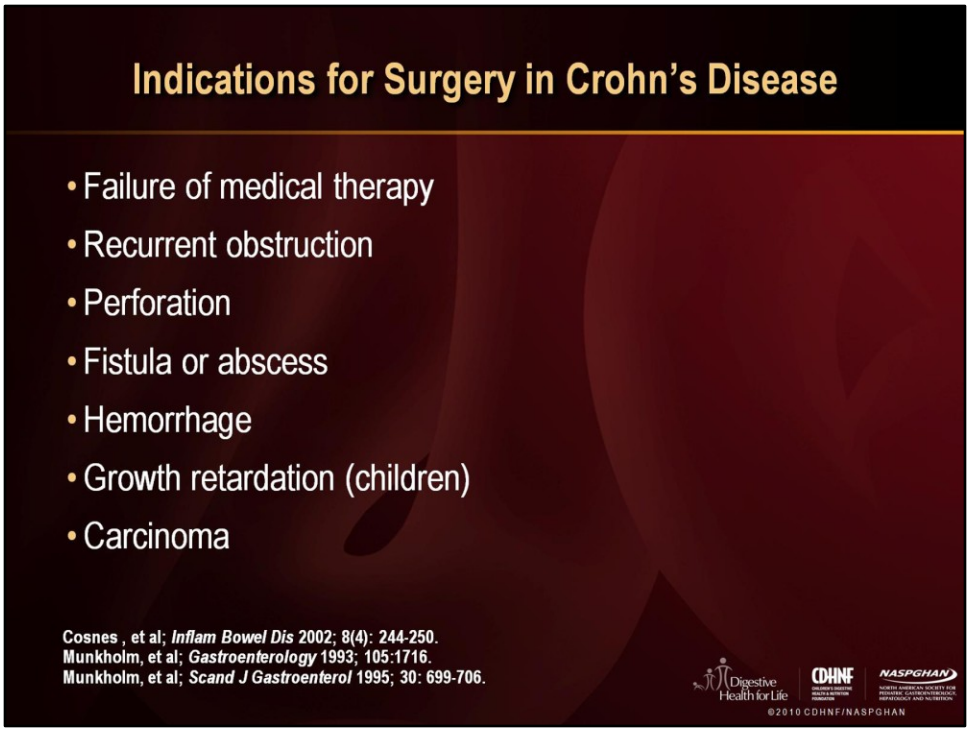


Indications for surgery in Crohn's disease include failure of medical therapy, intestinal complications including obstruction, perforation, intra-abdominal abscess, enterovesicular fistula, intractable hemorrhage, growth failure in children, and carcinoma.

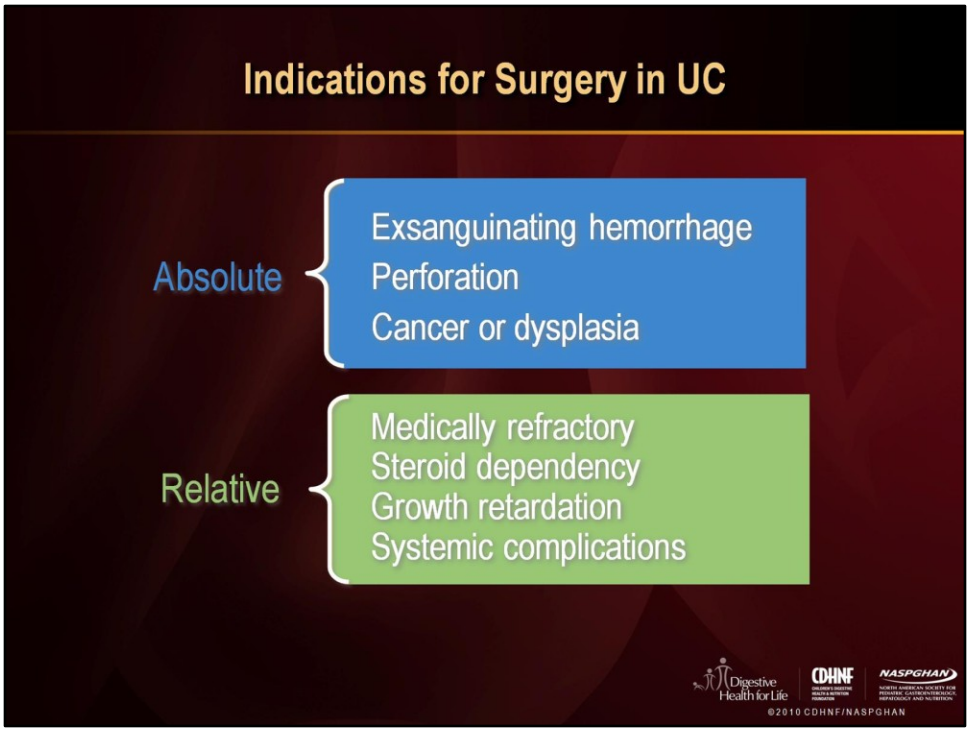
Up to approximately 90% of patients with develop a complication such as stricture or fistula over a span of 20 years. Of 100 patients with Crohn's disease, almost 70% of patients require some type of surgical intervention within 15 years of diagnosis, many require more than one.

Amongst patients with severe Crohn's disease approximately 60 % patients require surgical resection or stoma within 5 years of diagnosis.

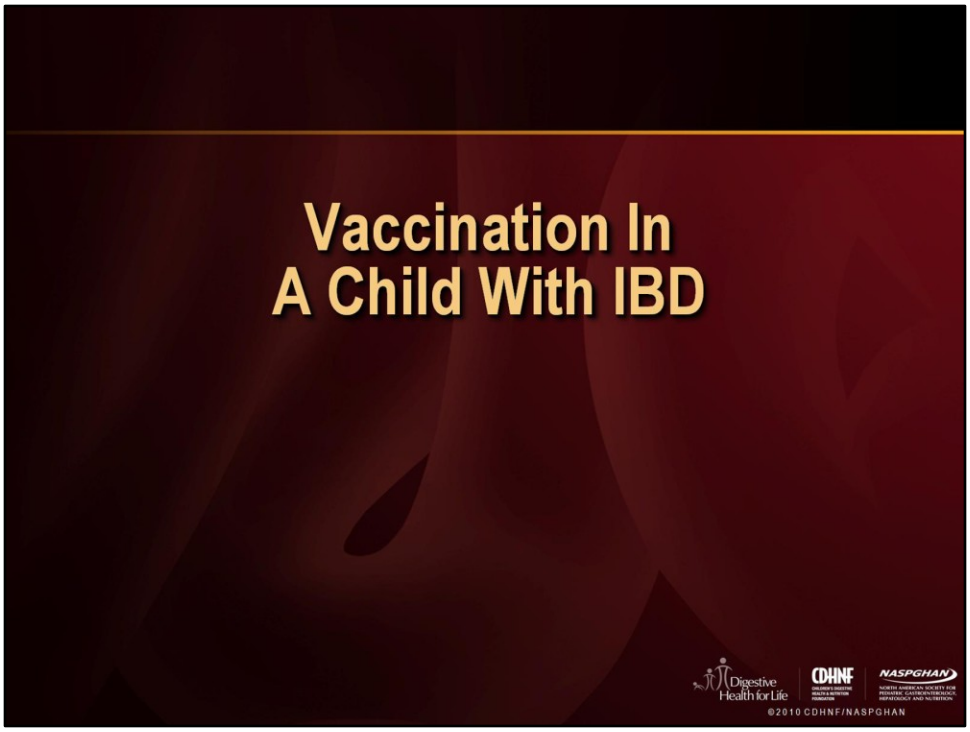
Cosnes J, et al. Long term evolution of disease behavior of Crohn's disease. Inflam Bowel Dis. 2002;8(4):244-250

Munkholm et al. Intestinal cancer risk and mortality in patients with Crohn's Disease. Gastroenterology 1993;105:1716

Munkholm et al. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995; 30: 699-706.



Approximately 30% of patients with ulcerative colitis undergo surgery within the first 10 years of their illness. Indications for surgery may be divided into absolute and relative indications. Absolute indications include exsanguinating hemorrhage and perforation. Patients with established carcinoma or dysplasia should undergo colectomy. Unresponsive, severe, acute disease, with or without megacolon, should be treated with a colectomy.


Vaccination In
A Child With IBD
Digestive Health for Life
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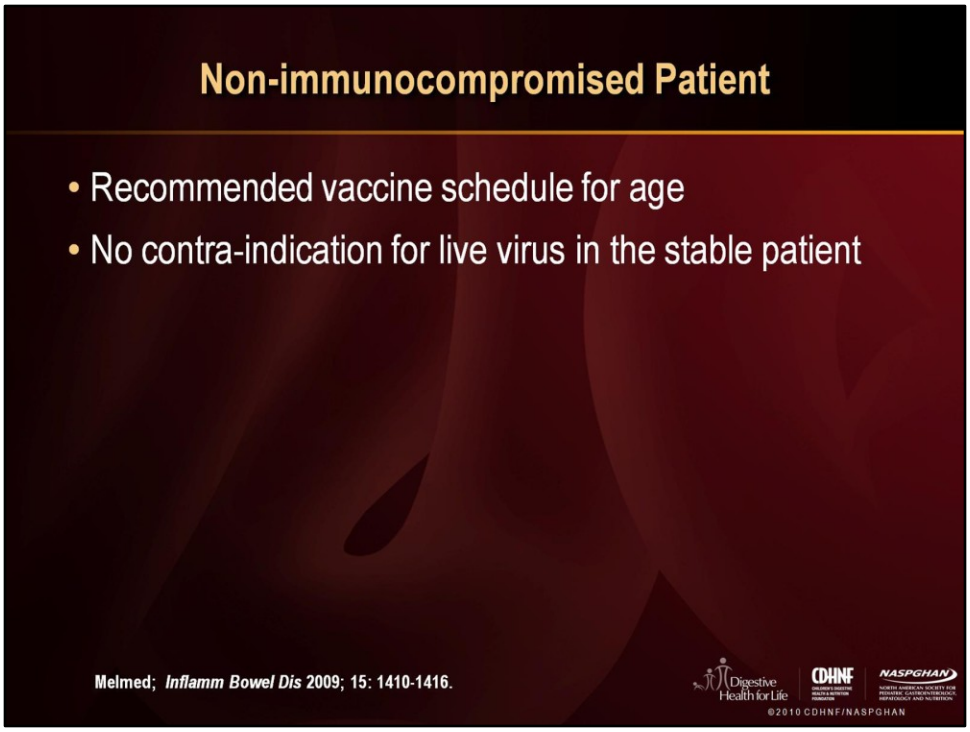
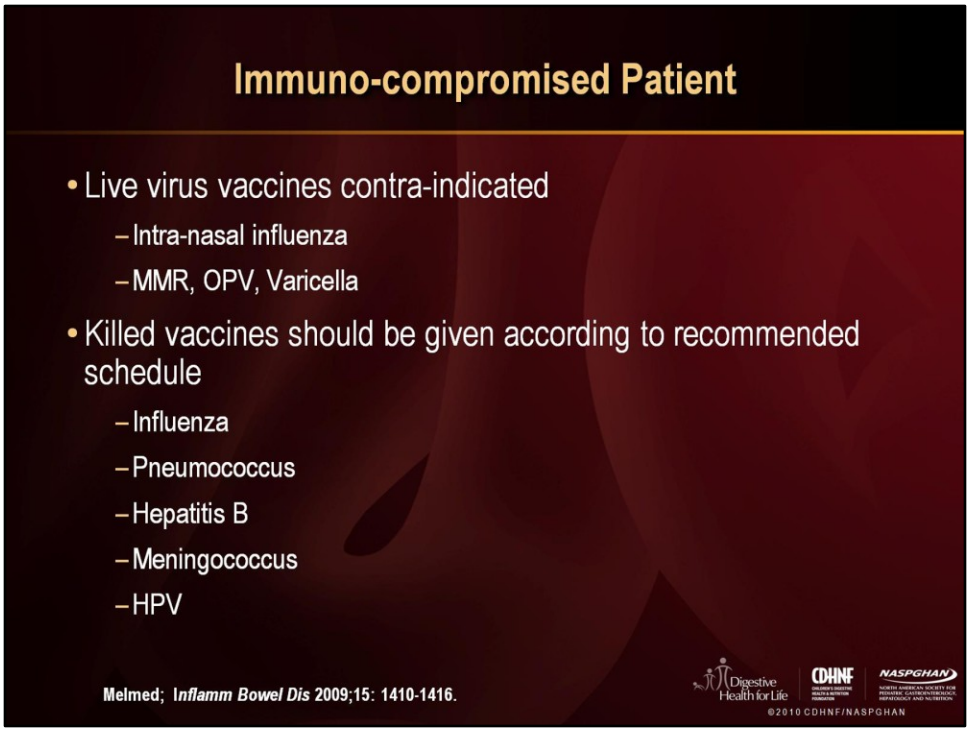


For the IBD patient who is not on immunosuppressive therapy i.e. steroids, immunomodulators, biologics, age recommended vaccination schedules should be followed. Live vaccines are not contraindicated in this group.

Ref:

Melmed, G. Inflamm Bowel Dis 15 (2009) 1410-1416



- Live virus vaccines contra-indicated
  - Intra-nasal influenza
  - MMR, OPV, Varicella
- Killed vaccines should be given according to recommended schedule
  - Influenza
  - Pneumococcus
  - Hepatitis B
  - Meningococcus
  - HPV


Bone Disease
Digestive Health for Life
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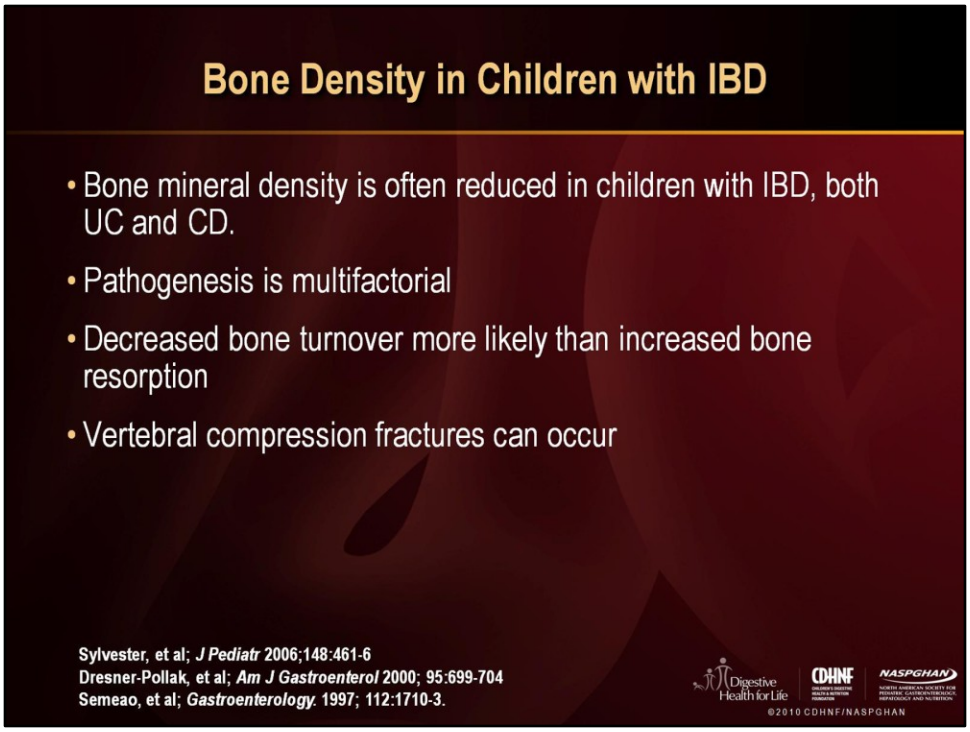


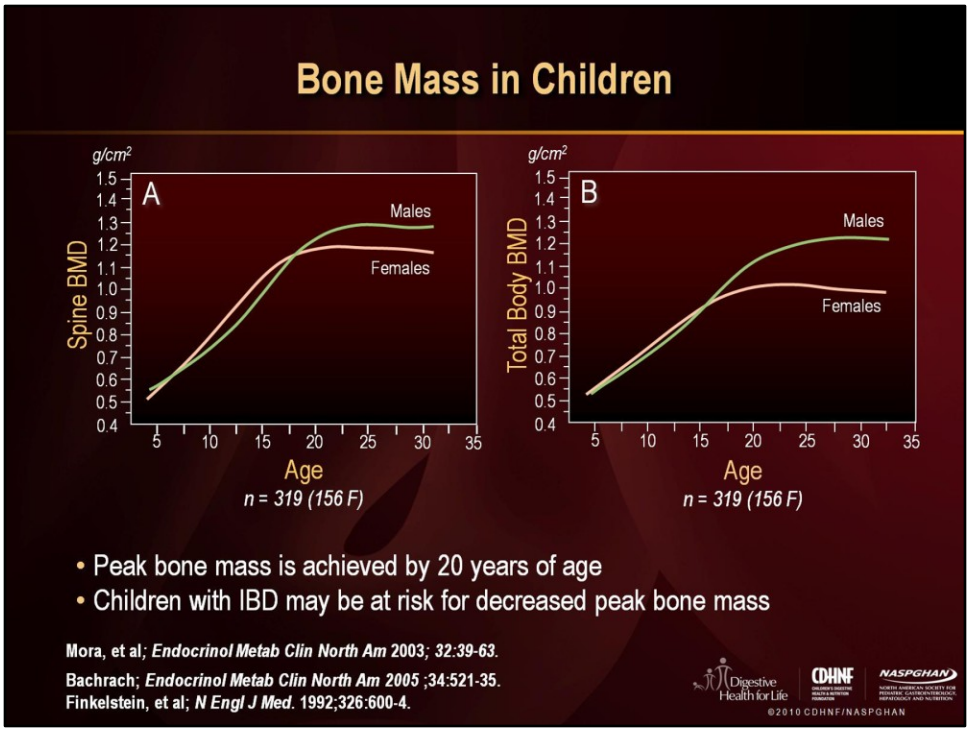
Childhood is characterized by rapid linear growth and active bone metabolism. In adulthood, growth ceases and bone activity is focused on preserving its structural integrity. Due to these important physiological differences, IBD affects bone differently in children and in adults. At diagnosis, children with IBD have decreased bone turnover while in adults, bone resorption by osteoclasts is increased and bone formation may be decreased. Although it is not known whether fracture risk is increased in children with IBD, vertebral fractures have been reported.

References:

Sylvester FA et al. Are activated T cells regulators of bone metabolism in children with Crohn's disease? *J Pediatr.* 2006;148:461-6

Dresner-Pollak R et al. Increased urinary N-telopeptide cross-linked type 1 collagen predicts bone loss in patients with inflammatory bowel disease. *Am J Gastroenterol.* 2000;95:699-704

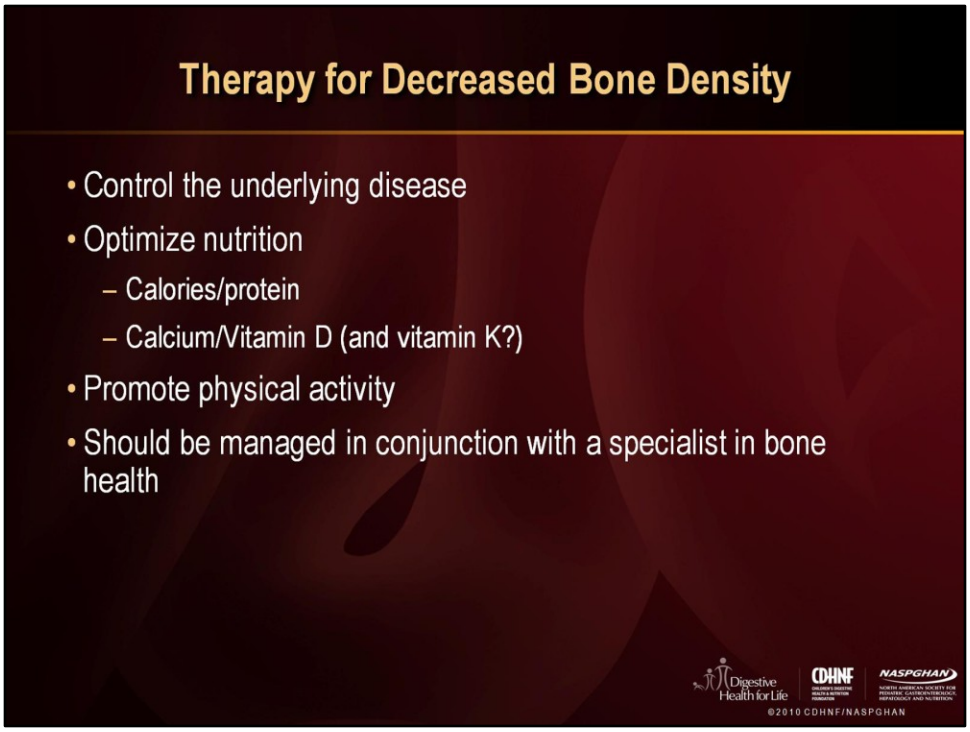
Semeao EJ et al. Vertebral compression fractures in pediatric patients with Crohn's disease. *Gastroenterology.* 1997;112:1710-3.



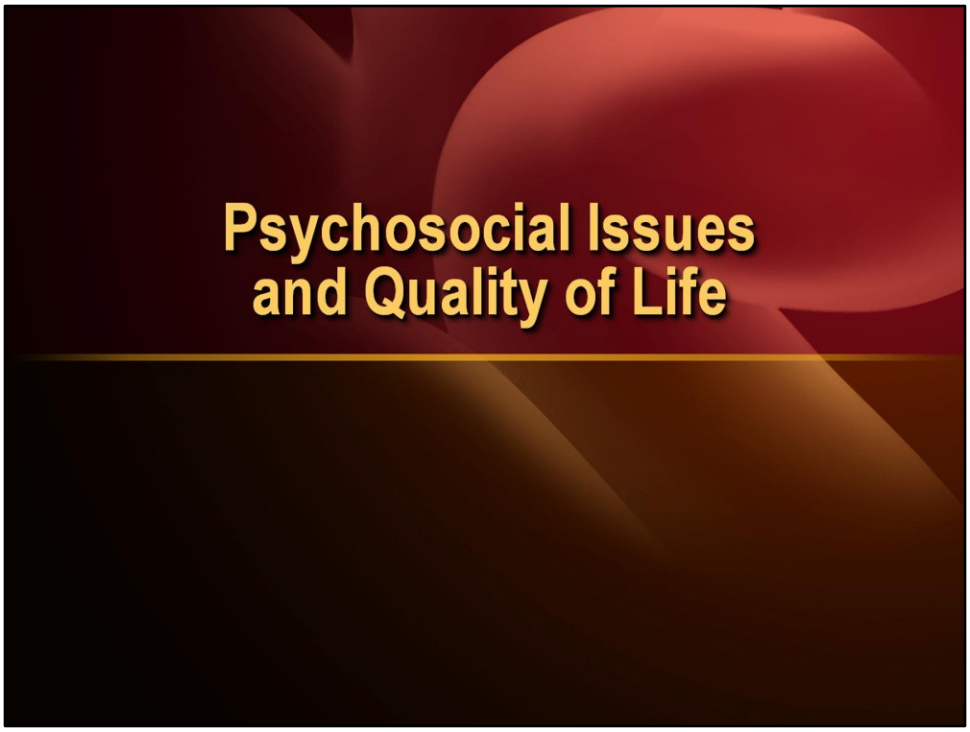
Volumetric bone density does not change significantly in children until late puberty. Therefore, changes in bone mass are largely due to changes in bone size. When bone mass is measured by dual energy X-ray absorptiometry, smaller bones with equal material density will appear less "dense" than larger bones. In addition, constant changes in bone shape and geometry in children can affect DEXA measurements. Although DEXA is precise and accurate, it is important to consider these factors when interpreting a study in children, especially when they are smaller than normal. Children with IBD with delayed puberty may be at risk for decreased peak bone mass.

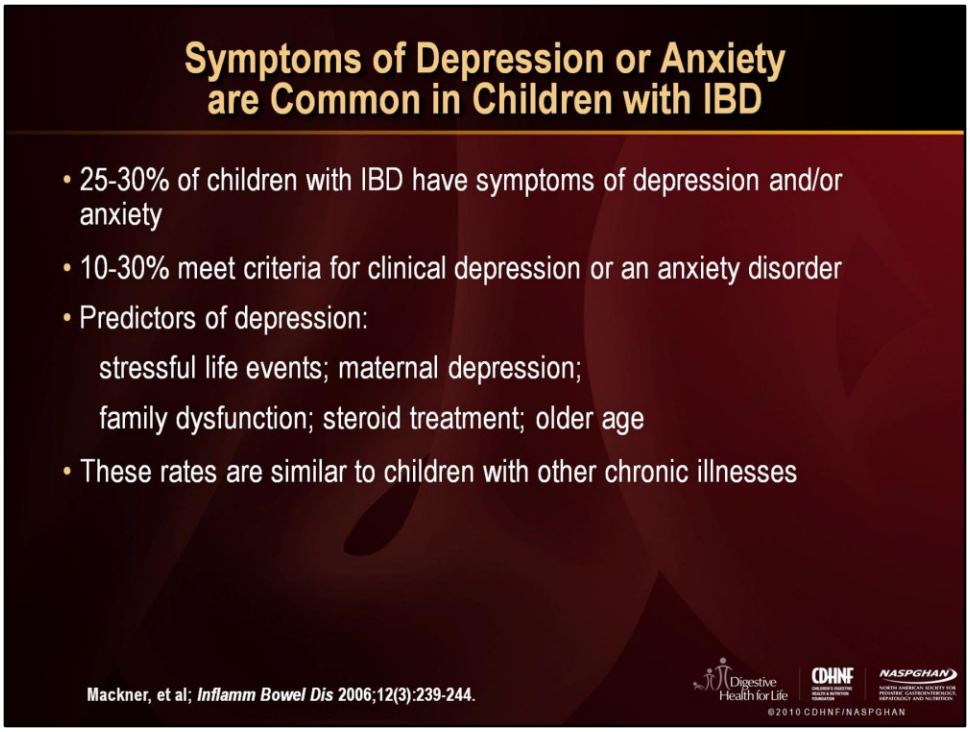
Osteoporosis and measurement of bone mass in children and adolescents.

Finkelstein JS, et al. Osteopenia in men with a history of delayed puberty. *N Engl J Med.* 1992;326:600-4



There are no proven therapies to increase bone mass in children with IBD. Since the main impact of IBD appears to be on overall growth and skeletal modeling, it probably makes sense to institute measures aimed at restoring growth and anabolism.


Psychosocial Issues
and Quality of Life

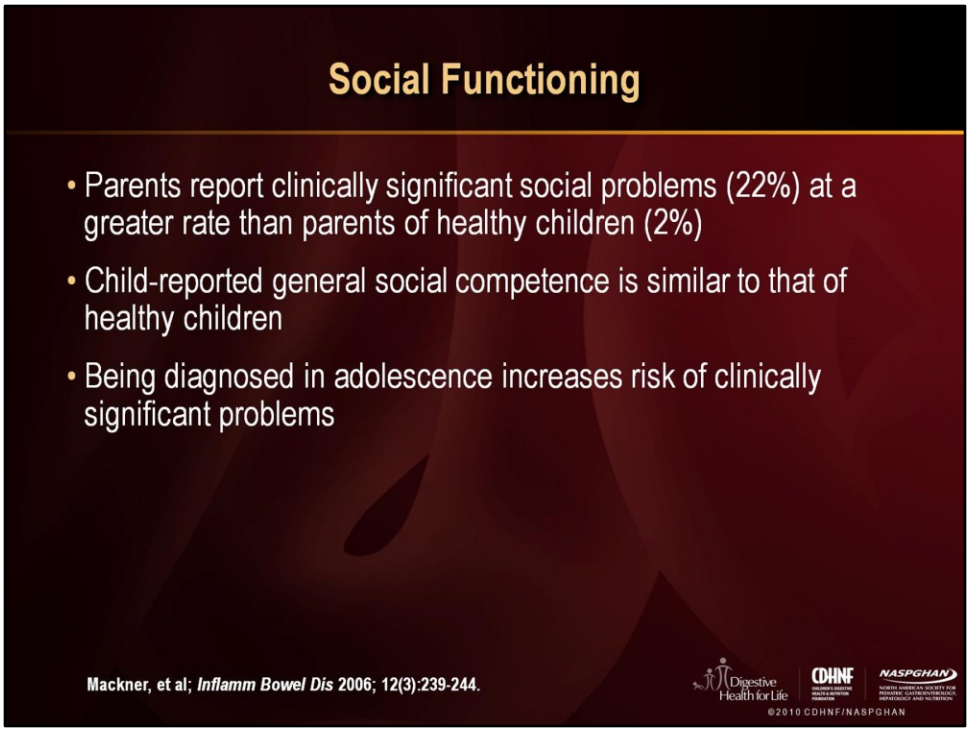


Children with IBD are generally well-adjusted. A subset have clinically significant difficulties in behavioral/emotional functioning.

There have been mixed results for disease severity as a predictor of depression. This is similar to findings in other chronic illnesses and may be related to differences in coping strategies (e.g., a child with more severe disease, but better coping skills may not have problems with depression).

References:

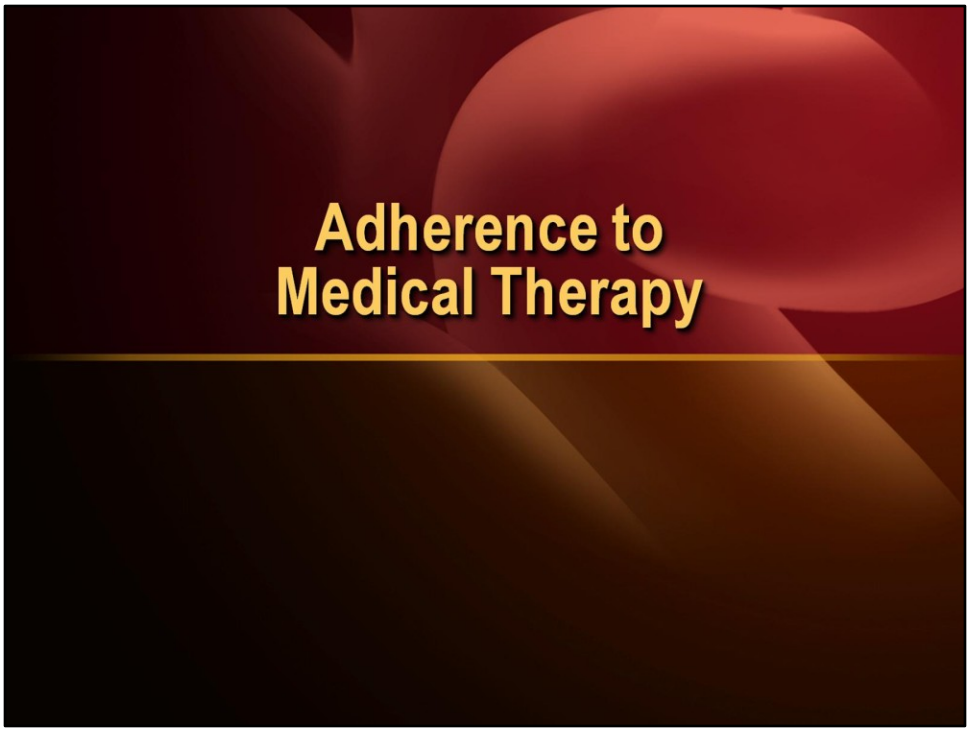
Psychosocial functioning in pediatric inflammatory bowel disease.

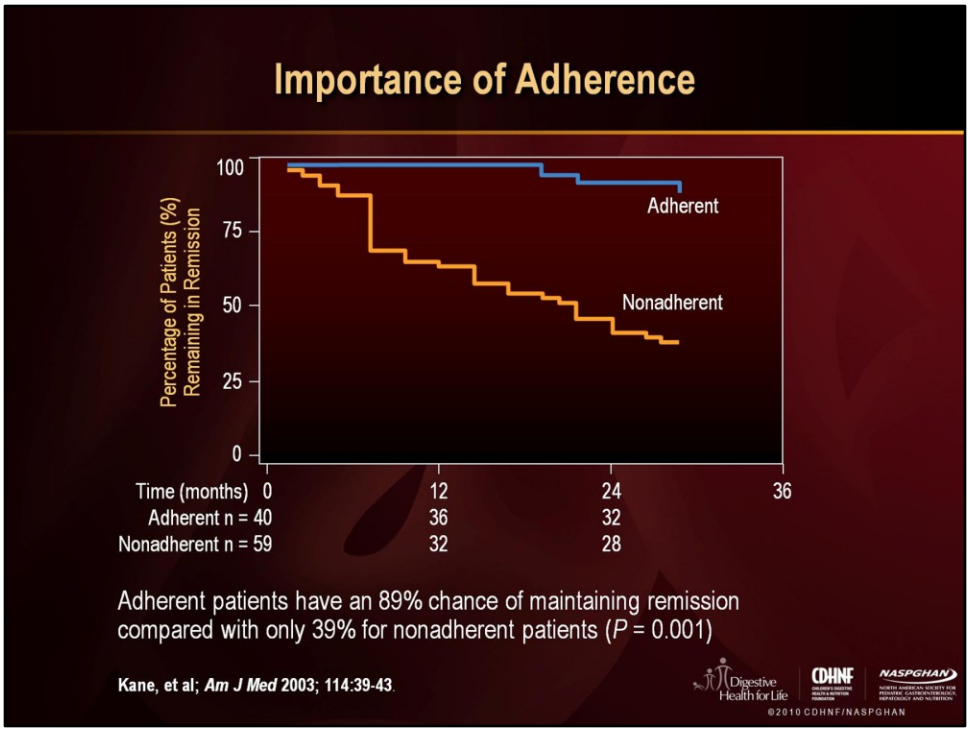


The potentially embarrassing and socially-limiting symptoms of IBD present significant challenges during adolescence when social functioning is highly valued.

References:

Psychosocial functioning in pediatric inflammatory bowel disease.


Adherence to
Medical Therapy



Even the most efficacious therapy will not achieve optimal effectiveness when adherence is poor.

In the study by Kane et al., non-adherence (defined as filling <80% of prescribed medication) to maintenance monotherapy with mesalamine was associated with a five-fold greater risk of clinical recurrence over 24 months than adherent patients. Clinical recurrence was defined as four or more bowel movements per day associated with urgency, pain or bleeding, or the presence of urgency, pain or bleeding. As shown in the Kaplan-Meier survival curve, adherent patients had an 89% chance of maintaining remission compared to 39% in those who were non-adherent (P=0.001).

References:

Kane S, Huo D, Aikens J, Hanauer S. Medication non-adherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med*. 2003;114:39-43.

Effective Communication Between Patients and Health Care Providers is Key

- Effective communication can improve trust in patient-provider relationship
- Enable patients/parents time to voice concerns and ask questions
- Empower child/parent to be involved in treatment plans & decision making

DiMatteo ; *Patient Educ Couns* 2004. Dec; 55(3):339-44.
Harrington, et al; *Patient Educ Couns* 2004 Jan;52(1):7-16.

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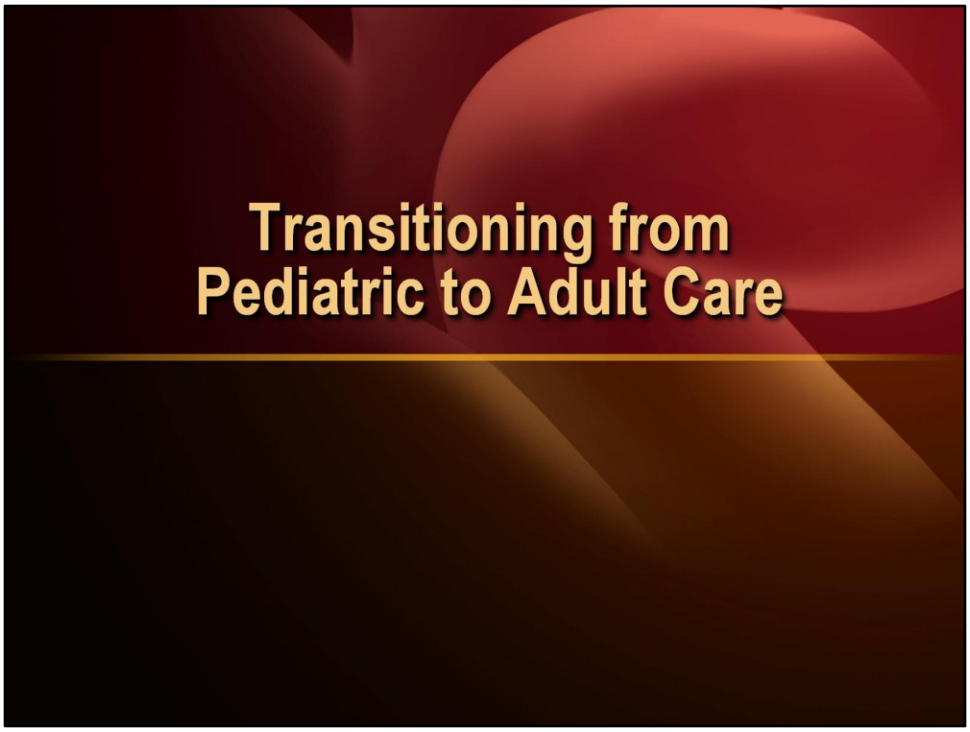
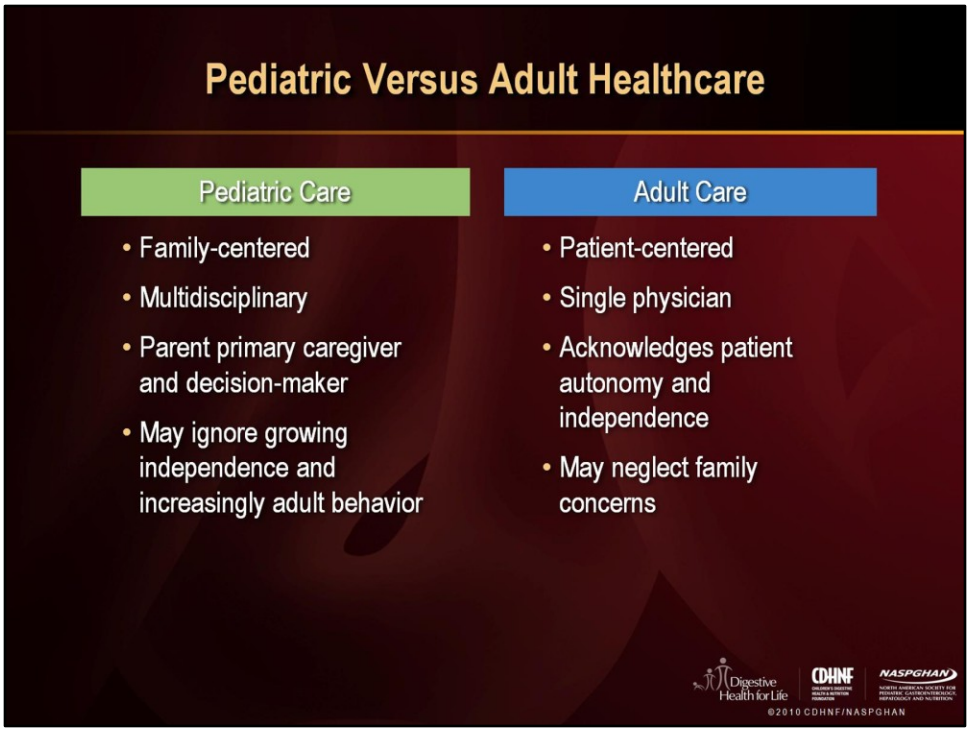
The quality of the physician-patient relationship is critical. Physicians must communicate the rationale for the therapies and the importance of adherence effectively and clearly to the patient. Treatment regimens must be practical and acceptable to the patient. The physician must work with the patient in setting up therapeutic regimens that are likely to promote adherence. Adherence should be closely monitored and assessed. This can be in the form of self-monitoring by the patient or, in the case of pediatric patients, involve their parents. In some situations, drug levels and the frequency of prescription refills may be obtained. It is important for adherence to be rewarded, whether through the physician, the patient or the parents. Physician acknowledgement of adherence may reinforce this behavior.

References:

Levy R, Feld A. Increasing patient adherence to gastroenterology treatment and prevention regimens. *Am J Gastroenterol*. 1999;94(7):1733-1742.

Kripalani S et al, *Arch Int Med*, 2007


Transitioning from
Pediatric to Adult Care



Health care provided in a pediatric setting differs from that provided in an adult care setting. There are a number of reasons behind these differences and most relate to the emphasis placed on different components of care and its delivery for the individual patient. Fundamental in these differences in the lack of autonomy in the child, where parents act as proxies when it comes to decision making surrounding management and care.

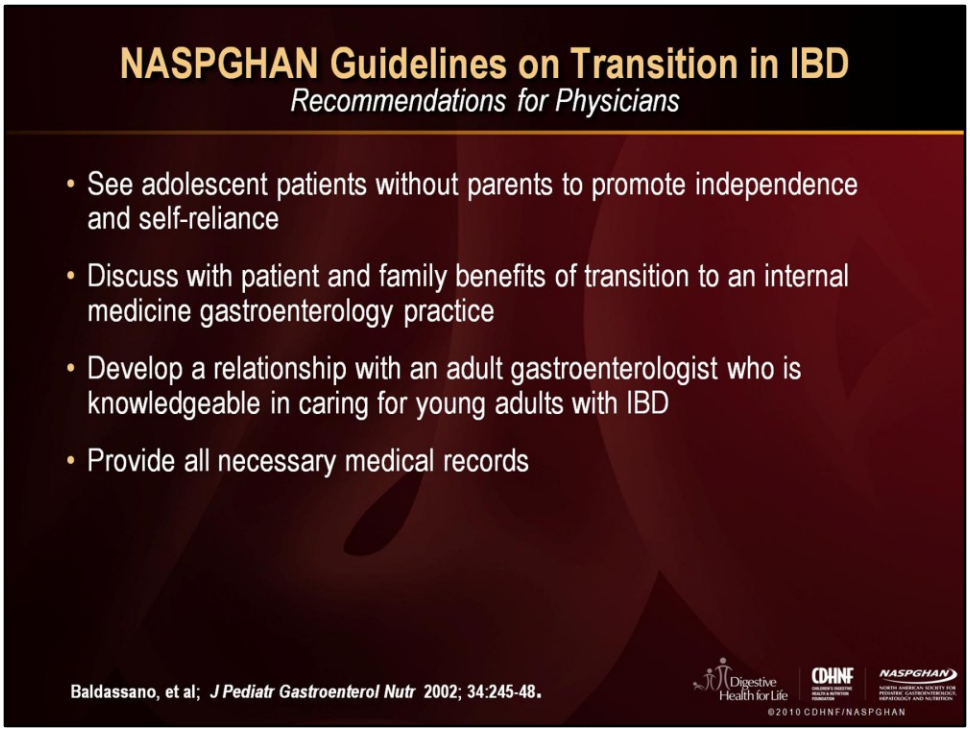
It is important when discussing transition, that the goals of this process are clear.

There is no evidence that particular models of transition of care are more effective than others. However, evidence would suggest that certain components are important. These components include:

- Planning and coordination
- Opportunities for young people to meet the adult healthcare team who will look after them before the transfer
- To be seen independently from their parents or caregivers

References:

While A, et al. Good practices that address continuity during transition from child to adult care: synthesis of the evidence. *Child: Care, Health and Development.* 2004;30:439-52



A medical position statement was developed by NASGHAN discussing transition of the patient with IBD from pediatric to adult care. This was based on expert opinion and experience. In this statement potential obstacles to transition (patient, family, pediatric caregiver and adult caregiver) are reviewed, and then recommendations are made directed at pediatric gastroenterologists on how to facilitate the transition process. They emphasize that the goal of transition program is to achieve for each chronically ill patient a continuum of care that includes normalization of social and emotional development and the acquisition of independent living skills.

References:

Baldassano R, Ferry G, Griffiths A et al. Transition of the patient with inflammatory bowel disease from pediatric to adult care: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr, 2002;34:245-248.