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Pediatric Inflammatory Bowel Disease

Perspective and Consequences

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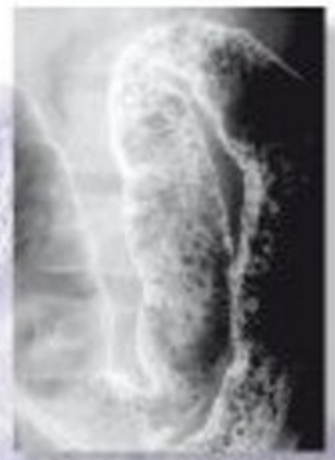

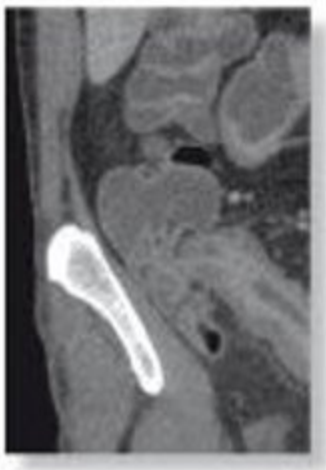

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Pediatric and Inflammatory Bowel Disease

Perspective and Consequences

Volume Editors

John A. Walker-Smith London
Emanuel Lebenthal Jerusalem
David Branski Jerusalem

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Preface

Chronic inflammatory bowel disease (IBD) encompasses Crohn's disease, ulcerative colitis and indeterminate colitis. These disorders are induced by interactions between genetic, host, environmental and immune regulatory factors.

The etiology of IBD is still obscure; however, a growing body of evidence suggests a dysfunctional mucosal immune system overacting with constituents of the commensal flora.

The disease is not uncommon in the pediatric population. The clinical presentation and therapeutic considerations including nutritional support and disease complications – especially failure to gain weight and short stature – are more specific for pediatric and adolescent patients suffering from IBD.

Early-onset IBD has a distinct phenotype and the difference from adult IBD makes it a unique subgroup, with the possibility of a wide range of causes.

The aim of this book is to increase the knowledge and understanding of pediatricians and physicians on IBD in infants, toddlers, children, adolescents and young adults.

This book covers most of the relevant topics related to pediatric IBD. Experts and leaders in the field of pediatric IBD from the USA, various European countries and Israel have contributed to this volume.

Derek Jewell from the UK presented new data on the genetics of IBD. Koletzko from Germany discussed the epidemiology of IBD. Cucchiara from Italy reported on the evolving topic of the pathogenesis of IBD. The clinical aspects of pediatric IBD included the following: Bouvaros from the USA described an approach to the clinical diagnosis of IBD, and Lebenthal and Branski from Israel and Walker-Smith from the UK presented early-onset IBD as a distinct topic. The third clinical chapter by Sanderson from the UK was dedicated to an important issue in pediatric IBD, namely growth and puberty.

The fourth clinical chapter by Sands from the USA highlights an important and relevant topic, i.e. the transition of the pediatric patient to the care of the adult gastroenterologist .

The book then continues with some very informative chapters which deal with considerations that need to be taken when forming a diagnosis.

The first is by Laghi from Italy on radiological and imaging features, the second is by Thomson from the UK on endoscopic findings, and the third is by Harpaz from the USA on pathology in pediatric IBD.

The concluding part of the book includes disease management.

The first by Rufo from the USA concentrates on pharmacological therapy, the second by Heuschkel from the UK on the important therapeutic role of nutrition in IBD, and the third written by Coran's group from the USA is on surgical considerations.

The editors wish to thank all the contributors to this book who are well-known authorities in the field and who invested their time and efforts into realizing this project.

The editors wish to express their appreciation to the professional team from Karger Publishing House who accompanied us all the way through the production of this book.

Last but not least, the editors wish to thank their wives Elizabeth Walker-Smith, Effie Branski and Chana Lebenthal for their patience and continuous support.

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Pathogenesis of Inflammatory Bowel Disease

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Abstract

Ulcerative colitis (UC) and Crohn's disease (CD), the primary constituents of inflammatory bowel disease (IBD), are inflammatory conditions induced by complex interactions between environmental, genetic, microbial and immunoregulatory factors. Although the etiology remains unclear, a growing body of data implicates a dysfunctional mucosal immune system that overreacts to normal constituents of the commensal microflora. Advances in the understanding of pathogenesis of IBD will allow to conceptually characterize these disorders into a spectrum of related, but distinct subgroups that have clear etiologies and open up the possibility for an expanded range of novel therapies with targeted efficacy.

Inflammatory bowel disease (IBD) is a disorder characterized by chronic inflammation of the gastrointestinal tract. There are two clinical subtypes, Crohn's disease (CD) and ulcerative colitis (UC). CD can affect any part of the intestine and is associated with discontinuous transmural lesions of the gut wall, whereas in UC lesions are continuous and superficial and inflammation is confined to the colon and rectum only. An etiologic model of IBD has been proposed, suggesting that individual expression of the disease could be influenced by complex interactions between environmental factors and promoting genes [1–3]. Concerning pathogenesis, there are multiple lines of evidence supporting that IBD may be favored by genetic background, making some individuals more susceptible than others. Thus, both CD and UC are currently considered as complex genetic disorders, with various genes playing a contributing role on the development of the disease. Although the precise molecular basis of the pathogenesis of IBD is not clear yet, results from research in animal models, human genetics, basic science and clinical trials have provided new important insights into the pathogenetic mechanisms promoting chronic intestinal inflammation. These studies suggest that CD and UC are heterogeneous diseases characterized

by an exaggerated T cell response to the commensal enteric flora developed in genetically susceptible hosts. This intriguing theory involves separate components (luminal microbes, genetic susceptibility, immune response, environmental triggers) that must interplay for the disease to become clinically apparent. The level at which this dysregulation occurs still has to be discovered; however, it is reasonable to believe that several defects can present alone or in combination, in different pathways [4, 5]. They include alterations in the composition of the intestinal microflora, an overall immune system deficiency including a defective mucosal barrier function, lack of microbial clearance activity, abnormal sensing and presentation of intraluminal antigens by antigen-presenting cells (APCs) and a generalized unbalanced responsiveness of the lamina propria immune cells, affecting lymphocytes in particular. Traditionally, IBD was meant to be a consequence of an impaired adaptive immune response. A more recent hypothesis suggests, however, that the primary defect could be caused by a defect in innate immune system [6]. Evidence of the latter can mainly be found through animal model studies mimicking human IBD-like condition, such as mice having a genetically induced defective innate immune response. These mice share several pathological features with IBD patients and eventually develop extensive inflammation of the gut [7–9]. The role of the main components (genetics, innate immunity, adaptive immunity, regulation, environmental triggers) featuring the precise cellular and molecular mechanisms at the basis of IBD will be discussed in more detail in the following paragraphs.

Genetics

In previous years, several epidemiological studies showed that genetic susceptibility is one major factor predisposing to IBD. This has also been confirmed by molecular studies from total genome scans and candidate gene analysis [10–12]. Considerable differences in the development of IBD can be found among ethnic groups, with a higher incidence of the disease among Caucasians, and lower rates in African-American and Hispanic and Asian populations. Moreover, familial studies have reported a strong familial association of the disease, with 5.5% up to 22.5% of patients with IBD having another family member also affected with IBD, clearly suggesting that the most important risk factor for IBD is having another family member with the disease. Siblings of affected patients are thus more likely to develop the disease than the background population, with a 13–36 and 7–17 range, respectively, for CD and UC. In addition, such risk is strongly increased in children having both parents diagnosed with the disease. A genetic contribution to IBD is also confirmed by twin studies: monozygotic twins with CD have indeed a much higher disease concordance (37%) than the one found in dizygotic twins (7%). Regarding UC, the concordance rates are respectively 10% for monozygotic twins and 3% for dizygotics, suggesting a weaker genetic predisposition compared to CD [13].

Since the advent of genetic research in IBD about 10 years ago, a number of susceptibility loci (named IBD 1–9) has been identified with varying degrees of replication and statistical power, leading to a clearer understanding of pathogenesis and ultimately better treatment strategies [14–18]. Susceptibility genes contribute, together with environmental factors, to the final phenotype of the disease, suggesting a strong genetic heterogeneity. Whereas some loci seem specific to CD (e.g. IBD1 on 16q) or to UC (e.g. IBD 2 on12q), others seem to confer susceptibility to IBD overall (e.g. IBD 3 on 6p).

Nod2/Card15 (IBD1)

The first gene to be associated with CD was Nod2/Card15 localized on pericentromeric region of chromosome 16 [19, 20]. Three common variants were associated with disease susceptibility: two missense mutations, *Arg720Trp* and *Gl908Arg*, together with to a frameshift mutation, *Leu1007fsincC*. Up to 10–30% of CD patients are heterozygous while approximately 3–15% are homozygous or compound heterozygous for Nod2/Card15 mutations, with the corresponding proportions from the control population repsectively of are 8–15% and 0–1% [16]. In Hugot's [21] initial study, allelic variants of Nod2/Card15 were present in 43% of patients with CD, even if the mutations are neither necessary nor sufficient for the development of the disease. Further studies proved evidence of a clear relationship between Nod2 mutations and some phenotypic associations such as earlier onset, fistulizing and fibrostenosing behavior [22–24].

Nod2/Card15 codes for a protein, an intracellular sensor of a bacterial component, which is expressed in monocytes, macrophages, dendritic cells, epithelial cells and Paneth cells. The protein consists of two N-terminal CARD regions, a central nucleotide-binding domain and a C-terminal leucin-rich-repeat region (LRR). The gene is involved in the recognition of the bacterial peptidoglycan-derived muramyl dipeptide (MDP) through the LRR region leading to the induction of immune response. Current evidence suggests that Nod2 interacts with a serine threonine kinase RICK (or RIP2), inducing the activation of NF-kB, a major transcriptional regulator of pro-inflammatory cytokines, including TNF-α, involved in intestinal inflammation [25]. The 1007fs mutation and to a lesser extent also the two other common CD-associated mutations were associated with an impaired activation of NF-kB in vitro due to a defective MDP binding [20, 26]. Nevertheless, this loss-of-function phenotype did not agree with the increased activation of NF-kB, followed by downstream effects on cytokine production and immunoregulation observed in CD patients [26–28]. Watanabe et al. [29] have attempted to reconcile these opposite results demonstrating that in Card15 defective cells, Toll-like receptor 2 (TLR2) was unable to downregolate NF-κB activation like cells carrying the wt protein actually do. More recent findings involving both human and mouse studies have not yet resolved such discrepancy and data still remain controversial. However, several hypotheses have recently been suggested in order to explain the difference in results between in vitro studies and in vivo observations. One

of these proposed that a loss-of-function phenotype, could involve different aspects of Nod2 activity, due to Nod2 variant forms. Kobayashi and colleagues [30] demonstrated a role of Nod2 in protecting the ileus from invasive bacteria, through the secretion of anti-microbial peptides in the Paneth cells, including alpha-defensins (also called cryptidins), which protect the host from invasion. This microbiological killing activity was impaired in CD patients, above all among those carrying the Nod2 mutation [30, 31]. Interestingly, Maeda et al noted on the other hand, that the introduction of the frameshift mutation into a mouse model leads to a gain-of-function phenotype with an elevated NF-κB activation in response to MDP and more efficient processing and secretion of the cytokine interleukin-1β (IL-1β) [32]. These effects were supposed to be linked to increased susceptibility to bacterial-induced intestinal inflammation and NOD2 was identified by the authors as a positive regulator of NF-κB activation and IL-1β secretion. Interestingly, the overall suggested in order to reconcile the difference among the experimental observations and to provide a plausible mechanistic explanation for the apparent inflammation-promoting functions of the Nod2 variants, could not be mutually confuted and may be valid in combination.

HLA Complex (IBD3)

The IBD3 locus on chromosome 6p encompassing the major histocompatibility complex has been implicated consistently for both CD and UC in a number of association studies [33–36]. In a few Japanese studies, HLA DR2 (DRB1*1502) has been implicated in UC, whereas, HLA DR3 (DRB1•0103) has been implicated in European studies. In CD, HLA associations are less convincing. HLA DR1 has been associated with the CD phenotype. However these results are not definitive and further studies are needed to clarify the role of the MHC complex in IBD.

SLC22A4/SLC22A5 (IBD5)

A recent study has shown an association between two functional mutations in the carnitine/organic cation transported (OCTN) cluster on 5q31 and CD. Differently, the same association was not found for patients with UC [37]. OCTNs help in transporting, distributing and eliminating charged organic cations (e.g. those found in drugs, xenobiotics, endogens metabolite) and thus are important for intracellular homeostasis. In addition, they transport the endogenous amine carnitine, an essential cofactor for lipid metabolism, helping in the beta-oxidation and playing an important role in cellular energy production. Mutations in the transcribed region of SLC22A4, which encodes OCTN1, and the promoter region of SLC22A5, which encodes OCTN2, are most actively expressed in the intestinal epithelium, macrophages and T cells and affect the transcription and function of these transporters. Although an association

with IBD5 could be documented in many population studies, there is still a great deal of uncertainty about the causal variant within the region. In fact, as for IBD5, several other genes, including IRF1 and P4HA2 could be equally to contain the IBD5 causal variant as the OCTN genes [38].

Other Susceptibility Genes

Multiple other IBD loci and alleles have been proposed throughout the human genome. The *Drosophila* discs large homolog (DLG)5 gene, underlying the chromosome 10 and originally identified by Hampe et al. [39], is a member of the membrane-associated guanylate kinase family which produces proteins or scaffolds involved in intracellular signal transduction to maintain epithelial structure. In the recent study of Stoll et al. [40], two haplotypes were associated with IBD by using a positional cloning approach. One haplotype, SNP G113A (characterized by a replacement of arginine to glutamine at amino acid position 30) was overtransmitted to affected offspring with CD and UC whereas the second haplotype, DGL5_e26 (characterized by the presence of an insertion of 13 base pairs in exon 26), was undertransmitted. Like the OCTN1 and OCTN2 variants, the G113A in DLG5 is associated with Card15 mutations in patients with CD.

Despite several replication studies have already confirmed the association between the DLG5 variants and the increased susceptibility to IBD, more work will be needed in the future to determine which one of the linkage peaks for the DLG5 genes is crucial and whether it predisposes to CD and/or UC.

The multidrug resistance gene (ABCB1/MDR1) encodes P glycoprotein-170 (Pgp-170) a membrane transport protein highly expressed in intestinal epithelial cells for which human polymorphisms have been reported (Ala893Ser/Thr and C3435T) able to alter pharmacokinetic profiles for a variety of drugs. Several lines of evidence suggest a role for MDR1 variants in the pathogenesis of UC [41] as well as CD [42].

PPAR belongs to the nuclear receptor family consisting of a group of approximately 50 transcription factors implicated in many different biological processes and highly expressed in the colon. A direct genetic relationship between increased susceptibility to CD and loss of expression of PPARγ variants was suggested in the SAMP1/YitFc mouse model which typically develops a Crohn's-like ileitis. In addition, PPARγ polymorphisms were also associated to human CD [43]. Besides, its expression is decreased in patients with active UC [44].

Immune Response

Immunity can be broadly classified as innate immunity and adaptive immunity and both immunity responses were shown to be strongly involved in the pathogenesis of

IBD. Adaptive immunity is mediated by B and T lymphocytes that proliferate clonally in response to a specific pathogen. Generation of adaptive immunity responses requires a number of days but is anamnestic through the generation of memory T and B lymphocytes. By contrast, the innate immunity is aimed at providing protection in the first minutes after the infection and is characterized by a nonspecific response to pathogens. Consequently, innate resistance is efficient at greatly reducing the pathogen load, although a complete elimination of invading microbial agents is achieved only when adaptive immunity is induced.

Innate immune Response

Antigen-presenting cells (APCs), such as DCs and macrophages, which are likely to play a central role in the innate host response to intestinal flora, are increased in number and activated in both forms of IBD. Professional APCs, together with intestinal epithelial cells (IELs), express PRRs which recognize PAMPs (pathogen-associated molecular patterns). These are mainly conserved bacterial and viral structures, such as lipopolysaccharides (LPS), lipopeptides, peptidoglycan, bacterial DNA, double-stranded RNA, which are shared by many pathogens but are not expressed by the host. Among PRRs, TLRs and NODs are the best known and the most studied. Mammals make use of both as detectors of invading pathogens.

TLRs are a family of 11 transmembrane proteins, all of which have a common extracellular leucine-rich domain and a conserved cytoplasmic domain containing the Toll/IL-1 receptor (TIR) homology domain [45]. Although each type of TLR binds a specific bacterial adjuvant (i.e. TLR4 and C14 bind LPS, TLR2 binds peptidoglycan, TLR5 binds flagellin), these signals all converge on a single pathway mediated by TIR signalling domain, resulting in the activation of the pro-inflammatory transcription factor NF-kB via the adapter proteins MyD88 and TIRAP/MAL. These interactions initiate the formation of a signaling complex involving interleukin-receptor-associated kinases (IRAKs), leading to degradation of IkB, which is the key regulator of NF-kB, as well as to the nuclear translocation of NF-kB. Activation of NF-kB stimulates expression of vast array molecules relevant to the pathogenesis of IBD. These include molecules involved in inflammatory response, such as IL-1β, TNF, IL-6, IL-8 and other cytokines, ICAM1 as well as and other adhesion molecules, and co-stimulatory molecules, (including CD40, CD80, CD86) and the inducible T cell co-stimulator (ICOS). Expression of each of these proinflammatory molecules is increased in active IBD [46].

Induction of tolerance has been reported by some authors to associate with suppression of TLR expression [47, 48]. The reason for this is that both TLR 2 and 4 were shown to be normally present in small amount in IECs in vivo, and consequently to minimise recognition of luminal bacteria in the healthy intestine [49]. Decreased expression of TLR 4 surface protein and absence of required co-receptor sub-units,

MD-2 and CD14, correlate with inhibition or downregulation of downstream immune responses in the tolerance of IECs to LPS [50, 51]. Subcellular compartmentalization (apical or basolateral) of TLRs also appears to be a critical determinant of immune responsiveness [52]. Various molecules have been reported to elude excessive inflammatory response and to maintain mucosal homeostasis by inhibition of TLRs pathways. Large amounts of Tollip, a TLRs signaling inhibitory protein which interferes and suppresses the activity of IRAK protein after TLR 2 and 4 activation, are produced in vitro and in vivo by different IEC lines [51, 53]. PPARγ, constitutively expressed in the epithelial surface layer of colonic cells, is also recently reported to trigger its tolerogenic effect through the of TLRs pathway [54].

The NODs family (also called CATERPILLAR), which comprises at present more than 20 different mammalian NOD-LRR proteins with high structural and functional homology, has rapidly gained scientific relevance by demonstrating that many of its members play an important role in immunity response. Recent research has mainly been focussed on two cytosolic receptors: Nod1/Card4 and Nod2/Card15. NOD1 is constitutively expressed in epithelial cells and its expression can be upregulated by IFN-γ, though not by TNF-α [55]. NOD2 is only expressed within IECs, APCs and Paneth cells and seems to be up-regulated by both cytokines [56]. These intracellular surveillance proteins detect bacterial peptidoglycan, even though they do require distinct motifs to achieve sensing [NOD2 specifically detects MDP, while NOD1 senses γ-D-glutamyl-meso-diamino-pimelic acid (iE-DAP)]. Detection through NOD1 and NOD2 initiates proinflammatory signaling via RIP2 interaction and NF-κB activation, which is necessary for clearance of infecting pathogens from the host. How exactly NODs proteins do become activated by their ligands still remains unclear. The involvement of NOD1 and NOD2 in immune homeostasis was first established when mutations in the genes encoding for these proteins were associated with development of IBD and of other immune diseases [57, 58]. In particular, the three common mutations of NOD2 were associated with an increased risk to develop CD, whereas NOD1 mutations seem to be involved in the development of both CD and UC [59]. In addition, the homozygous/heterozygous carriage of the NOD2 variants has been significantly associated with ileal disease involvement, structuring/stenosing disease behavior and a 2- to 3-year earlier age of disease onset compared to the one found among Nod2 wild-type patients [60, 61].

Adaptive Immune Response

T cells are abundant in all mucosal immune compartments, (including gut-associated lymphoid tissue, the epithelial layer and the lamina propria, LP) and are quite distinct from peripheral T cells both in phenotype and in function. The activated adaptive immune response in IBD is dominated by mucosal CD4+ lymphocytes, and the excessive proliferation of these effector T cells that overcomes a normal regulatory tone can

result in chronic inflammation. There is strong evidence that the cell-mediated arm of the adaptive immune response occurring in IBD may subsequently follow 1 or 2 pathways: an excessive T helper 1 (Th1) response, which is associated with CD, or an excessive T helper 2 (Th2) phenotype, linked to the development of UC. Activation of undifferentiated T cells is precipitated by APCs. T helper cells are mediators of inflammation producing different pattern of cytokines. Overproduction of IL-12, a macrophage-derived cytokine, shifts the immune response in a Th1 direction, charachterized by increased production of INF-γ, TNF-α, IL-1β, IL-2 and IL-6, while a predominant Th2 cell response is associated with increased amounts of IL-5, IL-10 and IL-13 [25, 62].

Recently, Th1 responses has been influenced by the discovery of the Th17 pathway, mediated by IL-17 [63], a cytokine with a strong proinflammatory activity and whose production is stimulated by the production of IL-6, TGF-β and IL-23 by innate immune cells. Increased expression of both IL-17 and IL-23 has been reported in IBD [64, 65].

In addition to the exogenous effects of APCs on T lymphocyte differentiation, it is also speculated that mucosal inflammation may result from a defect in the regulatory T (Tregs) cells activity. Tregs, which are characterized as CD4+ CD25+, are functional subsets of T cells that downregulate adaptive immune responses by interfering with dendritic cells activation and T cells proliferation, contributing, in this way, towards the maintenance of intestinal immune homeostasis to enteric bacterial antigens. Some CD4+Tregs produce IL-10 and/or TGF-β when activated via the antigen-receptor pathway. The latter is indeed documented by several experimental studies showing that IL-10-deficient mice develop colitis, whereas delivery of TGF-β or IL-10 ameliorates their gastrointestinal features [62].

Lymphocytes Trafficking

Tissue infiltration by leukocytes is a common hallmark of several chronic inflammatory diseases including IBD, as well as arthritis, lupus, diabetes.

Human IBD is characterized by leukocyte extravasation, lymphocytes in particular, into the gut, where these cells induce and sustain chronic intestinal inflammation [66]. Lymphocyte homing to both normal tissues and sites of inflammation is partly regulated by differential expression of cell-surface homing receptors, and their bonds with tissue specific vascular addressins which are sites of lymphocyte recruitment from blood.

Endothelial cell adhesion molecules play an essential role in the development of chronic inflammation by recruiting leukocytes, lymphocytes in particular, by promoting leukocyte rolling, firm adhesion and extravasation [67]. In IBD, the expression of endothelial adhesion molecules like ICAM-1(intercellular adhesion molecule-1), VCAM-1(vascular cell adhesion molecule-1) and MAdCAM-1 1 (mucosal addressin

cell adhesion molecule-1) is observed in experimental models of colitis [68–71] as well as within the inflamed human colon in Crohn's disease and ulcerative colitis conditions [72, 73].

Among the adhesion molecules upregulated in IBD, MAdCAM-1, the mucosal cell adhesion molecule is thought to be crucial for the development of chronic inflammation in the gut. MAdCAM-1 is normally expressed in the gut, and its expression is dramatically increased during inflammation [68, 74]. Such a strong functional significance of MAdCAM-1 increased expression in IBD can be supported by several reports demonstrating that immunoneutralization of either MAdCAM-1 or OF $\alpha_4\beta_7$ integrin, its lymphocyte ligand, do decrease inflammation and mucosal damage in various animal models of colitis [75, 76].

MAdCAM-1 expression can be influenced by several cytokines including TNF-α and IL-lβ. the precise signal transduction pathways involved with MAdCAM-1 are, however, still not well understood. Despite the current lack of knowledge in this regard, being MAdCAM-1 induced by Th1 cytokines, it is likely that its induction is mechanistically similar to that of other adhesion molecules like ICAM-1 and VCAM-1. These adhesion molecules are also induced by Th1 cytokines and require activation of the NF-kB/PARP. The activation of these transcription factors also leads to intracellular oxidants formation since mobilization of these adhesion molecules in response to cytokines can be prevented by antioxidants like PDTC or NAC. Physiologically, the expression of these cell adhesion molecules also appears to be limited by the formation of NO through either constituitive or inducible forms of nitric oxide synthase (eNOS, iNOS) itself.

Endothelial cells in the small intestine selectively express also CCL25 (formerly known as thymus-expressed chemokine, TECK), an adhesion molecule that mediates the homeostatic recruitment of CCR9-expressing T cells [77]. The crucial role played by this molecule during the early stages of chronic ileitis has been recently demonstrated in mouse models [78].

Recent discoveries have provided new insights into cellular trafficking in the gut with new molecular targets for blocking inflammation in IBD patients. This is strongly supported by the use of monoclonal antibodies directed against several integrins which seems to be effective in the treatment of both CD and UC [79, 80].

Environment

Environmental factors are thought to play an important role in the development of IBD, of its course and prognosis, as confirmed by the higher incidence of the disease in industrialized countries [1]. Despite the extensive epidemiological research effort in the last few years, the identification of specific environmental factors and the causal association between some of them and the disease still remains a challenge. However, some of the most relevant environmental factors potentially related to IBD are discussed.

Demographic Factors and Lifestyle

Most of the studies, aimed at investigating the prevalence of IBD in the developed countries, USA and western and central Europe [81] included, suggest an association of environmental factors with a western lifestyle and an overall improved socioeconomic status. This may also account for the north-to-south variation and the higher frequency found in the urban communities when compared to rural areas. Interestingly, an increased incidence has been recently reported also in Asia [82], maybe as a result of a 'westernization' of lifestyle in terms of diet, smoke, pollution, etc. [81]. It is noteworthy that an inverse relationship between sanitation and IBD is commonly reported: poor sanitation seems to be a protective factor, suggesting that improved life-style hygienic conditions, may lead to an alteration of the intestinal flora by the decrease in exposure to critical bacteria.

Childhood Factors

It has been postulated that some events during early childhood can influence the development of IBD. A recent meta-analysis shows a protective effect of breastfeeding on the risk of the of both CD and UC, even if most studies included suffered from potential recall bias and the results cannot be considered conclusive [83]. The role of measles infection or vaccination with mycobacterium on IBD remains controversial [81], similar to the role of appendectomy which seems to be protective for UC [84] while a risk factor for CD [81].

Diet

Although it is reasonable to look at an unhealthy diet as a potential risk factor for IBD due that dietary antigens are the second most common in the GI tract after bacterial antigens, studies conducted until now revealed to be inconclusive. An association between increased sugar intake and CD [85] has been postulated, and there is currently evidence that an elevated uptake of fatty acids increases the risk for IBD [86].

Cigarette Smoking

The strongest environmental factor influencing IBD is tobacco smoking with striking opposite effects on CD and UC [87]. It has been demonstrated that current smoking is protective against UC and that, paradoxically, former smokers are more likely to develop UC than people who never smoked in their life [88]. Differently, cigarette

smoking represents a risk factor for the development of CD. Smokers with CD have higher disease recurrence and undergo more frequently to surgery [86, 89]. However, the association between smoking and CD may not be applied to all ethnic groups, in fact for Jewish patients living in Israel smoking is not associated with an increased risk to develop CD [90].

Intestinal Microbiota

Mammals, particularly humans, have a dynamic relationship with environmental bacteria. Bacterial density in the intestinal lumen is particularly well controlled, showing a strong gradient from the stomach to the colon where up to 10^{11} organisms per gram of stool are present, belonging to 500–1,000 different – mostly anaerobic – species [91]. Colonization of the gut by commensal bacteria has a positive effect on the mammalian host by exerting protective functions against potentially intrusive pathogens through nutrient and receptor competition and through production of antimicrobial factors such as colicins [92]. The gut flora also affects structural functions, such as strengthening the monolayer of epithelial cells exposed to various injuries and exerts metabolic functions by synthesizing vitamins and providing short chain fatty acids as carbon source for colonic epithelial cells, and by metabolizing dietary carcinogens [91]. The bacterial flora of the gut also affects gut development and maturation of the mucosal and systemic immune systems: germ-free mice show reduced steady-state activity of both the mucosal immune system, with smaller Peyer's patches and lower numbers of intraepithelial lymphocytes, and of the systemic immune system, with lower amount of cytokines and serum antibodies, particularly IgA [93]. Commensal bacteria also modulate the fine-tuning of T cell repertoires and regulate the differentiation of gut-resident T cells (that can generate T helper 1 [Th1], Th2, Th17, and/or regulatory T [Treg] cell phenotypes). This may in turn act as a feedback mechanism to influence the diversity and density of gut flora [94].

Enteric microflora can stimulate immune responses either by functioning as adjuvants or antigens. As adjuvants they activate innate immune responses, including dendritic cells and other APCs, while as antigens they stimulate the clonal expansion of T cells that selectively recognize the antigen through their T cell receptors [4]. Interestingly, various bacterial adjuvants, e.g. lipopolysaccharide, peptidoglycan, flagellin and nonmethylated DNA (CpG motif), may bind selectively to different TLRs on innate immune cells, epithelial cells and mesenchymal cells. These bindings result in activation of NFκB and the mitogen-activated protein kinases that trigger the transcription of a host of proinflammatory and regulatory genes [95, 96]. It has been shown that activation of NFκB by APCs following binding with microbial adjuvants induces the expression of MHC class II antigens, co-stimulatory molecules, IL-12 and IL-23, which can activate Th1 and Th17 cells, respectively, in presence of the appropriate antigens [4].

Aggressive T cell responses to luminal commensal bacteria have been reported in hosts' genetically susceptible, such as IBD patients and animal models among which genetically engineered rodents and mice with spontaneous mutations (C3H/HeJBir and SAMP/YitFc) [97]. An increasing number of experimental and clinical studies implicate bacteria colonizing the gastrointestinal tract in the pathogenesis of IBD [97]. Disease may occur due to a loss of tolerance to resident intestinal bacteria in susceptible individuals, but to date there is no compelling evidence of an etiological role for any singular pathogenic microorganism [98]. Both bacterial species and host specificity have been demonstrated for the induction of experimental colitis. In particular, there is experimental evidence that different bacterial species can cause different disease phenotypes in a single host and that different bacterial species provide the dominant stimuli for disease; interestingly, it has also been shown that different probiotic species can provide selective treatment in hosts with different genetic backgrounds [99].

Many studies have shown that bacterial flora differ between patients with IBD and healthy people. Patients with IBD have higher amounts of bacteria attached to their intestinal epithelial surface, even in the non-inflamed mucosa, than healthy controls [100]. Swidsinski et al. [101] have shown that bacteria are from diverse genera and some of them, especially *Bacteroides* spp, were identified in the epithelial layer, in some instances intracellularly. Indeed, the role of *Bacteroides* spp in IBD is still unclear: these anaerobic bacteria have been shown to exhibit proinflammatory properties in several IBD animal models, but a protective role and even a decrease in the relative proportion of the phylogenetic group have been postulated in other studies [102, 103]. Moreover, distinct adherent or invasive strains of *Escherichia coli* have been identified in the ileal mucosa of patients with CD and the involvement of a new potentially pathogenic group of adherent invasive *E. coli* has been suggested [104]. These *E. coli* adhere to epithelial cells via type 1 pilli, invade macrophages by active monofilament-dependent and microtubule-dependent mechanisms and are able to replicate within phagocytes [105]. It is of interest that upon infection with some strain of *E. coli* monocytes of patients with CARD15 polymorphisms show reduced TNF and IL-10 production as compared to normal controls [104]. These findings are consistent with immunohistochemical evidence of increased *E. coli* mucosal adherence, invasion of ulcers and fistulae, and their presence within lamina propria macrophages of CD patients and with the view that a defective clearance of intracellular infections exists in patients with CARD15 polymorphisms [106]. A recent study has shown a higher number of mucosa-associated aerobic and facultative-anaerobic bacteria in biopsy specimens of children with newly diagnosed IBD than in controls. An overall decrease in some bacterial species or groups belonging to the normal anaerobic intestinal flora was also suggested by molecular approaches; in particular, occurrence of *Bacteroides vulgatus* was low in CD, UC and indeterminate colitis specimens [107]. Recently, a breakdown in the balance between putative species of 'protective' versus 'harmful' intestinal bacteria,

a concept referred to as 'dysbiosis', has been postulated: this could lead to a pro-inflammatory luminal milieu that drives chronic intestinal inflammation in a susceptible hosts [108]. Studies have implicated organisms such as *E. coli, Bacteroides*, *Enterococcus* and *Klebsiella* species in the pathogenesis of human and experimental intestinal inflammation, whereas various *Lactobacillus* and *Bifidobacterium* species have predominantly protective effects and have been used therapeutically as probiotics, although the latter have produced contradictory results in the maintenance therapy of IBD [109, 110].

In conclusion, there is now good evidence that bacteria or bacterial components play a role both in triggering and aggravating IBD in humans as well as in animals. It is also agreed that some microbial factors could have different effects at different steps of the IBD process (onset or maintenance of chronic inflammation). Identifying the changes in the microbiota in the various mucosal or luminal ecological niches of the patients could be of clinical usefulness since this can contribute at discovering new antibiotic or ecological treatments. Moreover, genetic manipulating of probiotics in order to deliver bioactive compounds at target intestinal sites offers strategies for innovative treatments.

Conclusions

Recent advances in the research on mechanisms of IBD and the resulting therapeutic modalities have been tremendous, especially if compared with the advances made in all previous years of modern IBD investigation. The IBD originates from a strong interaction among genetic, immunologic, microbial and environmental variables. The most commonly held view is that IBD comes from an immunological hyperresponsiveness to unknown components of the bacterial flora harboring the intestinal lumen, primarily because of a genetic failure to downregulate such a response. Evidence has been accumulated to suggest that chronic intestinal inflammation develops through different mechanisms which indicate that CD and UC are heterogeneous disorders having similar downstream inflammatory pathways. This heterogeneity involves genetic, phenotypic, immunologic and bacteriologic aspects; furthermore, it involves therapeutic options and explains the lack of universal therapeutic response to any single drug. It is anticipated that in the future, the scientific discoveries in IBD mechanisms will be translated back into clinical practice, where treatments tailored for specific subtypes will likely occur.

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Epidemiology in Pediatric Inflammatory Bowel Disease

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Abstract

The peak incidence of inflammatory bowel disease (IBD) composed of Crohn's disease (CD) and ulcerative colitis (UC) occurs in patients between the ages of 15 and 25 years; however, both diseases may manifest from infancy. Patients with disease onset during childhood or adolescence account for approximately 7.2–20% of total cases. The wide range is, at least in part, explained by the different cut off age for the definition of childhood IBD in the different studies (from 14 until 20 years of age). Among childhood IBD, early onset IBD (below 8 years of age) appears to be different epidemiologically and is characterized by predominance of colonic involvement and high positive family history. In contrast to the findings in adult onset CD, pediatric CD is more common in males. Several pediatric epidemiology studies in IBD showed a rising incidence over the recent years for CD, with no change or even a decrease for UC. This increase is particularly evident in countries with a formerly low rate like previous socialistic countries in Eastern Europe, and Asian and Arabian countries. A north-south gradient in IBD incidence has been found in Europe and the United States. Previously noted racial and ethnic differences seem to be narrowing. A cleaner environment, lack of infections and exposure to certain microbes and an urban place of living have been identified as risk factors for childhood onset IBD. The temporal changes in the incidence in different geographic regions may help in identifying more environmental risk factors and to develop strategies for risk reduction in high risk population.

Over the last decades many epidemiological studies on inflammatory bowel disease (IBD) have been performed, both in adults and children [1–3]. Differences in incidence across age, time, and geographic region suggest that environmental factors significantly modify the expression of Crohn's disease (CD) and ulcerative colitis (UC). Most information pertaining to the epidemiology of IBD is based upon adult studies.

The incidence of pediatric IBD cases is defined as the number of new cases (CD, UC and indeterminate colitis) per year per 100,000 inhabitants of the same age range at a given geographical area. Prerequisites for the calculation of incidence data are [4]:

1 information about the background population under investigation (e.g. number of children and adolescents <16 years of age living in a defined area);
2 a health care system that provides complete information on all children of the defined age group with the diagnosis of IBD, and
3 well-defined criteria for the diagnosis of IBD, preferentially follow-up data for confirmation of the diagnoses, because in quite a proportion of pediatric patients, the diagnosis may change (from IC to UC or CD, from UC to CD, etc.) [5, 6].

Very few of the published studies on epidemiology of pediatric-onset IBD fulfill these criteria. In addition, some of the data are gathered retrospectively, some prospectively. Some investigators did rely on one source of information, for example hospital charts, some used two or more sources (regular questionnaires of physician plus pathological reports) [7].

To address the problem of a well-defined diagnosis, the IBD working group of European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recently published 'The Porto Criteria' which details consensus based diagnostic criteria for childhood IBD [8]. Intensive work up is required including ileocolonoscopy in all children with IBD. In all cases with CD and indeterminate colitis (IC), in addition, upper endoscopy with serial biopsies and a visualization of the small bowel by radiography (barium follow through or enteroclysis) or MRT is mandatory. This should result in better documentation of the final diagnosis (CD, UC or IC) and completeness of all IBD cases. However, long term follow up data of children which are diagnosed by this intensive work up will bring the evidence how certain the diagnosis is based on these criteria.

Incidence and Prevalence of Pediatric Inflammatory Bowel Disease

The peak incidence of IBD occurs in patients between the ages of 15 and 25 years. Most children with IBD are diagnosed in late childhood and adolescence. However, both CD and UC have been reported as early as in infancy [9, 10]. In the young age group, indeterminate colitis is more common [11]. The incidence in children reported in the different studies and countries are reported in table 1. However, it is emphasized that the methodology is very different as is the cut-off for age. Some studies aimed to identify all IBD cases in a certain region, other relied on the reporting of all pediatric hospitals, which may underestimate the incidence. Therefore, incidence rates may not be comparable between countries. Kappelman et al. [12] evaluated the prevalence of IBD in the US using health insurance data.The prevalence of CD and UC in children younger than 20 years was 43 (95% confidence interval [CI], 40–45) and 28 (95% CI, 26–30) per 100,000, respectively. In adults, the prevalence of CD and UC was 201 (95% CI, 197–204) and 238 (95% CI, 234–241), respectively. In most pediatric studies, there are more CD patients than UC, is some cohort the relation is almost 2:1.

Table 1. Incidence rates of CD and UC in different European and North-American populations

Geographic area	Age years	Time period	CD	UC	IBD total, including IC	Setting R=retrospective P=prospective	
Scotland [50]	<17	1968–1983 1983–1998	0.7 2.3	1.9 1.6		hospital admissions data	R
Scotland [15]	<16	1981–1995 1995–1997	2.3	1.2		population	P
Wales [53]	<16	1996–2003	3.6	1.5	5.4	population	P
UK [54]	<16	1998–1999	3.0	1.4		population	
Northern France [2]	<17	1988–1999	2.3	0.8	3.1	population	P
Norway [55] Norway [56]	<16	1990–1993 1993–1998 1999–2004	2.7 1.95 3.64	2.0 3.67 2.04	4.7 5.6 5.7	population	P R P
Sweden [18]	<16	1984–1986 1993–1995	1.2 1.3	1.4 3.2	4.6 7.0	population	P
Stockholm [19]	<16	1990–2001	4.9	2.2		population	P
Copenhagen [57]	<15	1961–1987	0.2	2.0	2.2	population	R
Netherland [7]	<17	1999–2001	2.1	1.6	5.2	population	P
Czech Republic [21]	<15	1990–2001 1990–2001	0.25 1.25			hospitals	R ≤1999 P >1999
Finland [17]	<18	1987–2003 1998–2003	1.7 2.6	2.2 3.2	3.9 7.0	hospitals	R
Canada [28]	<17	1991–1996	3.7	2.7		hospital	P
Wisconsin USA [20]	<18	2000–2001	4.6	2.4		population	P

The incidence and prevalence of IBD varies by geographic location and over time. The global distribution of CD and UC are similar. Both occur more commonly in North America, the United Kingdom, and Scandinavia than in southern Europe, Asia, and Africa [3, 13]. There seems to be a north-to-south gradient with higher incidence rates of both CD and UC in northern locations, even within individual countries, for adults and children [12, 14]. The Scottish registry identified during a 15-year period (1981–1995) 580 Scottish children (<16 years of age at symptom onset) with newly diagnosed IBD. The incidence of juvenile-onset CD was significantly higher in northern (3.1, 95% CI: 2.6–3.8) than in southern Scotland (2.1, 95% CI: 1.9–2.4, $p < 0.001$). The incidence of juvenile-onset UC did not show north/south variation ($p = 0.677$) [15].

Time Trends

When an increasing incidence was noted in children living in industrialized countries, it was first unclear whether this is due to widespread use of upper and lower endoscopy in the diagnostic work up of children regardless of the age of the child rather then a real increase in incidence. However, it is now generally accepted that incidence particularly of CD is increasing, in both, adults and children, while no change or even a decreasing incidence is observed for UC.

The rising incidence of CD has been noticed in Western European countries like Scotland [16], Finland [17], Sweden [18, 19] and the US [20], but particularly in countries of the former Eastern bloc in Europe like Czech Republic [21, 22], Hungary [23] or former German Democratic Republic, but also in Asia and Arabian countries [24–27]. Hildebrand et al., reported from Stockholm, Sweden, that the incidence per 100,000 increased from 2.4 between 1990 and 1992 to 5.4 between 1996 and 1998 [19] (table 1). In contrast, the incidence of ulcerative and indeterminate colitis marginally decreased between 1990 to 1992 and 1996 to 1998 (3.9 and 3.0 per 100,000, respectively).

Sex Distribution

Most pediatric studies found that the relative risk of developing CD is significantly higher in boys than in girls (RR ~1.5) [2, 6, 15, 20, 28–30]. There is no sex difference regarding pediatric onset UC.

Ethnic Predisposition

Initial studies suggested a lower rate of IBD in non-Caucasian populations in the US. Although the incidence of IBD among African-American in developing countries such as Africa is low, data from urban areas of the US suggest that rates are similar in African-American and Caucasian populations [13], while Mexican Americans had more UC and less CD compared to Caucasian and African-American living in Texas [31]. A pediatric study from British Columbia, Canada, noticed a higher incidence for South Asian population (15.2 IBD patients/100,000) compared with non-South Asian children (5.2/100,000) [32]. The ratio of UC to CD was higher in Asians, and more boys were affected. Most cases occurred in the second generation of immigrants.

Both CD and UC occur more commonly among Jewish than non-Jewish peoples. Jewish people living in the US have higher rates than Jewish people with the same genetic background living in Israel. The rates of IBD in Israel vary by the place of birth. The prevalence rates for CD among immigrants from Europe in the US are higher than in patients of Jewish descent from Asia and Africa [33]. Although the

prevalence of IBD tends to be higher overall, disease rates in people of Jewish origin vary by geographic region and parallel those of the general population. The higher rates of IBD in those with Jewish origins across different countries support a genetic predisposition; yet, the geographic variation of IBD rates also suggest potential environmental factors that may influence such as an inherited predisposition.

Pediatric Early-Onset Inflammatory Bowel Disease

Several groups looked at age-related variations in the distribution of IBD phenotype, sex distribution and genetic background. Heyman et al. [6] analyzed the data of 1,370 children from 6 large centers in different geographic areas of the USA. Both, incident and prevalent cases were included. The diagnosis was confirmed in 87 (6.1%) under 3 years of age, 211 (15.4%) before 6 years, 654 (47.7%) at 6 to 12 years, and 505 (36.9%) at 13 to 17 years. More than 63% of children younger than 8 years of age had isolated colonic disease, in contrast to only 35% of those 8 years of age or older ($p < 0.0001$). Among children younger than eight years, indeterminate colitis and UC were more frequent than CD (adjusted risk ratio 3.7 [95% CI 1.6–5.2] and 2.4 [95% CI 1.8–3.2]), respectively. The proportion of cases of indeterminate colitis decreased with increasing age, from 33% in those diagnosed before 3 years of age to 9% among 13- to 17-year-olds, suggesting that indeterminate colitis may represent an evolving form of IBD that presents before definitive phenotype, or that current classification criteria to differentiate UC from CD may not be applicable to young children. Paul et al. [10] confirmed that isolated colonic disease was most frequent in early-onset CD below 5 years of life (colonic 76.5%, ileocolic 24%) compared with ileocolic disease (ileocolic 45.5%, colonic 26%, ileal 19.4%, proximal 6.3%) in the older age group. Very early onset IBD seems to reflect a subgroup of patients characterized with severe colonic involvement. Within a 6-year period, 10 infants with IBD were identified in a single center in Paris [9]. All infants presented with rectal bleeding. Four patients had definitive diagnosis of CD; ulcerative or indeterminate colitis was diagnosed in 2 and 4 children, respectively. Seven patients had a severe onset of disease requiring bowel rest, parenteral nutrition and steroid medication, followed by azathioprine or cyclosporine medication. Surgery was necessary in 3 of 10 patients. Disease relapses were frequent and observed in 8 of 10 children. Although no immunodeficiency could be identified, an underlying defect cannot be excluded.

Environmental Risk Factors for Childhood Onset Inflammatory Bowel Disease

The lack of total concordance of disease among monozygotic twins, differences in rates of IBD among migrant populations and the rising incidence support a role for environmental factors in the development of IBD.

Seasonality of Date of Birth and Childhood onset IBD

Several studies looked at the months of birth and risk for IBD. In a study in Slovak children, the number of births was markedly higher than expected between June and October and lower between December and March. This is similar to patterns found in children with type 1 diabetes mellitus [34]. In UC, there was a slight increase between June and August and a decrease between December and February. In a Belgian cohort of >1,025 mostly adults with IBD, a significant reduced risk to develop CD was observed for people born in June, while the incidence peaked in persons born in April and August [35]. In contrast, no seasonality was found in British children with CD and UC [36].

Smoking

A recent meta-analysis confirmed that smoking is an important environmental factor in IBD with differing effects in UC and CD [37]. Current smoking increased the risk for CD (OR 1.76; 95% CI 1.40–2.22) and former smoking for UC (OR 1.79; 95% CI 1.37–2.34), while current smoking had a protective effect on the development of UC when compared with controls (OR 0.58; 95% CI 0.45–0.75). In a Swedish-Danish twin cohort smoking was inversely associated with UC (OR 0.4; 95% CI 0.2–0.9) and associated with CD (OR 2.9; 95% CI 1.2–7.1) [38]. More recently, Mahid et al. [37], suggested from a survey in Kentucky in childhood IBD that not only active smoking during adolescence, but even passive smoke exposure in early childhood influences the development of IBD. CD and UC patients were more likely than controls to begin smoking regularly by ages 10 and 15, respectively, suggesting that becoming a regular smoker at a younger age may be associated with a subsequent diagnosis of IBD. CD patients were more likely than controls to have prenatal smoke exposure (OR 1.72; 95% CI 1.1–2.71) and were more likely to have passive smoke exposure during childhood, with 1 or both parents or other household members being smokers (OR 2.04; 95% CI 1.28–3.31). In contrast, data from the population-based national register in Sweden which linked the Swedish Medical Birth Register and the Swedish Hospital Discharge Register during the period 1987–2000 identified 455 singleton infants who later developed IBD [39]. Data for these children were compared with data for all children born in Sweden during the same period. The authors found that smoking during early pregnancy reduced the risk of IBD (OR 0.71, 95% CI 0.55–0.91). For UC the odds ratio was 0.70 (95% CI 0.56–0.86), and for CD 0.73 (95% CI 0.58–0.94).

Perinatal and Early Exposures to Nutrients in the First Year of Life

The influence on the type of feeding (breastfeeding or formula feeding) on the development later in life is controversial. Breastfeeding stimulates the development and

maturation of the gastrointestinal mucosa of infants and reduces the risk for gastrointestinal infections in infancy. Several case control studies suggest that IBD patients were less likely to have been breastfed infants. Most studies used population based controls [40]. When nonaffected siblings were used as controls to account for the genetic background, children with CD were more than three times less likely to have been breastfed than their unaffected siblings [41]. No association with breastfeeding practices and the risk of developing UC in childhood was found with the same study design [42]. A recent meta-analysis of 17 published studies support that breastfeeding reduces the risk for both CD (0.67, 95% CI 0.52, 0.86) and UC (0.77, 95% CI 0.61, 0.96). The effect was even stronger, when only high quality studies were considered [40]. The recently published population based study on risk factors on childhood IBD from Northern France did not confirm the protective effect of breastfeeding [43]. In fact, children with CD had been breastfed on average of 2 weeks longer than the non-CD controls. Like in all case control studies, the choice of the controls may be crucial. It may also be possible that the certain risk or protective factors may act differently on the cohorts under investigation [44].

The 'hygiene hypothesis' suggests that a lack of exposure to enteric pathogens early in childhood due to cleaner environments may increase susceptibility to chronic intestinal inflammation later in life. In a study from Scotland, the relative risk of developing IBD for children living in areas with a high deprivation score compared to the most affluent areas was significantly lower for IBD in total ($p = 0.016$) and CD ($p = 0.033$), with no significant differences for UC ($p = 0.17$) [15]. The decrease in childhood infection may be causative for the rising prevalence of T helper type 1 (Th-1) and T helper type 2 (Th-2)-mediated autoimmune/inflammatory and allergic diseases. Both, allergic disease (asthma, allergic rhinitis, and atopic eczema) and IBD, particularly CD, occur more commonly in the same patient than expected by chance [43, 45, 46]. This could be due to genetic factors predisposing to both inflammatory diseases or due to the same environmental factors. A common genetic link could be a polymorphism in the NOD2/CARD15 gene, which is involved in microbial sensing and barrier function and may play a role in both, IBD and allergic diseases [47, 48]. For allergic disease, the contact to farm animals in the first year of life was found to be highly protective for later allergic rhinitis and asthma [49]. Radon et al. [46] conducted a multi-center study at 13 pediatric referral centers across Germany and identified cases of IBD between 6 and 18 years old. Controls consisted of inpatients undergoing strabismus surgery at a nearby ophthalmologic referral center. Two controls were selected for each case, matched for birth year, resulting in a cohort of 1,133 cases and 2,483 controls. After controlling for other confounders, the odds of developing CD and UC after regular contact with any farm animal during the first year of life were reduced significantly (adjusted odds ratio (AOR) for CD 0.5, 95% CI 0.3–0.9; AOR for UC 0.4, 95% CI 0.2–0.8). In a separate model analyzing regular contact with different types of animals (cats, dogs, pigs, cattle, and sheep or goats), the odds of CD or UC were decreased by contact with cattle (CD OR 0.4, 95% CI 0.2–0.9; UC

OR 0.3, 95% CI 0.1–0.9). Living in an urban area increased the odds by 50% (AOR 1.5 for both; CD 95% CI 1.1–2.0; UC 95% CI 1.1–2.1). Living with at least two older siblings reduced the odds of developing CD by 40% (AOR 0.6, 95% CI 0.4–0.8). A recent Canadian study from Manitoba also described an association with pets and consumption of unpasteurized milk early in life with a decreased risk of CD [50], while another Canadian investigation in pediatric IBD from Quebec, Canada refuted it [51]. However, Amre et al. [51] studied an urban population from Montreal, the Manitoba population in the Bernstein study was 60% urban, while the German population by Radon et al. [46] was less than 20% urban. Further research focussing on gene-environment interactions in industrialized countries, investigations in countries in epidemiologic transition where the prevalence of IBD is currently on the rise are needed. This may assist to derive strategies that may more effectively prevent, diagnose, and treat these diseases not only in European and North American populations but also in emerging nations.

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Genetics of Inflammatory Bowel Disease

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Abstract

B. B. Crohn himself noted an increased incidence of regional ileitis in family members and since then twin studies and large-scale population studies have confirmed an increased sibling risk for both Crohn's disease (CD) and ulcerative colitis (UC). Unlike single gene disorders, CD and UC are thought to result from a complex interplay of multiple genes and environmental factors. The confirmation of CARD15 as a CD susceptibility gene in the late 1990s caused much excitement in the field of complex diseases in general and since then the rapid rate of progress in molecular genetics, with the advent of large-scale affordable genotyping techniques, has resulted in large collaborations and the identification of over 30 inflammatory bowel disease-associated genes. These discoveries have given insight into the underlying pathophysiology of disease and with that have the potential to inspire novel and specific treatments for these diseases. The background to these discoveries and their implications form the basis of this chapter.

The precise aetiology of either Crohn's disease (CD) or ulcerative colitis (UC) is unknown, but it is generally considered that both diseases result from an aberrant intestinal immune response to bacterial microflora in a genetically susceptible individual. They are often collectively referred to as inflammatory bowel disease (IBD). Twenty-five percent of IBD presents in childhood and childhood incidence may have increased over the last 30–40 years [1]. This chapter will discuss, first, the epidemiological evidence for a genetic basis of IBD and the broad linkage studies which have uncovered what are known as the IBD susceptibility loci. Then it will discuss the evidence for the various disease susceptibility genes within these loci, their association with disease overall and the clinical manifestation of the disease (phenotype), emphasising studies in children. Finally, the relevance of pharmacogenetics in IBD, the role of genetic counselling and future prospects will be discussed.

Genetic Epidemiology

Epidemiological research provides evidence for the existence of genetic determinants of IBD susceptibility. It has long been observed that cases of IBD cluster within families. Population studies have shown that 10–29% of patients with IBD have a positive family history [2, 3]. Data from the paediatric IBD consortium show that in their cohort of 1,370 paediatric IBD cases, overall 39% had a family history of IBD [4]. In CD the average monozygotic twin concordance rate reported is up to 50% and 5% in dizygotic twins [5, 6]. The rate is lower in UC with 18% concordance in monozygotic twins and 4% in dizygotic twins [7–9]. The higher concordance rate in monozygotic vs. dizygotic twins highlights the role of genetics; on the contrary the disease concordance is significantly lower than 100% highlighting a major role for environmental and developmental factors. The relative risk to a sibling (λS) of a patient with CD has been estimated at between 13 and 35 and for UC 7–17 [10]. This highlights the evidence for a stronger genetic contribution to CD than UC. Equivalent figures in type 1 diabetes, schizophrenia and cystic fibrosis are 15, 8.6 and 400, respectively.

Of multiply affected families with IBD 75% are concordant for disease type, with the 25% being 'mixed' (having one member with UC and one with CD) [11–13]. These data support the existence of some genetic variants that are specific for CD or UC and others that are common for both diseases, the phenotypic expression being influenced by environmental factors. Genetic variants also impact on disease location particularly in CD where the percentage of familial cases is lower in CD confined to the colon than in ileal disease [14]. Familial cases have an average age of onset about 5 years younger than sporadic cases (22–23 vs. 27–28 years) suggesting the presence of an 'early onset gene' [15–17]. Genetic anticipation may be another explanation whereby a decrease in the age of onset and an increase in severity of disease is seen in subsequent generations as in the case with Huntington's disease. In CD familial series an earlier age of onset is consistently seen in affected children than affected parents [18]. However, these findings are open to bias as an increased awareness of diagnosis may lead to diagnosis at an earlier age.

Linkage Studies

Two main types of genetic studies have been used in IBD research, namely genetic linkage and association studies. Linkage studies type a large cohort of affected relative pairs (e.g. affected sibling pairs) with microsatellite markers spaced throughout the genome. If a particular genetic marker is identified in which more that 50% allelic sharing is observed within the pair, this would imply that a disease associated gene resides in this general area. Once linkage is identified by these genome wide searches, genetic association studies can be used to identify the specific underlying gene.

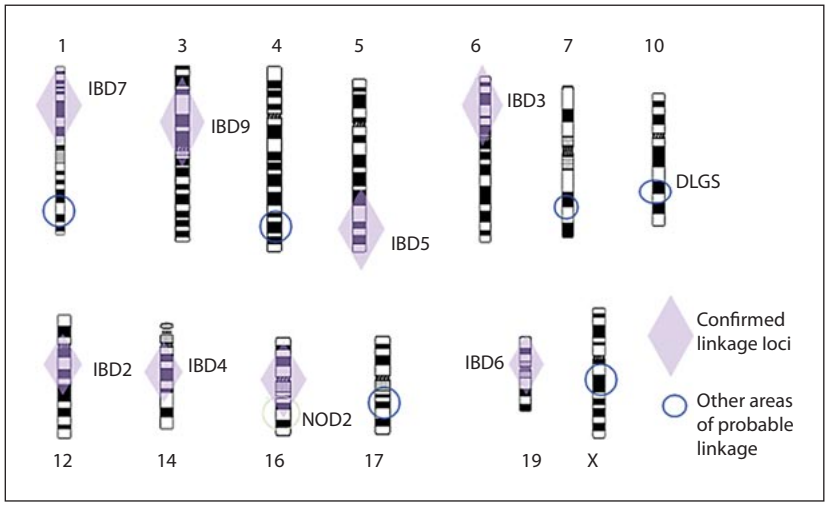

Fig. 1. IBD linkage loci.

Potential candidate genes are identified and, in general, differences in allelic frequencies are sought in cases compared to controls. Family-based cohorts can also be used in a similar way comparing unaffected parents to affected siblings using transmission disequilibrium testing (TdT), the advantage being that a family association avoids many potentially confounding factors that can occur in case control studies.

Figure 1 highlights the chromosomal regions implicated in IBD from genome-wide linkage studies. A meta-analysis of 10 genome-wide linkage studies showed evidence of linkage to chromosome 2q, 3q, 5q, 7q and 16 (NOD2/CARD15 region) for IBD overall; Chr 2q, 3q ,6p,16, 17q and 19p for CD; and 2q for UC [19]. Looking specifically at patients with early onset of disease some studies have found a stronger linkage to markers on Chr 1, 3, 16, and 12 in families with at least one member less than 20 years old at diagnosis [20, 21]. This may suggest that, similar to other polygenic diseases, the genetic contribution is greater in familial cases.

Until recently, linkage data have not been used to look at phenotypic association due to lack of power. However, the NIDDK/ IBD genetics consortium recently gathered phenotypic data from four previously genotyped genome scans to assess phenotypic subsets that contribute to the major IBD susceptibility loci. The cohort consisted of 904 affected individuals, making this the largest phenotyped cohort collected and thereby having adequate power for meaningful subset analyses. They found the following: IBD1(CARD15) increases the risk of small intestine CD; IBD2 increases risk of colonic CD; IBD2 has a strong link to extensive UC, which is a novel finding, and IBD3 and Chr 3q linkage regions contribute to both small intestinal and colonic CD [22].

CARD 15/NOD2

The proof that this principle for gene identification can be successful was shown by the identification of the CARD 15 gene (formerly known as NOD2) in the IBD1 locus on Chr 16 as a disease susceptibility gene. This has been a major breakthrough for IBD research specifically and polygenic diseases in general. Hugot et al. [23] fine mapped the IBD1 linkage locus and identified CARD15 as the underlying gene in 2001. At the same time two separate investigators using a candidate gene approach also identified CARD15 [24, 25]. Thirty non-conservative polymorphisms have been identified within this gene but three SNPs (G908R, 1007fsCins, R702W) account for approximately 82% of the mutated alleles [26]. Replication studies have confirmed that these three SNPs are independently associated with disease [27–29]. A gene dosing affect is seen in most studies with carriage of one copy of the risk allele increasing the risk of developing CD 2- to 4-fold and carriage of two copies of risk alleles increases the risk of disease 20- to 40-fold in adults. Studies from France, Germany, UK and USA have shown that up to 40% of patients with CD (vs. 14% of controls) will have one or more of these mutations [26, 27]. However, allelic frequency is much lower in other countries, e.g. Ireland, Scotland, Scandinavia and Iceland (8–15%) and NOD2 mutations are not found in patients with CD in Japan, Korea or China [30–32]. A population attributable risk for CD of 26% in non-Jewish Caucasians has been calculated from meta-analysis of the three CARD15 mutations in 29 studies [33]. Jewish patients, who tend to have the highest frequency of mutations, have an even greater population attributable risk [34]. The prevalence of the different types of NOD2 mutation also varies; the most prevalent NOD2 mutation in non-Jewish Caucasian CD patients is the R702W mutation whereas the G908R mutation is the most prevalent in the Ashkenazi Jewish CD patients (18% in children and 11% in adults) [35].

In comparison with adult CD populations, there is much less information available on CARD15 in exclusively paediatric populations. Table 1 summarises the studies to date. The largest is a Scottish study by Russell et al. [36] who have a well-phenotyped homogenous cohort. They found the population attributable risk for the three CARD15 mutations was 7.9%. This is substantially lower compared to the studies in adults included in a recent meta-analysis of 42 trials (12.7–21.8%) [37]. Russell's group went on to look at patients at diagnosis and follow-up and found that CARD15 variants were associated with decreased albumin and raised CRP at diagnosis ($p = 0.001$ and 0.04 respectively). At follow-up, the CARD15 variants were associated with need for surgery (39.5 vs. 12.8%, $p = 0.0002$) and this was also true on multifactorial analysis ($p = 0.004$, OR 1.5–14.7). Jejunal and ileal involvement, raised CRP, lower weight/height centile and stricturing disease ($p = <0.05$) were all significantly higher in patients carrying the disease-causing mutations (DCM) ($p = 0.009$, $p = 0.0009$, $p = <0.05$, respectively).

Table 1. Comparison of major paediatric studies of CARD 15 and association with disease

Study	Population		Healthy controls – allelle frequency					Crohn's disease – allelle frequency				
		Average age at diagnosis (range)	n	1007 fsInsC	G908R	R702W	carriage of atleast one variant	n	1007 fsInsC	G908R	R702W	carriage of atleast one variant
Tomer et al.	New York/ Caucasian	11.8 (0.3–18)	136	3.6	5.8	1	11	101	17	11	6	31
Sun et al.	German/ Saxon	11.2 (1–17.5)	NA	NA	NA	NA	NA	55	25.4 [1]	5	14	65
Wine et al.	Israeli	12.1 (0.9–18)	NA	NA	NA	NA	NA	93	10	22	9	35
Lesage et al.	European	20.7 (3–61)	103	2	1	4	NA	906	11	6	11	27
Weiss et al.	Jewish	11.9 (0.8–16)	NA	NA	NA	NA	NA	67	8	18	5	0.51
Kughastan et al.	White American	12.4 (4–18)	601	2.2	1.5	5.4	18.2	164	13.1	6	6.6	51.4
	African American	12.1 (3–18)	124	0.4	9	1.7	18	58	0.8	0	0.8	
	Hispanic American	12 (2–16)	124	0.4	1.2	2.8	8.8	18	2.2	0	0	4.4
Ideostrom et al.	Swedish	10.9 (2.8–16.9)	NA	NA	NA	NA		58	1.7	0	2.6	0.086
Meinzer et al.	French/ Swedish	12 (NA)	NA	NA	NA	NA	NA	44/55	NA	NA	NA	NA
Ferraris et al.	Italian	11.3 (2–18)	101	NA	NA	NA	5	54	NA	NA	NA	41
Russell et al.	Scottish	11.5 [2]	245	1.4	0.2*	5.5	19.8	167	4.2	2.2	6.2	19.8

[1] Versus 11% in a similar adult CD population.
[2] Median age, all <16 years.
* p value CD vs. controls = 0.06.

Genotype/Phenotype Relationship

CARD15 mutations are particularly associated with ileal CD rather than colonic disease [26–28, 38]. The majority of studies have shown no association with UC [25]. Ileal involvement is associated with an earlier presentation of CD and two of these

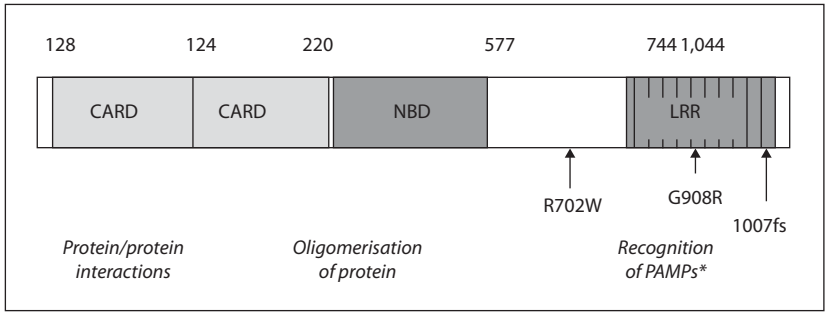

Fig. 2. Functional domains of NOD2/CARD15. PAMPs = Pathogen-associated molecular pattern. * Pathogen-associated molecular pattern.

studies also found an association between mutation of both CARD 15 alleles and earlier age onset of adult CD (16.9–23 vs. 19.8–29 years, respectively) [26, 38]. Many but not all studies show an association with stricturing disease which may be explained by the tendency for ileal disease to stricture [26, 39, 40]. Analysis of disease behaviour is complicated by changes in disease behaviour with time and inconsistencies in classification schemes between groups [41].

CARD15/NOD2 Function

CARD15/NOD2 gene encodes for a protein expressed constitutively in Paneth cells, a subset of epithelial cells at the base of intestinal crypts predominantly in the terminal ileum [42–46]. It is also expressed in the cytoplasm of monocytes and tissue macrophages, and expression can be induced on intestinal epithelial cells [47].

Figure 2 demonstrates the structural domains of CARD15, highlighting the function of each domain. CARD15 is a member of the CATERPILLAR group of proteins, implicated in pathogen recognition in both plants and animals. A rare monogenic dominant disorder called BLAU syndrome (characterised by uveitis, arthritis with granuloma formation and rashes) is caused by mutations in the nucleotide-binding region (NBD) of CARD15. However, in CD the majority of mutations occur in the leucine-rich repeat domain (LRR). The LRR is of particular importance as it serves as a receptor for muramyl dipeptide (MDP), a small molecule derived from the cell wall peptidoglycan (PGN) of Gram-positive and Gram-negative bacteria [48]. When MDP binds to the LRR, a conformational change occurs in the molecule resulting in downstream activation of NFκB via RICK/RIP2 and of caspase 3 via the CARD domains. Our knowledge of the function of NOD2/CARD15 is rapidly expanding and it has become apparent that experimental results are dependent on the model used. They can be summarised as follows:

Epithelial cell lines transfected with the mutated NOD2/CARD15 gene fail to upregulate NFκB, and hence gene transcription, in response to MDP compared with

cells transfected with the wild-type NOD2/CARD15. Furthermore, intracellular killing of salmonella is impaired in cell lines expressing the mutated gene [44]. This decrease in NFκB activity is the opposite of what is seen clinically.

Genetically engineered mice deficient in the NOD2/CARD15 gene are healthy and have no intestinal inflammation. However, compared with mice expressing wild-type NOD2/CARD15, the deficient mice are more susceptible to infection with *Listeria monocytogenes* when administered intra-gastrically (but not intravenously or via the peritoneum). More organisms were present in the liver and the spleen than in the wild-type mice but no intestinal inflammation was observed. Interestingly, the expression of certain cryptidins was low in the mice containing the mutated gene and was even lower following infection [49]. Cryptidins (equivalent to human defensins) are antimicrobial peptides, secreted upon recognition of MDP, to protect the host from invasion.

Maeda et al. [50] created a 'knock-in' mouse model whereby the wild-type NOD2 was replaced with a homolog of the most common NOD2 mutation *(3020insC)*. These mutant mice exhibited elevated NFκB activation in response to MDP and increased secretion of the pro-inflammatory cytokine interleukin-1β (IL-1β). They then induced colitis using DSS (dextran sodium sulfate) and found that the mutant mice had more severe colitis, increased macrophage apoptosis and levels of IL-1β.

In humans, peripheral blood mononuclear cells produce several cytokines (TNF, IL-1B) in response to activating Toll-like receptors with their appropriate ligands. This response is augmented in the presence of MDP in individuals with wild-type NOD2/CARD15 genotype but not in individuals who possess one or more mutations. It has been shown that Paneth cells fail to secrete much alpha-defensins 5 and 6 in biopsy specimens from patients with NOD2 mutations, a finding analogous to NOD2 deficient mice [51].

In summary, the identification of NOD2/CARD15 mutations in many patients with ileal CD and the association with a deficient anti-microbial defence, has provided insight into the complex balance between tolerance to food antigens and commensal bacteria and the rigorous immune response to foreign pathogens occurring at the luminal wall, so much that CD has been described as the archetypal inflammatory barrier disease [52]. Its identification has sparked interest in basic research into gut immunology and could lead to some novel therapies for CD.

Chromosome 5Q/IBD5 Cytokine Cluster

The IBD5 locus on chromosome 5q31 is the only other locus that has been clearly demonstrated to confer increased risk for CD in multiple studies. A Canadian study of 158 sib-pairs confirmed a previous suggestion of linkage to Chr 5q31–33 [53, 54]. In this study Rioux et al. [53] found a modest genome-wide association between Chr 5q and CD (lod score 2.4). Subsequently, this same group used linkage disequilibrium mapping to define a 250kb haplotype spanning the Chr 5 cytokine cluster and found a strong association with CD. This 250-kb interval is defined by 11 single nucleotide polymorphisms (SNPs)

that are in almost complete linkage disequilibrium (LD) with each other. Heterozygous carriage of the risk alleles increases the risk of CD 2-fold compared to a 6-fold increase with homozygous carriage [55, 56]. The Chr 5q31 region contains a cluster of cytokine genes involved in immune response but, due to the tight LD in this region, it is hard to dissect out a disease-causing gene from the many potential candidate genes. The OCTN (organic cation transporter gene cluster) genes are attractive candidate genes in this region that have been associated with other chronic inflammatory disorders [57]. Solute carrier family 22 member 4 (SLC22A4) and SLC22A5 are encoded for by OCTN 1 and 2, respectively, and play an important role in the energy supply to epithelial cells. They are known to mediate the transport of carnitine and many other organic cations and have recently been identified as the ergothioneine transporter [58, 59].

In 2004, Peltekova et al. [60] after resequencing five genes in the cytokine cluster, reported an association between CD and polymorphisms in the SLC22A4 and SLC22A5 genes as well as a two-locus haplotype (SLC22A4 1672T/ SLC22A5–207C), the two-allele (TC) risk haplotype. They performed functional studies suggesting that the 1672C→T missense substitution in SLC22A4 and the -207G→C transversion in the SLC22A5 promoter resulted in impaired transporter or transcription function of the OCTNs respectively. Based on their functional work and their observation that the OCTN variants were significantly associated with CD even in the absence of IBD5 risk haplotypes, Peltokova suggested that SLC22A51672T and –207C variants per se were causative for CD. A German study, and a further Canadian study, initially confirmed this association between SLC22A-TC haplotype [61, 62]. However, the German study was unable to establish an effect for OCTN1/2 independent from the IBD5 risk haplotype [62]. In a well-designed Scottish study including 374 patients with CD, Noble et al. [63] confirmed OCTN1/2 was associated with CD, but using a more detailed selection of tagging SNPs to examine the extended haplotype, they did not confirm an independent association and this was also the case in a recent European study [64]. Overall, the association between the TC haplotype and CD has been replicated in at least six independent Caucasian cohorts but the role for other candidate genes within this extended haplotype cannot be excluded [65–70]. The North-American IBD consortium reported on a large cohort of affected offspring and parents that supports this assessment. They concluded that a set of polymorphisms spanning three other genes (IRF1,PDLIM, and P4HA2) may equally as likely to contain the IBD5 causative variants as OCTN [71]. This study found the association to IBD5 was exclusive to the non-Jewish IBD population.

Studies on a Japanese population failed to show any association, however, again highlighting the population-specific variations in genetic susceptibility to IBD [67, 72, 73]. No evidence has been found for an association between IBD5 and CD in the high-risk Jewish population [61, 67].

IBD5 epistasis has been shown with CARD15 in CD [60, 61, 66, 69]. Mirza et al. [66] found that when they stratified the CD offspring in their large TdT sample (511 affected offspring) and a case control group (n = 943), the association with 5q31 risk

haplotype was present only in cases with at least one of the known CARD15 disease susceptibility alleles. They determined that the combined population attributable risk for the CARD15 and IBD5 alleles was 33%. Other studies have found that CARD15 and IBD5 act independently of each other but perhaps they were underpowered to detect a relationship [29, 55, 65, 67, 68, 74]. In a genome-wide scan Van Heel et al. [75] found evidence for epistasis between chromosome 19 (IBD6) and CD pairs possessing one or two copies of the IBD5 risk haplotype ($p = 0.0005$).

IBD5 and Phenotypic Associations

There are inconsistent data regarding phenotypic association. A UK case-control study first reported an association with perianal CD [76]. More recently, the Scottish study mentioned above found an association with markers of more severe disease such as stricturing or penetrating CD or the need for surgery. No association with disease location or UC was seen in this study [64]. A study of 981 IBD patients from Leuven could not demonstrate an association of OCTN1 and OCTN2 variants with UC, CD or IBD globally but did show an association with perianal and penetrating CD [77].

There have been some reports describing a role for IBD5 in UC with an equal number of contradictory reports [65–68, 74, 76]. Two studies describe the potential epistatic interactions of IBD5 and CARD15 in UC [68, 78]. In the paper by Torok et al. [62] the SLC22A-TC haplotype was associated with earlier onset of disease but this has not been replicated.

IBD5 and Paediatric Disease

Two studies have focused specifically on IBD5 in paediatric CD patients and some predominantly adult studies have also included children. In Rioux's initial genome-wide scan, the genetic data were stratified by age and the highest lod score (3.9) was found in families of early onset of disease (≤16 years); however, there were only 50 of these families [79]. Scotland has a higher rate of paediatric IBD than elsewhere in the UK with a threefold rise in the past 30 years. Satsangi's group examined 299 well-phenotyped Scottish children (200 with CD, 74 with UC, and 25 with indeterminate colitis, IC), together with 502 parents (for transmission disequilibrium testing) and 256 controls, to determine the contribution of the IBD5 locus to disease. They confirmed that allele frequencies of the OCTN1/2 variants were significantly higher in IBD/CD cases ($p < 0.04$) versus controls but independence from SNPs on the surrounding IBD5 haplotype could not be confirmed. Using anthropometric data, they found that carriage of the SLC22A-TC haplotype was more common in children with lower weight, height and BMI centiles at diagnosis of CD than those with higher centiles (OR 3.4, 2.44 and 2.49, respectively).

The other paediatric study genotyped 264 Caucasian CD children and 527 controls. An association between OCTN1/2 TC haplotype and CD was confirmed but no correlation with phenotype was found [80]. Neither this American study nor the Scottish study found any interaction between CARD15 and IBD5 haplotype in paediatric IBD.

Summary of IBD5 Locus

A risk haplotype on Chr5q31 for CD has been confirmed but great challenges remain in identifying causal variants in complex diseases in regions of extensive linkage disequilibrium [63]. Polymorphisms in this region appear to be associated with lower BMI and lower height in a paediatric CD cohort but this awaits replication. Also there are other genes of interest in this region, e.g. RAD50, which is involved in TH2 cytokine genes expression, and which need further investigation [81]. Hopefully, in the near future consortia with well-phenotyped, prospectively collected cohorts together with functional work on animal models of colitis and patients will lead to a better understanding of this fascinating region.

IBD2/ Chromosome 12

Evidence for linkage on this region to IBD was first shown in a UK genome-wide scan (GWS) (lod score of 5.4) and has been replicated in various populations [82–86]. This region shows strongest linkage with UC with weaker linkage with CD and IBD in general. Like other susceptibility loci, there is variation across populations with no association found in the Flemish population and significant variation across African-American and Jewish-Caucasian populations [87, 88]. Achkar et al. [22] in a recent study combining data from 904 phenotyped cases showed that the IBD2 locus is associated with extensive UC and because of this suggested that this form of UC should be considered a pathophysiologic subset of disease. STAT6, a key transcription factor involved in Il-4 and IL-13-mediated TH2 responses [89], is an attractive candidate gene in this region but a positive association has not been confirmed [84, 90]. Therefore, specific disease-causing mutations in this region remain to be identified.

IBD3/Chromosome 6

The major histocompatibility complex (MHC) region on chromosome 6p21.1–23 is one of the most extensively studied regions in IBD. Linkage studies have clearly established that this region contributes to IBD pathogenesis (both CD and UC). Linkage has been consistently replicated across different populations which may suggest that there are several susceptibility factors in the extended MHC [19, 91, 92]. Calculations derived from studies of HLA allele sharing within families suggest that this region contributes between 10–33% of the total genetic risk of CD and 65–100% of the total

genetic risk of UC [93, 94]. Association studies into candidate genes have not been so successful due to the strong linkage disequilibrium, high gene density and extensive polymorphism in this region. HLA proteins present peptides to T cell receptors. Class I proteins are present on all cell types and consist of a single heavy chain encoded by three polymorphic genes (HLA-A, HLA-B, HLA-C). In contrast, class II molecules are normally only expressed on specialised immune cells and are composed of α and β chains encoded by three genes (HLA-DP, HLA-DQ, HLA-DR). Early data on this region was inconsistent reflecting small sample sizes, low resolution genotyping techniques and lack of appreciation of genetic heterogeneity. Focussing on more recent studies, the most consistently replicated association with UC is with the rare allele HLA-DRB1*0103. This rare variant is present in 0.2–3.2% of the population, 6–10% of all UC cases and 15.8% of extensive UC cases and 14.1–25% of severe UC requiring colectomy [94–96]. HLA-DRB1*0103 is also associated with isolated colonic CD. The odd's ratios for isolated colonic disease range from 5.1 to 18.5 in non-Jewish Caucasians [38, 97]. Despite the strength of this association Ahmad et al. [98] noted that this allele was present in no more than 32% of patients with isolated colonic CD, indicating that whilst the marker has a high positive likelihood ratio, the negative likelihood ratio limits its clinical application.

The most consistent association of CD is with the common HLA allele, HLA-DRB1*0701. Three studies from the UK (n = 244), Spain (n = 210), Canada (n = 432) showed that this association was specifically for people with ileal involvement [38, 97, 99] and in the UK and Canadian study the association was only found in patients who did not possess any of the three common CARD 15 mutations. The classic autoimmune haplotype A1-B8-DR3 is associated with colonic disease although large replication studies are needed to look at the linkage disequilibrium with other disease associated alleles [38].

The Oxford group have looked extensively at genotypes associated with extra-intestinal manifestations of disease. Type 1 peripheral arthropathy, which affects fewer than 5 joints, with one large joint usually involved and is associated with disease activity, is associated with HLA-B27, HLA-B35 and HLA-DRB1*0103. Type 2 is characterised by non-destructive inflammation of the small joints, is not associated with disease activity and has been found to be associated with HLA-B44 [100].

TNF is an important candidate gene located within the IBD3 linkage region. No association has been found with SNPs within the coding region of the gene. However, SNP –857C in the promoter region has been reported to be associated equally with UC and CD in both family-based and case control studies, with conflicting data on CARD15 epistasis [101, 102]. Orchard et al. [103] have found a strong association between another polymorphism in the promoter region of the TNF-α gene (–1031C) and the risk of developing erythema nodosum.

With the advent of ever faster and cheaper genotyping methods and a greater understanding of haplotype structure and appropriate statistical methods further research in this region polymorphic region is awaited with interest.

Other Candidate Genes

DLG5

This an attractive candidate gene on the chromosome 10 linkage region [104] which codes for a scaffolding protein important in signal transduction and epithelial integrity. A detailed study by Stoll et al. [105] found association between one of two haplotypes and CD. However, this has not been replicated despite eight well powered studies in various populations [62, 73, 77, 102, 106–109]. Ferraris et al. [110] in their early onset cohort (134 CD and 91 UC all diagnosed < = 18 years) did not find any disease association.

NOD1

Based on its structural and functional similarity with CARD 15 this gene (located on Chr. 7p) has been investigated for association with IBD. A strong association between a complex functional NOD1 (CARD4) insertion/deletion polymorphism and IBD was found by a group at Oxford University [111]. This same group originally identified linkage on 7p14 in a genome-wide scan [83]. Hugot's group [112] had previously failed to find any association with disease (although only one SNP was tested) and a more recent smaller Cambridge study did not replicate an association [113]. Further studies are needed to determine if the discrepancy is due to population heterogeneity or a false-positive finding in the Oxford study.

IL23R and ATG16L1

Recent publications implicating these two genes highlight the changing face of genetics research. A group of USA and Canadian researchers genotyped over 1,000 subjects for 308,332 autosomal SNP using a commercially available chip and achieved genotyping success rates of >94%. From this vast array of SNPs, they found one novel significant association with the IL23R gene. They then went on to test this SNP as well as 9 others within the gene in two independent cohorts (one case-control and another family-based cohort) and confirmed a significant association with IBD [114]. This association has been replicated by the Wellcome Trust Case Control Consortium who examined 1,902 CD cases, 975 UC cases and 1,345 controls. They observed an allele frequency at the same coding variant on IL-23R of 2.5% in ileal CD and 6.2% in controls ($p = 1.1 \times 10–12$), odds ratio of 0.38 (95% CI 0.55, 0.96). No subphenotypic association was found [115]. IL-23 is required for murine experimental colitis and promotes activation of T cells and perpetuation of organ-specific responses [116, 117]. Further confirmatory studies will help define whether this pathway may prove an effective target in future IBD treatments.

Schreiber's group used a similar approach using 19,779 non-synonymous SNPs to genotype 735 CD patients and 368 controls. They took the most significant 72 SNPs and genotyped an independent cohort of trios as well as a case control cohort and found a significant association with a coding SNP on the ATG16L1 gene with CD

specifically [118]. This is an intriguing candidate gene as it encodes a protein in the autophagosome pathway that process intracellular bacteria.

MDR1

The multidrug resistant gene MDR1 encodes the membrane transport protein *p*-glycoprotein-1 and is located in the Chr 7q linkage region. Two polymorphisms (C343T and Ala893Ser/Thr) have been found to alter the pharmacokinetics of certain drugs in humans. Taken together with the fact that MDR1 knock-out mice develop colitis, MDR1 is a good positional and functional candidate gene. A meta-analysis of 9 association studies was done to clarify conflicting results. It found that C3434T allele showed association with UC (but not CD) with an OR of only 1.12. There is a suggestion that the TT genotype is associated with more severe UC and steroid use [119].

TLR4

The Toll-like receptors, like CARD15, are pattern recognition molecules involved in innate immunity. A TLR4 variant, Asp299Gly, affects the receptor's response to lipopolysaccharide and increased susceptibility to Gram-negative infections. A positive association with TLR4 variants and both CD and UC has been replicated in a number of studies [120–123].

Pharmacogenetics

Pharmacogenetics is the study of how genetic differences influence the variability of patients' responses to drugs. Thiopurine-based meracaptopurine (6MP) and its prodrug azathioprine (AZA) are widely used in the treatment of children with IBD albeit cautiously owing to its well-known toxicity such as bone marrow suppression, hepatitis and pancreatitis. The therapeutically active metabolites of 6MP and AZA are 6 thioguanine nucleotides (6 TGNs). TGNs are broken down by xanthine oxidase and thiopurine S-methyltransferase (TPMT). Xanthine oxidase is, however, absent in haematological tissue. Therefore, if the TPMT pathway is defective high levels of myelotoxic TGNs accumulate. Polymorphisms in the gene encoding TPMT are associated with lower enzyme activity. One may thus ask if we screen for these polymorphisms will we detect the patients who are more likely to accumulate TGNs and consequently are at higher risk of toxicity. This has been tested in two small paediatric cohorts (22 and 72 patients, respectively) [124, 125] and no association between polymorphisms and toxicity has been found. In the larger study of these two small studies, 11 children had adverse advents but only one was found to have a polymorphism in the TPMT gene. These negative findings may be due to small sample size as there is some association found in larger adult studies [126]. It is estimated from the adult CD literature that to prevent one adverse event 300 patients need to be tested for polymorphisms. There are multiple polymorphisms in the drug pathway (e.g. HPRT gene) that could

result in toxic levels of metabolites and it is impractical to test for all of them. Regular blood tests to check white cell count are necessary even if TPMT testing is negative. Therefore, the British Society of Gastroenterology does not recommend routine testing of TPMT polymorphisms [127].

As regards the use of genetics to guide other IBD treatments, the evidence is sparse and there are few specific trials. The one exception is a trial performed by the Belgian group who looked specifically at 287 consecutive CD patients receiving infliximab therapy and genotyped them for twenty one apoptosis genes. They observed that polymorphisms in FasL/Fas system and caspase-9 influence the response to infliximab in luminal and fistulising CD. The strongest association was seen between the Fas ligand –843 TT genotype and non-response. Concomitant mercaptopurine/azathioprine therapy, however, was able to overcome the effect of unfavourable genotypes in luminal disease [128].

Subgroup analyses of association trials have revealed areas for future research. For example, the frequency of the IBD5 homozygous mutant genotype is significantly increased in CD patients lacking response to infliximab (RR = 3.88, 95% CI = 1.18–12.0, $p < 0.05$) [129].

A more recent interesting finding is the significant association between the TT genotype of exon 21 MDR1 polymorphisms and a higher risk of ciclosporin failure in adult patients with steroid resistant UC ($p = 0.0001$) [130]. If further studies confirm this then other more effective treatments can be favoured or surgery considered earlier.

Genetic Screening

From a practical point of view, how can knowledge of the genetics of IBD assist in patient management? At present it can help to answer otherwise awkward questions such as 'My wife has Crohn's disease. What is the chance of my son developing it?' This can be answered knowing that all first-degree relatives have a 10- to 15-fold increased risk of developing IBD. So, in the UK where the average incidence is 6.5/100,000, the incidence in first degree relatives goes up to 65–97.5/100,000. We can also advise patients on the impact of environmental factors such as smoking as without doubt these impact on disease expression, with CD more likely in those who smoke and UC in those who do not [131]. However, testing for NOD2 mutations is not predictive as the disease penetrance (the percentage of individuals with a particular genotype developing disease) of compound heterozygotes is only 10%. Currently, genetic screening is not appropriate even in high-risk groups as the predictive tests do not exist and presymptomatic preventive therapy is not available. Another commonly asked question is can the course of disease be predicted through genetic testing. To date we know that ileal involvement and stenoses are more frequent in patients carrying two NOD2 mutations and patients with this phenotype are more likely to require surgery. However, NOD2 mutations are only present in a small proportion of patients and testing is not sensitive or specific enough

to be used as a predictive tool. It may be considered clinically if drugs known to cause stenosis are being considered for the patient. It is hoped that the combination of known genetic variation will allow a molecular classification of IBD. Work is being done to put together a gene chip with all the known disease associated polymorphisms on it so that, with refinement, we can potentially profile patients so that disease course can be predicted. This may then help guide treatment, e.g. if it is known that a UC patient is unlikely to respond to available therapies, surgery may be recommended at an earlier stage thus minimizing drug side effects and complication rates.

Conclusions

Since the first genome-wide study in 1996, considerable advances in our understanding of the genetics of IBD have occurred. However, we are still far from understanding the complex interaction between multiple susceptibility and disease-modifying genes and environmental factors occurring within the gut mucosa. In recent months, new genes have been identified renewing enthusiasm in this field. Advances in technology such as gene chips allowing thousands of SNPs to be tested on large cohorts as well as new computational and statistical techniques to analyse the results greatly increases the potential for future discoveries. Large collaborative studies both in Europe and the US using these chips are on-going and the results are eagerly awaited. Such advances may allow a molecular classification of IBD and even individualise patient treatment accordingly.

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Addendum

Since going to print, there has been a series of genome-wide association studies of CD and UC patients published so that over 30 genes have now been shown to be associated with IBD [1, 2]. The studies have identified novel pathways some of which are common to both CD and UC (Stat3, JAK2, IL23R) and other that are disease specific (e.g. CD and ATG16L1 and IRGM, EGM1 and UC) [3].

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Pathology of Inflammatory Bowel Disease in Children

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Abstract

Accurate pathological diagnosis is essential to the optimal management of children with chronic inflammatory bowel disease. Although the conventional pathologic characteristics of ulcerative colitis and Crohn's disease are generally familiar to clinicians and pathologists, they must also be aware of many potential diagnostic pitfalls resulting from variations on the classical pathologic paradigms, endoscopic-histopathologic discordance, biopsy sampling variations, and mimicry of inflammatory bowel disease by other disorders.

Optimal management of children with inflammatory bowel disease (IBD) depends on accurate clinical and pathological distinction between its two principal forms, chronic ulcerative colitis (UC) and Crohn's disease (CD), and the exclusion of other disorders. Although the classical gross and histopathological characteristics of UC and CD are entrenched in medical teaching [1, 2], 15–30% of pediatric patients with IBD defy definitive classification at their initial evaluation even with the benefit of clinical, endoscopic and radiological data, and some remain unclassified during follow-up even after colectomy [2, 3]. Obstacles to accurate diagnosis may include variations on the classical pathological paradigms of IBD, endoscopic-histopathologic discordance, biopsy sampling variations, and confusion with other chronic disorders.

Normal Mucosal Histopathology and Variations

Normal, optimally oriented large intestinal mucosa contains uniformly straight, parallel, closely spaced crypts. These extend from the surface to the muscularis mucosae and are lined mostly by absorptive and goblet cells in roughly equal proportions along with few basal endocrine and Paneth cells [4]. The lamina propria contains mononuclear inflammatory cells, which form a gradient that dissipates from the surface to

the base. Lymphoid aggregates are occasionally found within the lamina propria or straddling the muscularis mucosae (so-called lymphoepithelial complexes); in children, these are generally larger, more numerous and more likely to contain germinal centers compared with adults.

The cecum normally contains widely spaced crypts and increased mononuclear inflammatory cells, which can be misconstrued as signs of inflammation. Paneth cells normally occur in the cecum and ascending colon. More distally, they signify an underlying chronic inflammatory disorder such as IBD, which may be helpful in the recognition of quiescent IBD that has otherwise normalized. Crypt distortion may occur in the normal rectum due to the presence of muciphages, or in samples taken close to the anorectal junction. Irregular crypt branching and budding are abnormal and considered hallmarks of IBD, but symmetrical bifurcation occurs during normal crypt replication [5].

Ulcerative Colitis

UC classically features continuous, diffuse, circumferential, mucosal-based chronic inflammation which involves the rectum alone or in contiguity with part or all of the colon. Children are far more likely than adults to present initially with extensive colitis or pancolitis [6–12], and those who present with limited colitis are more likely to experience anatomical extension over time [10].

The gross features of UC reflect the current state of acute inflammatory activity superimposed on accumulated structural changes resulting from previous bouts of inflammation. Activity is manifested by hyperemia, granularity, friability, erosions, superficial fissuring, broad-based ulcerations, bloody exudates and toxic dilatation. Chronic, structural changes include atrophy, coarse mucosal folds, mucosal bridges, inflammatory polyps, global foreshortening, loss of haustrae or stricture (fig. 1). In cases of partial large bowel involvement, the transition from diseased to normal mucosa may be gradual or abrupt.

Microscopically, UC features chronic inflammation that is limited to the mucosa and superficial submucosa. Since the deep submucosa is not well sampled in routine flexible endoscopic biopsies, the presence of chronic submucosal inflammation is not a reliable marker of CD. Typically, the lamina propria is expanded by a full-thickness infiltrate of mononuclear inflammatory cells that separates the crypts from one another and from the underlying muscularis mucosae. Lymphoid hyperplasia usually predominates in the distal colon and rectum but may be prominent throughout the colon, especially in children. Active disease is manifested by neutrophil infiltration of the surface and crypt epithelium, i.e. cryptitis and crypt abscesses, and may progress to crypt drop-out and ulceration. Epithelial regeneration and injury occur simultaneously, resulting in branching and budding of crypts, reactive nuclei, mitotic activity and reduced goblet cell mucin. Severe inflammation eventuates in atrophy and

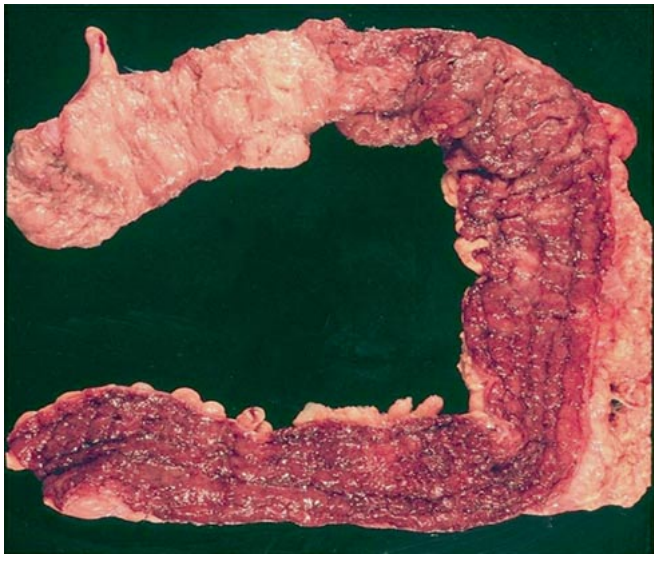

Fig. 1. Gross appearance of UC. This specimen from a 16-year-old patient shows hyperemia and longitudinal ulcerations extending continuously from the distal margin (lower left) to the ascending colon (top center), where there is an abrupt transition to normal.

architectural disarray, however mild inflammation may permit eventual normalization. Other changes include thickening, splitting or scarring of the muscularis mucosae and fatty replacement of the submucosa. The muscularis propria and serosa are generally spared, but can show scarring in the aftermath of fulminant colitis.

Crohn's Disease

CD may affect any part of the alimentary tract in a segmental, transmural fashion. Compared with adults, children and adolescents have higher rates of ileocolic (21–52%), ileal (19–38%) and jejunal disease (10–26%), and lower rates of colonic disease (6–14%) [13]. However, high rates of colonic disease (77–89%) have been reported in studies of children under 5 years, suggesting that children with CD of very early onset may comprise a distinct subgroup [12, 14].

The gross changes include segmental mural thickening, rigidity and stenosis, mucosal edema, serpiginous linear ulcerations or cobblestoning, sinus tracts, fistulae, mesenteric hypertrophy and creeping fat on affected serosal surfaces (fig. 2). Microscopically, the features of mucosal inflammation may be very similar to those of UC, although often patchier and featuring more pseudopyloric metaplasia and less crypt distortion and mucin depletion [15]. Additionally, they may include aphthous ulcers, chronic fissures and sinus tracts lined by granulation tissue.

CD usually affects all layers of the bowel wall. Microscopically, the muscle fibers of the muscularis mucosae are segmentally hypertrophied, splayed and disorganized, and the submucosa is expanded by lymphocytic aggregates, dilated lymphatics, hypertrophied myenteric nerves, fibroadipose tissue and granulomas. The muscularis

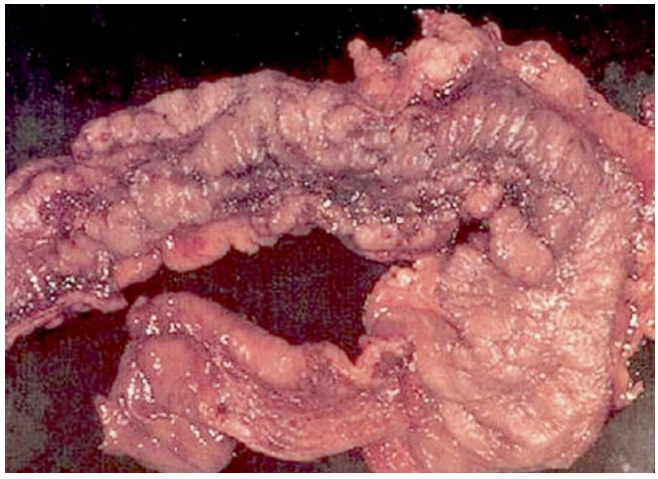

Fig. 2. Gross appearance of Crohn's ileocolitis. This specimen from a 17-year-old patient shows mural thickening and ulceration of the terminal ileum (bottom) and distal colon (top) with sparing of the intervening colon. Note the asymmetrical ulcerations in the colon, and the fat wrapping along the cut edges of the specimen.

propria, which is usually least affected, may contain hypertrophied myenteric nerves, granulomas and lymphoid aggregates. The serosal fat is typically fibrotic, hypertrophic and infiltrated by lymphoid aggregates and granulomas.

The clinical and pathological manifestations of CD are classified as inflammatory, stricturing, or fistulizing [16, 17]. Stricturing occurs most commonly in patients with isolated ileitis and fistulization in those with colitis or ileocolitis [16]. It may be accompanied by cicatricization, myenteric nerve hypertrophy and disorganization of the muscular and neural elements, resulting in gross mural thickening, rigidity and fibrostenosis. In fistulizing disease, the wall is disrupted by sinus tracts, leading to the formation of internal or external abscesses, phlegmons, intra- or extraintestinal fistulae or free perforation. Longitudinal studies have shown that patients who present initially with inflammatory disease usually progress to either stricturing or fistulizing disease, but that those with stricturing or fistulizing disease at the outset usually remain phenotypically stable [18]. Perianal fissuring in CD is pathologically analogous to, and statistically associated with, fistulizing CD of the colon [19].

The granulomas of CD are typically non-necrotizing, occur in both diseased and otherwise normal segments, and can involve any layers of the wall, the subserosa or the regional lymph nodes [20]. Although their prevalence in resection specimens is reportedly 50–60%, this figure is subject to so many variables, i.e. numbers and sizes of tissue sections, numbers of slides per section, the care with which granulomas are sought and interobserver variations, that it is merely a rough estimate [20, 21]. The frequencies of granulomas in endoscopic biopsies of the ileum and colon have ranged from 8% to over 50% in different studies, the higher rates correlating with multiplicity of biopsy samples and serial sectioning of the tissue blocks [2, 22–27]. As a rule, granulomas are encountered more frequently in children than adults and in active than quiescent disease [21, 24, 27, 28].

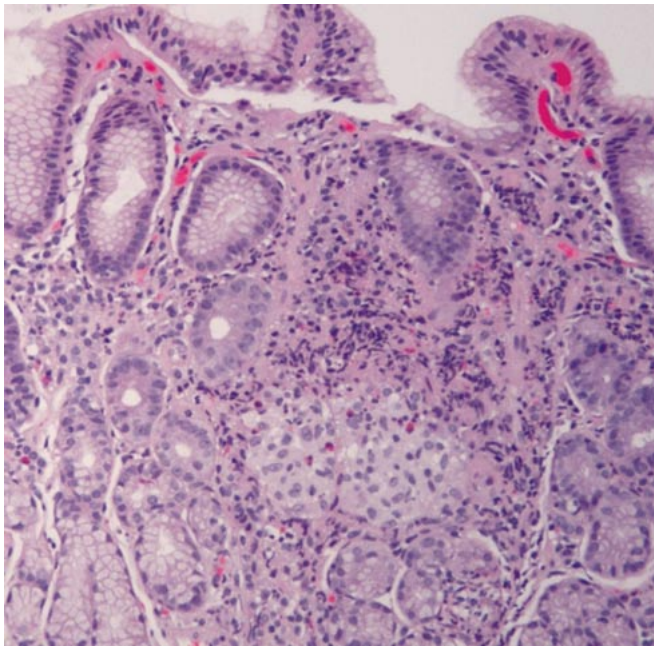

Fig. 3. Crohn's gastritis manifested by non-necrotizing granulomas and adjoining focus of mononuclear inflammatory cells infiltration.

Upper gastrointestinal inflammation can be detected in the biopsies of most children with CD (fig. 3) [22, 29–34]. It occurs even in asymptomatic patients and in the absence of endoscopic or radiological abnormalities [22, 29–33], although authorities disagree whether its overall incidence correlates with the incidence and severity of inflammation [22, 30]. In a controlled prospective biopsy study of 30 patients with CD by Tobin et al. [30], esophagitis was observed in 72%, gastritis in 92% and duodenitis in 33%, including moderate or severe inflammation in 12, 27 and 11%, respectively. Although the microscopic lesion known as focal (or focally enhanced) gastritis, which features a localized, mixed inflammatory infiltrate of neutrophils and mononuclear cells, has been reported in 52–65% of children with CD [35–37], identical changes may occur in children with UC and in adults with various other disorders [38]. Lymphocytic esophagitis, a lesion characterized by increased intraepithelial lymphocytes surrounding the esophageal papilla, has been associated with CD in a recent study consisting largely of children [39], but requires confirmation in a larger and controlled study.

The high prevalence of upper gastrointestinal inflammation in children with CD has provided a rationale for performing diagnostic upper endoscopy in patients whose diagnosis remains ambiguous after lower endoscopy [22, 33, 34]. Nonetheless, caution is required in interpreting nonspecific inflammatory changes, since they occur almost as frequently in children with UC (see below) [22, 30, 33, 35, 40, 41]. Rather, the value of routine upper endoscopy as a means of subclassifying children with IBD depends on the detection of specific histologic findings, particularly granulomas or possibly aphthous ulcers. The prevalence of upper gastrointestinal granulomas in

children with CD in prospective biopsy studies (subject to the aforementioned methodological caveats) ranges from 7 to 40%, and does not correlate with the presence of ileocolonic granulomas [30, 31, 33, 42–44]. Based on a prospective study of 54 children whose lower endoscopic and clinical findings were nondiagnostic for UC, Castellaneta et al. [22] reported that diagnostic yield was maximized when visible upper gastrointestinal lesions, such as foci of gastric body erythema and edema, were targeted for biopsy. The authors were thereby able to establish a diagnosis of CD in 11 of 13 unclassified patients, accounting for 20% of their total study population.

Gross-Microscopic Discordance in Inflammatory Bowel Disease

The anatomical extent and distribution of colitis in IBD can have important diagnostic and clinical implications. However, neither direct endoscopic visualization nor microscopic examination alone is completely reliable in assessing the extent and distribution of colitis. Studies comparing gross and microscopic findings at colonoscopy have reported discordances in both directions, i.e. more extensive disease by gross visualization than by microscopic endoscopic assessment and vice versa [45–51]. Microscopic inflammation in grossly normal mucosa is usually mild, though not invariably so [49], and may include diagnostic granulomas [20]. Endoscopic evaluation for colonic involvement by IBD must therefore include sampling endoscopically normal areas. By the same token, the microscopic as well as endoscopic findings should both be factored into the assessment of disease extent and distribution.

Variations on the Classical Inflammatory Bowel Disease Paradigms

Deviations from the classical features of UC and CD are increasingly recognized as potential sources of diagnostic confusion in pediatric patients with IBD. Pathological overlap between UC and CD occurs in 10–15% of resected colons [52–54].

Fulminant UC often exhibits changes that are considered emblematic of CD, such as transmural chronic inflammation, fissuring, or discrete ulceration of otherwise normal mucosa. However, colons from less severe cases of UC may also display CD-like features, such as pseudopyloric metaplasia, deep lymphoid aggregates and neural hypertrophy [53–58]. When overlapping features are encountered in the resected colon, the term ‘indeterminate colitis’ is traditionally employed as a temporary diagnostic classification. Most cases behave clinically as UC on follow-up, e.g. tolerating sphincter-sparing ileoanal anastomoses, especially if clinical and radiological data are also factored into the diagnosis [58]. Patients who have not yet undergone a colectomy but whose clinical, endoscopic and laboratory data fail to provide a definitive diagnosis are more appropriately referred to as ‘unclassified IBD’; however, some authorities include them under the heading of indeterminate colitis as well [3,

54, 57–61]. Studies of children with ambiguous diagnoses at their initial evaluations suggest that many remain unclassified on follow-up, leading some authorities to view them as a distinct IBD subcategory [3].

Rectal Sparing and Patchy Inflammation

Relative rectal sparing and discontinuous inflammation are considered characteristics of CD, but may occur in patients with UC as well. In adults, they seem to develop over time as a consequence of therapeutic intervention or spontaneous healing [51, 62–66] (fig. 4), but in children they have been described at initial presentation. Markowitz et al. [67] reported that among 12 previously untreated children with IBD ultimately proven to have UC at colectomy, 2 had normal endoscopic appearances of the rectosigmoid, 1 had a normal rectal biopsy, and 6 others had unusually mild, patchy inflammation in their rectal or sigmoid biopsies. The subjects with atypical findings were collectively indistinguishable from their more typical UC counterparts with respect to clinical characteristics. Washington et al. [68], who compared individual morphological features in initial rectal biopsies from 53 children with UC to those in 38 corresponding adults, concluded that the pediatric biopsies were significantly less likely to show diffuse architectural abnormalities diagnostic of IBD (32 vs. 58%), but more likely to show atypically mild and focal inflammatory changes instead. However, the differences might have been attributable to a significantly shorter duration from symptom onset to diagnosis among the children (17.5 vs. 55 weeks, respectively) [68]. Robert et al. [64] observed fewer features of disease activity in colonic biopsies from 25 untreated children with new-onset UC than in biopsies from 15 adult controls. Likewise, Glickman et al. [69] observed relative sparing of the rectum in 23% of 73 children with untreated new-onset UC, complete rectal sparing in 3%, and little or no crypt distortion in 21%.

The impact of clinical variables on histology among children with new-onset UC has not been completely elucidated. Robert et al. [70] reported that a subgroup of 12 children aged 10 years and less had significantly fewer colonic features of disease chronicity, such as architectural distortion and plasmacytosis, than older children in their series, suggesting an age-related progression to the more conventional histology of UC.

Discontinuous Ulcerative Appendicitis and 'Isolated Cecal Patch'

Microscopic appendiceal inflammation has been reported in the colon resection specimens of 50 and 56% of children with CD and UC, respectively [71], similarly to the corresponding rates in adults [72–78]. 'Ulcerative appendicitis' may occur discontinuously in adults with UC who have distal or subtotal colonic disease and should not be misconstrued as evidence of CD [72–76]. Isolated inflammation of the cecum, or a 'cecal patch', that has been reported in endoscopic series in 26–75% of adults with distal

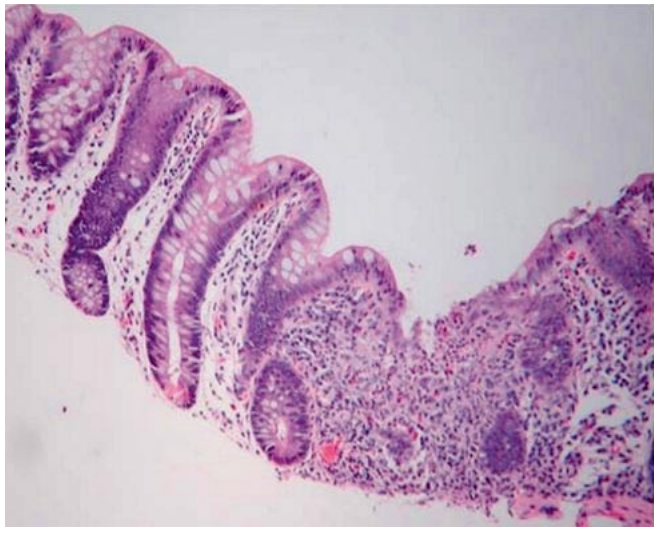

Fig. 4. Focal active chronic colitis. Although this pattern of mucosal inflammation is frequently observed in Crohn's colitis, in this case it occurred in a biopsy from the transition zone between diseased and normal mucosa in a child with UC.

or subtotal UC [79–82], but has not been studied specifically in children. It seems to be closely linked to ulcerative appendicitis, since the region of cecal inflammation nearly always includes the appendiceal orifice [78, 81, 83].

Giant Inflammatory Polyposis

Inflammatory polyps in IBD result from mucosal ulceration, often combined with an exuberant granulation tissue response. Rarely, collections of inflammatory polyps form segmental mass-like agglomerations of polypoid mucosa and entrapped feces, causing obstructive symptoms, anemia or overt bleeding and radiological features of a mass lesion (fig. 5) [84]. Pathologically, the involved segments may exhibit CD-like features such as deep fissuring and chronic transmural inflammation which originate within crevasses at the bases of the polyps even in cases of UC. The distinction between UC and CD in such resection specimens is therefore based on the pathology of the remainder of the colon. In the author's experience, most such cases occur in patients with UC and behave accordingly on follow-up. Although published descriptions of giant inflammatory polyposis in children are rare, a recent paper has described this disorder in two children with CD and cystic fibrosis, noting the presence of a copious mucinous component [85].

Backwash Ileitis

Nonspecific ileitis occurs in approximately 20% of colectomy specimens from adults with UC [86–88]. It typically accompanies pancolitis and extends continuously for a

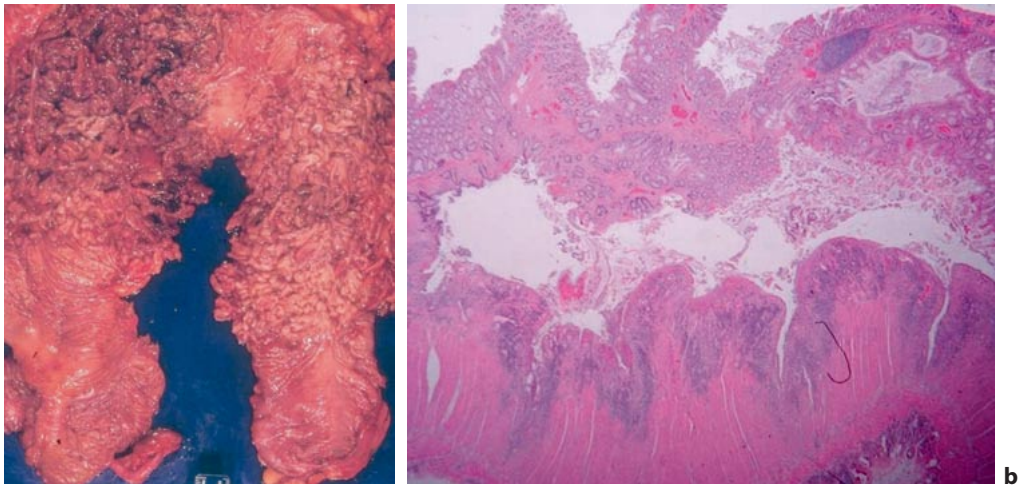

Fig. 5. Giant inflammatory polyposis in ulcerative colitis. **a** Gross specimen features two discrete colonic segments occupied by masses of finger-like polyps. **b** Microscopic view of polyposis shows diffuse ulceration, multiple deep fissures, and subserosal inflammation (lower right). Confluent inflammatory polyps form an overlying canopy. The fissuring and subserosal inflammation may closely mimic CD.

short distance from the ileocecal valve. The histology is nonspecific and comparable in severity to that in the cecum, featuring crypt inflammation, varying degrees of villous flattening, occasional erosions and epithelial regeneration [86, 87]. Pathological distinction from CD in resection specimens is generally straightforward, since transmural chronic inflammation and linear ulcerations are absent. However, endoscopic biopsies may be difficult to interpret, since CD-like features such as mucinous gland metaplasia and crypt distortion can also occur in backwash ileitis [87]. Ileitis in patients with sparing of the contiguous colon is rare and of uncertain significance [87].

Cryptolytic Granulomas

Ruptured crypt abscesses occur in many types of colitis, occasionally evoking a nonspecific granulomatous reaction that mimics the granulomas of CD [15, 89–91]. Referred to as cryptolytic granulomas, mucin granulomas, or crypt-associated granulomas, these lesions are usually but not invariably histologically distinctive (fig. 6). Helpful features include 'missing' crypts and persistence of microabscesses and xanthoma cells. Obviously, pathologists must avoid overinterpreting these nonspecific lesions given the serious implications of a misdiagnosis of CD.

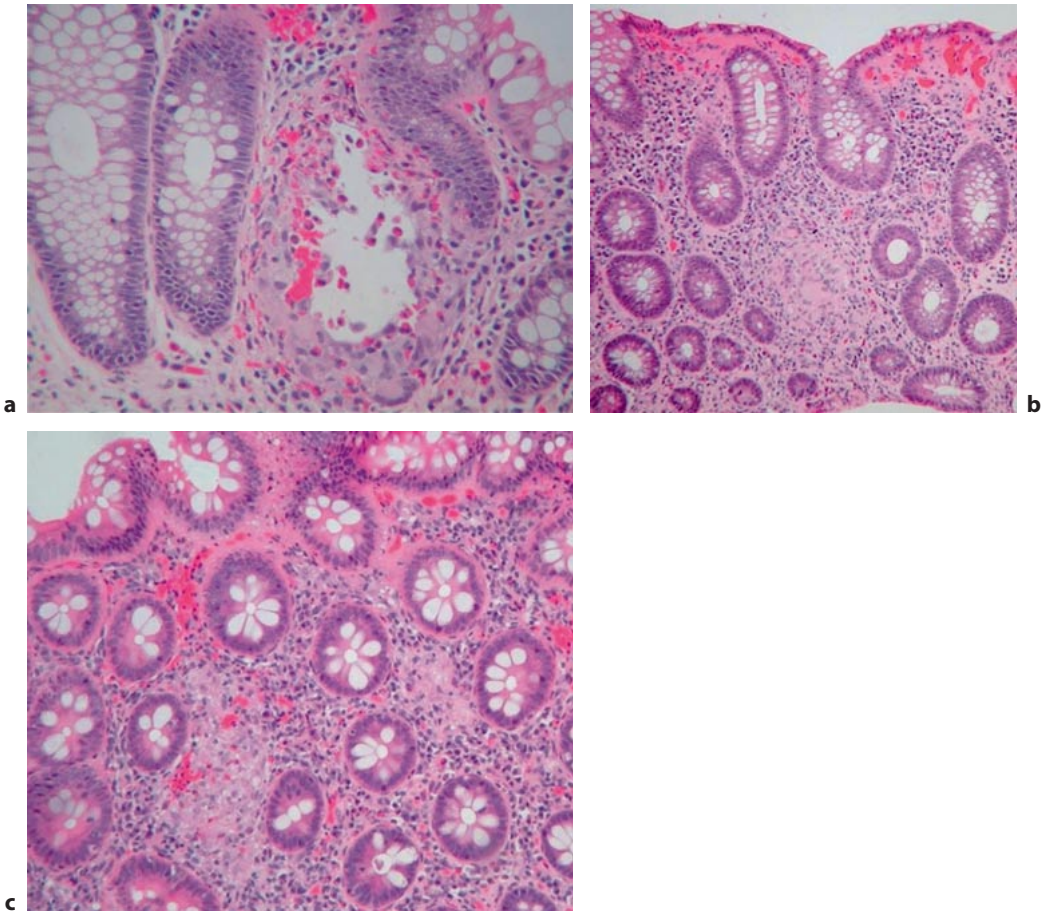

Fig. 6. Cryptolytic and Crohn's granulomas. Ruptured crypts in a variety of colitides can elicit the formation of nonspecific granulomas which should not be mistaken for those of CD. **a** Granulomatous inflammation surrounding the remnants of a ruptured crypt abscess. **b** Granuloma replacing a missing crypt. This pattern should be interpreted with caution to avoid a misdiagnosis of CD. **c** Crohn's granulomas situated in the lamina propria between intact crypts.

Upper Gastrointestinal Inflammation in UC

Endoscopic studies have reported nongranulomatous inflammation of the proximal gastrointestinal tract in children [30, 35, 36, 40, 41] and adults [92–94] with UC. Tobin et al. [30] reported esophagitis, gastritis and duodenitis in 72, 92 and 33% of their series of children with CD, respectively, but also in 50, 69 and 23% of those with UC. Others have reported otherwise unexplained focal active gastritis (also referred to as focally enhanced gastritis) in 52–65% of children with CD but also in 8–20% of children with UC [35, 36]. It follows that the mere presence of nonspecific inflammation in upper gastrointestinal biopsies is insufficient evidence on which to base a diagnosis of CD.

Superficial CD

CD rarely presents as a continuous mucosal-based enteritis or colitis, the latter closely resembling UC both clinically and pathologically [95–97]. In the author's series of 10 cases of 'superficial Crohn colitis,' which accounted for approximately 1% of colectomies evaluated from patients with IBD, all of the patients were initially diagnosed with UC on clinical and endoscopic grounds [95]. Pathologically, their colectomy specimens showed diffuse, mucosal-based, extensive or pancolitis, only 2 showing limited areas of transmural inflammation <5 cm in length, and 2 others accompanied by classical transmural CD in the ileum. The diagnoses were all based on the presence of granulomas, but these were usually sparse, i.e. 1 granuloma per 10 histologic sections in all cases but one. On follow-up, 3 of 4 patients who underwent construction of an ileoanal or Kock pouch experienced severe pouch symptoms requiring resection. Of the other 6 patients, 5 had severe CD-like complications including rectovaginal fistulae, abdominopelvic abscesses and perirectal fistulae. Although the reported cases all involved adults, the author has since encountered a similar case in a child.

IBD Mimics

Infectious Colitis

Acute infectious colitis is usually diagnosed on the basis of symptoms, laboratory findings, risk factors, a self-limited course, or response to antibiotics [98]. However, the distinction from IBD can be challenging in the face of unusually severe or persistent symptoms. Indeed, infections are a risk factor for the development of IBD [99] and may progress to IBD [100]. Microscopically, conventional self-limited bacterial and viral colitides are most distinctive during the first days after symptom onset [101]. Biopsies reveal edema, neutrophil infiltration of the lamina propria and the surface and crypt epithelium, and reduced goblet cell mucin. However, the crypt architecture and mononuclear cell gradient are preserved. Clinical remission, which typically will have begun by the second week, is accompanied by regeneration, and leads to complete normalization within 3–4 weeks [23, 101]. In contrast, biopsies taken shortly after symptom onset from patients who ultimately prove to have IBD show basal lymphoplasmacytosis, suggesting the existence of a preclinical phase of unknown duration [15, 23, 101]. Nonetheless, crypt distortion and disarray usually take several months to develop [23, 102].

Persistent infections may gradually overlap histologically with IBD, featuring basal mononuclear inflammatory cells or focal active inflammation but lacking significant crypt distortion or Paneth cell metaplasia [98]. As a rule of thumb, the neutrophils in such cases are found in both the lamina propria and epithelium, whereas in IBD they invade the epithelium more selectively [pers. obs.].

Juvenile Polyposis

Children with juvenile polyposis may present with IBD-like symptoms such as diarrhea, abdominal pain, rectal bleeding and anemia [103], and their colon polyps may be mistaken endoscopically for inflammatory polyps of IBD. The resemblance may be histological as well, especially among small polyps, potentially compounding the clinical misdiagnosis. If the intervening mucosa has been sampled, the pathologist may be alerted by a lack of expected colitic changes. However, any minor abnormalities such as mucosal expansion, nonspecific inflammation or bifurcated crypts may be taken to support the erroneous diagnosis [104]. Accordingly, the pathologist should not report a firm diagnosis of IBD unless there is clear-cut evidence, such as diffuse inflammation and crypt distortion in the intervening mucosa.

Systemic Vasculitides

Children with systemic vasculitides may present with clinical features suggestive of IBD including diarrhea, weight loss and abdominal pain, as well as endoscopic evidence of intestinal inflammation. Accurate diagnosis is important, since untreated vaculitis may carry significant morbidity and mortality. On the basis of a clinical series of 10 cases, Brogan et al. [105] recently reported several criteria that may be helpful in avoiding misdiagnosis. These include extraintestinal manifestations disproportionate to the severity of colitis (e.g. rash, myalgia, renal dysfunction, polyarthritis, testicular pain), visceral angiographic evidence of vaculitis, biopsy evidence of vasculitis from sites of extraintestinal involvement, and gross vasculitic foci on endoscopy. Endoscopic biopsies were less sensitive, revealing fibrinoid vascular necrosis in only 1 of 10 cases and otherwise no significant changes or mild chronic nonspecific inflammation.

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Early-Onset Inflammatory Bowel Disease: Infant, Toddler, and Pre-School

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Abstract

Early-onset inflammatory bowel disease (IBD) has a distinct phenotype and should be considered as a specific entity. IBD of very early onset includes ulcerative colitis, Crohn's disease, and a relatively high proportion of indeterminate colitis. Overall, the disease manifestations are primarily colonic, with severe perianal disease, and severe extra-gastrointestinal manifestations. Early-onset IBD presents with very severe manifestation and guarded prognosis with life-threatening signs and symptoms and needs an aggressive therapeutic approach. Early-onset IBD is unique in its association to metabolic diseases, neutrophil defects, and immunodeficiency states, chronic granulomatous disease, neutropenia, cyclic neutropenia, Wiskott-Aldrich syndrome, leukocyte adhesion defect, hypogammaglobulinemia, common variable immunodeficiency, and other immunodeficiency states. Early-onset IBD can be associated with Hermansky-Pudlak syndrome, glycogen storage disease type 1B, primary defects in tryptophan handling, and familial Mediterranean fever. It is controversial whether the ensuing Intestinal inflammation in metabolic disorders, neutrophil defects and immunodeficeincy states are a form of Crohn's disease and ulcerative colitis, or a presentation of the primary disease. The very early-onset IBD presents a unique opportunity to study the impact of immunological status, neutrophil role, phagocytic function, gut microflora, metabolic pathways, and environmental factors on the genetic predisposition and the natural history of IBD.

Early-onset inflammatory bowel disease (IBD) is referred to infants, toddlers and preschool children under the age of 6 years. As many as 25% of the patients diagnosed with IBD will present before the age of 20 years [1]. Study of 1,370 children diagnosed with IBD [2] revealed 15.4% (211 patients) diagnosed under the age of 6 years. Early-onset IBD has a distinct phenotype and the differences from adult IBD might be considered as a specific entity [3, 4].

Although less prevalent in infants and very young children, a number of case reports and two series documented the onset of IBD at a very early age [2–11]. The incidence of IBD in children in general and Crohn's disease (CD), specifically, has increased over the past two decades [1].

Early-onset IBD represents a unique cohort of patients that can and should be evaluated in relation to genotype-phenotype presentation, innate host-immune responses, environmental influences on disease development, natural history of the disease and the impact of immunomodulatory agents. For early-onset IBD, there are several lines of evidence supporting the impact of age of onset, heritability, environmental variance, etc. In early-onset IBD, there is a higher proportion of those reporting a family history of IBD, increased linkage evidence at the IBD1and IBD5 loci and a mutation for nucleotide-binding oligomerization domain 2 (NOD2) [12].

There are phenotypic differences in early-onset ulcerative colitis (UC) as compared to adult-onset UC. -Early-onset UC presents an extensive disease and a rare occurrence of proctitis. In early-onset CD, there is a preponderance of colonic disease and perianal abnormalities such as fistulae as well as more severe inflammatory disease presentation. Early-onset IBD is associated with immunodeficiency states, neutrophil defects and metabolic diseases, higher anti-*Saccharomyces cervesiae* antibodies (ASCA) seropositivity rates, and a more rapid and progressive disease course [3, 4, 13].

The prevalence of indeterminate colitis (IC) in early-onset IBD is high. The IC might rapidly progress to pancolitis with a prevalence that is higher than that observed in adults [14]. However, sometimes it may recover spontaneously.

The long-term outcome of early-onset classical IBD is especially important because of the relative risk of cancer in prolonged and early-onset IBD. This could be due to either the disease itself or be secondary to the prolonged treatment with chemotherapeutic agents and biological therapeutic modalities, or both [15]. Therefore, surveillance for potential cancer markers and the cumulative effects of immunomodulatory agents can help in the prolonged management of early-onset IBD.

The etiology of IBD is complex and involves both genetic and environmental triggers including but not limited to defects in bacterial clearance, defective mucosal barrier and persistent dysregulation of the immune response to commensal gut microflora. Early-onset IBD might be instrumental in elucidating issues related to altered immune homeostasis within the intestinal mucosa in genetically predisposed individuals. It was shown that in patients with very early-onset IBD in the first year of life, 5 of 10 patients were treated extensively with antibiotics prior to the diagnosis which raises issues of uncontrolled inflammatory response that might be triggered by deleterious changes in the intestinal microflora early in life [9], or to the specific infectious agent for which antibiotics has been prescribed. The question of infections perinatally and early in life can be tested in relation to some infections that are possible risk factors in IBD like *Mycobacterium paratuberculosis* infection, or wild-type measles infection [9].

Genetics

CD and UC are related polygenetic diseases, sharing some but not all susceptibility loci [12, 16–19].

Familial occurrence of CD is well established, e.g. in monozygotic twins 44–58% have disease concordance in contrast with up to only 3.8% in dizygotic twins.

Familial occurrence in UC is 14–19% in monozygotic twins and up to 5% in dizygotic twins [1].

The IBD1 gene is a NOD2 caspase recruitment domain 15 (CARD15). The importance of germline variation of NOD2/CARD15 in CD disease, the putative function of the NOD2/CARD15 protein, and the mechanisms whereby NOD2/CARD15 dysfunction affects intestinal inflammation of CD are still not clear. It is apparent that NOD2/CARD15 is an intracellular receptor for muramylpeptide, common to the Gram-positive and Gram-negative bacterial cell wall, indicating a primary dysfunction of the innate immune system in the pathogenesis of IBD [20].

Recent studies have identified the IL-23 receptor gene, ATG16L1, and the immunity-related GTPase family M gene as determinants of susceptibility to CD [19].

Whereas some genes influence disease susceptibility, others modulate the course of the disease. Mutations in certain genotypes are associated with an increased incidence of growth failure in CD [18,19].

A recent multicenter study [21] of pediatric-onset IBD identified a previously unreported loci on chromosome 20q13 (rs2315008 [T] and rs4809330 [A] and chromosome 21q22 (rs2836878 [A]) located close to TNFRSF6B and PSMGI genes, respectively [21].

There is evidence that genotype and allele frequencies may be different in the early-onset IBD population for some genes (e.g. NOD2) and similar to adult populations in other genes (IL23R, IBD5). Data also suggest a protective effect of the disc's large homolog 5 genes in young females, partially explaining the higher male to female ratio in early-onset CD. On the other hand, early-onset CD genetic variants in NOD2 are associated with markers of CD severity [15–18].

Mutations not in linkage with disequilibrium that has background mutation P268S of the NOD-2/CARD15 gene might play a role in early-onset disease [17, 18]. The younger the age at diagnosis the more patients presented with colonic disease. Also, more TLR4Asp299Gly variants were found when the age of onset was younger [17, 18].

For knowledge of individual genetics of early-onset IBD patients, functional genomic, epigenomic, microbiomic states, environmental factors – combined with an increasingly high-resolution view of molecular, cellular, and organ system biology – should provide improved knowledge of the disease mechanism and offer predictive methods for disease course and severity.

Epidemiology

The incidence of IBD in general and CD specifically has increased over the past two decades in both children and adults [1].

An epidemiological study of 1,370 children with IBD from six pediatric centers in the USA, revealed 87 infants and toddlers (6.1%) under the age of 3 years.

Overall, a positive family history with IBD was found in 29% of pediatric patients [2]. The proportion of early-onset IBD with affected first-degree relatives was significantly greater than in older children. The infants and toddlers up to 3 years with IBD have a very high (44%) percentage of first-degree relatives with IBD [2].

More than 63% of children younger than 8 years of age had isolated colonic disease [2]. Conversely to those 8 years and older, only 35% had isolated colonic disease ($p > 0.001$). The distribution of CD lesions in the gut tended to differ according to age at diagnosis. Patients with isolated colonic CD comprised 31% of the children younger than 6 years, in comparison to 20% of children from 6 to 12 years [2]. Male predominance of 63% in preschool-aged children with IBD was significant specially in the youngest groups up to 2 years of age.

A role of breastfeeding in preventing IBD was suggested in the past. A meta-analysis study of all published studies [22] has concluded that breastfeeding has a protective effect on the risk of developing IBD. The risk of CD decreased by 33% and the risk of UC decreased by 23%. Klement et al. [22] emphasized that of 17 published studies, only 4 were of high methodological quality. Early-onset IBD in a large prospective cohort study of a group of infants with several risk factors might be instrumental in answering this important question.

Clinical Presentation

Early-onset IBD in infants younger than 2 years of age has usually a very severe presentation and prognosis and needs an aggressive therapeutic approach. It is associated with immunodeficiency in a high proportion [3, 4].

There are various specific disorders in early childhood presenting with IBD (table 1).

A unique feature of early onset is the association with genetic disorders of phagocytic function such as chronic granulomatous disease (CGD) [23], genetic disorders of neutropenia (severe congenital neutropenia, glycogen storage disease (GSD) type 1B [24]), cyclic neutropenia and neutropenic enterocolitis that is most often associated with leukemia and its treatment. In addition, immunodeficiency disorders such as Wiskott-Aldrich syndrome, leukocyte adhesion defect [25], hypogammaglobulinemia and common variable immunodeficiency may present as IBD [26]. Colonic ulcers may occur during the neutropenic period [23]. CGD is often a chronic relapsing and remitting condition with two overlapping phenotypes, UC and CD [23].

In one series approximately 45% of patients with early-onset IBD were diagnosed with Wiskott-Aldrich syndrome, CGD and hypogammaglobulinemia [23, 27]. There are reports [23, 27] of different genetic neutrophil defects associated with colitis. The leukocyte adhesion defect (LAD)-1 is characterized by absent or dysfunctional

Table 1. Diseases associated with early-onset IBD

Neutrophil defects
Severe congenital neutropenia
Cyclic neutropenia
Leukocyte adhesion defect
Phagocytic defect
Chronic granulomatous disease
Immunodeficiency disorders
Common variable immunodeficiency
Wiskott-Aldrich syndrome
Hypogammaglobulinemia
Glycogen storage disease type 1B (neutrophilic defect)
Hermansky-Pudlak syndrome (albenism, hemorrhagic diathesis, ceroid deposits)
Defects in tryptophan handling
Hartnap disease
Kynurenine hydroxylase defect
Niacin deficiency
Hirschsprung's disease (congenital aganglionosis)
Ulcerating enterocolitis
Familial Mediteranean fever

β_2-integrin leading the defective chemotaxis, adherence, phagocytosis and bacterial killing. This disease presents with extensive inflammation and ulceration of the right colon and terminal ileum, leading to adhesions and strictures [25], which might resolved after bone marrow transplantation.

Granulomatous colitis is associated with Hermansky-Pudlak syndrome (albinism, hemorrhagic diathesis and pigmented reticuloendothelial cells) [28]. Anal pathology can be severe. Fissures, tags and hypertrophy of perianal skin are common [28]. It is a lysosomal storage disorder and the question is how the production of ceroid deposits is associated with lesions that histologically present and act like CD.

Defects in tryptophan metabolism resulting in niacin deficiency (nicotinic acid or nicotinamide) can be associated with colitis indistinguishable from UC. How niacin deficiency results in colitis is an open question. Tryptophan metabolites are central in a large number of biochemical reactions. Thus, a metabolic disorder like a primary defect in trytophan handling, either through malabsorption (Hartnup disease) or tryptophan metabolism (kynurenine hydroxylase defects) [29], might have a role in causing colitis. It is a matter for debate whether the ensuing inflammation

in metabolic disorders is, in some cases, a form of CD or UC or whether the colitis is unique to the underlying disease in every case.

Enterocolitis secondary to an established disease process like Hirschsprung's disease reveals histological features of multiple crypt abscesses, fibropurulent debris and mucosal ulcerations commensurate with severe colitis [30]. Furthermore, the morphological features of enterocolitis persist in most of the cases even 1 year after the excision of the aganglionic part and resolution of clinical enterocolotis [30, 31]. The etiopathogenesis of enterocolitis is presumably an infective agent, or infants with Hirschsprung's disease may have a defect in mucosal defense. Whether the enterocolitis is due to nonimmunological mucosal defenses [22] or there is a defect in cellular immunity [22], an additional possibility is the potential role of a compromised circulatory system [33].

A severe disease presenting as early-onset IBD is ulcerating enterocolitis. Ulcerating enterocolitis in infancy might be indicative of underlying immunodeficiency or immunodysregulation. A group of such infants suffers intractable ulcerating enterocolitis in which there is a panenteritis with marked oro-anal involvement and deep flask-like mucosl ulcers throughtout the colon. These infants have a high risk of developing lymphomatous proliferation partly due to underlying immune dysregulation [34].

The most relevant question in early-onset IBD is to find out if children with IBD and associated diseases have a chronic enterocolitis as a manifestation of the primary disease or that we are dealing with an IBD associated with another disorder.

An increasing number of studies indicated that early onset of classical IBD is more common and severe in patients with familial Mediterranean fever (FMF) [35].

Especially in this age group, one should search for an infectious agent as the symptoms and signs at presentation of early-onset IBD can be attributed to infection by micro-organisms such as *Shigella, Salmonella, Campylobacter, E. coli, Yersinia enterocolitica, Entameoba histolytica* and *Cryptosporidium*.

Food-allergic colitis presents with bloody diarrhea and often with mucous, and can be confused with early-onset IBD [36]. In cases of early-onset IBD allergic colitis was considered in 37% of patients and caused a significant diagnostic delay [36].

Another entity that may mimic IBD presentation even in young childhood is eosinophilic gastroenteritis. The clue to the accurate diagnosis of the latter is the abundance of eosinophils in the intestinal wall.

Early-onset IBD is a very severe disease. 25% of patients required total parenteral nutrition, 12% underwent colectomy and 18% died before the age of 2 years [37].

CD should be suspected in any infant or toddler presenting with intractable diarrhea of infancy, prolonged bloody diarrhea, failure to thrive, malnutrition, anemia, hypoalbuminemia and severe perianal disease that includes ulcerations, mucosal and skin tags, perianal abscesses, fistulae and fissures. Some present with severe aphthous stomatitis [38, 39]. Pyoderma gangrenosum has also been described more frequently in patients with early-onset CD [40].

The severity of early-onset IBD and the indication for surgery should be looked at and correlated with laboratory findings of hypoalbuminemia, leukocytosis, thrombocytosis or thrombocytopenia, elevated C-reactive protein ANCA and ASCA levels. The severe manifestations early in life with a primary colonic disease, perianal abscesses, fistulae and strictures are more prevalent in early-onset IBD. The poor growth of early-onset IBD can be due to the severity of presentation early in life and improving growth and nutrition are key issues in the management [41].

Children under 8 years of age are much more likely to have isolated colonic disease than later in childhood [2–4]. This finding can reflect either a higher prevalence of IC and UC or more frequent isolated colonic involvement in children with CD. The finding of more frequent isolated colonic disease in early-onset CD was emphasized in several studies [2, 3, 37–41]. Early-onset IBD is characterized by a 'panenteric' phenotype with less-isolated ileal disease in comparison to adults [41]. UC presents with extensive colitis in 82% of young children compared to 48% in adults. Also early-onset IBD children progressed to develop extensive colitis during follow-up more than adults. It is possible that the high proportion (one-third) of early-onset IBD diagnosed as IC [2–4, 41] might represent an evolving form of IBD that presents early in life, prior to a definitive disease phenotype, especially during infancy and toddler period.

Treatment

Most of the patients with early-onset IBD before the age of 2 years require an aggressive, multi-drug immunosuppressive approach including corticosteroids, chemotherapy and anti-tumor necrosis factor-α (TNFα) [42–45].

Total parenteral nutrition and colectomy have been required in a high percentage of infants with early-life IBD [42–45].

Treatment with corticosteroids is needed in early-onset IBD. However, after 1 year 58% of pediatric patients with CD and 43% of pediatric patients with UC are steroid dependent or require surgery. These findings emphasize the severity of early-onset IBD and the need for steroid-sparing medications and specific immunomodulators [42–45]. Although corticosteroids and 5-acetylsalicylic acid are reported to be useful in CD patients, most of the patients diagnosed with IBD very early in life, fail to respond, and immunosuppressive agents such as azathioprine, 6-mercaptopurine or cyclosporine and TNF like inflixamab and thalidomide were utilized. The standard dose of AZA 6-MP may not be adequate for IBD patients 6 years of age and younger. Closely monitored dose escalation beyond the standard dosing range is effective and well-tolerated. Pediatric CD was characterized by frequent occurrence, with time of a severe phenotype with extensive complicated disease. Immunosuppressive therapy may improve the natural history and decrease the need for performing surgery. Infants less than 6 months of age presenting with infantile pancolitis UC were associated with

FMF gene mutations and treated with corticosteroids, azathioprine and 5 ASA but did not improve until colchicine, an anti-FMF drug was added [35].

Risk factors for surgery in early-onset IBD include leukocytosis, hypoalbuminemia and ASCA, ANCA positivity, as well as infant onset, poor growth, abscesses, fistulae and strictures [37].

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Radiological and Imaging Features

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Abstract

Imaging offers several modalities in the assessment of pediatric inflammatory bowel disease. These modalities are represented by conventional barium studies, sonography and cross-sectional imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI). We briefly review the technical features of these techniques and our findings in cases with pediatric Crohn's disease, ulcerative colitis and indeterminate colitis. Choice of the appropriate imaging technique depends on the clinical setting. Thanks to technical developments, sonogaphy, CT and MRI now play an emerging role in the diagnostic process in children as well as in the adult population. Nevertheless, conventional barium studies still play a role in the assessment of the gut since they are widely available, easily performed and clearly depict superficial changes in the mucosal layer of the gut. Cross-sectional imaging like sonography and MRI can easily depict mural thickening of Crohn's disease and offers a noninvasive and ionizing-free imaging modality for assessment of the small bowel. Especially MRI with adequate intestinal distention can provide us with excellent information on the presence, extension and activity of Crohn's disease. Nevertheless, MRI requires patient compliance that is not always easy in children.

In the past, diagnostic imaging of the gut was performed using conventional barium X-rays. However, especially in small bowel diseases, imaging techniques have changed dramatically in the last decade since the development of cross-sectional imaging, i.e. ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) [1–4].

The major advantage of cross-sectional imaging, either US, CT, or MRI, compared to conventional barium X-rays, is the possibility to achieve direct visualization of the bowel wall. This means a complete change in the diagnostic approach: from analysis of the colonic surface to direct evaluation of parietal thickness, and evaluation of different layers as well as assessment of peri-intestinal involvement. The analysis of these

cross-sectional images offers a unique opportunity for the diagnosis and follow-up of inflammatory bowel diseases (IBDs).

Cross-sectional imaging now offers new study techniques, such as small intestine contrast-enhanced ultrasonography (SICUS), CT and MR enterography and enteroclysis [6, 7]. Developed originally in adult populations, these tests have been subsequently optimized in children with similar results [8–10]. Consequently, the spectrum of imaging tests available for the evaluation of the small bowel is extremely broad.

From a clinical point of view, it is still unclear which of the tests represents the ideal approach to gut imaging. However, it is widely accepted that the imaging examinations will differ based on the intestinal segment to be explored, the clinically suspicious, and, most important, on whether the clinical presentation occurs in an acute or non-acute clinical setting. Moreover, pediatric imaging presents some challenging issues compared to the adult population, such as patient cooperation (not always achievable in children) and reduction of radiation dose exposure. For this reason, US and MRI should always be preferred over CT or conventional X-rays whenever possible; on the other hand, in acute clinical settings, CT still remains the technique of choice.

Small Bowel Imaging: Diagnostic Techniques

Several diagnostic options are available for evaluation of the small bowel: conventional barium X-rays, US, CT and MRI.

Conventional Barium X-Rays

Conventional barium X-rays include small bowel follow-through (SBFT) and enteroclysis (SBE). The difference between them is the method by which intestinal distension is achieved.

Indeed, SBFT is performed using oral administration of barium sulphate for bowel distension and opacification. This classic single contrast study is very easy to perform. After barium administration, several films are acquired during the transit of barium sulphate through the small bowel. Different projections, sometimes with abdominal compression, are obtained in order to have a full evaluation of overlapped intestinal loops [11].

Conversely, SBE is a double-contrast study of the small intestine. Bowel distension is obtained by the administration of contrast through a naso-jejuneal (NJ) tube. The placement of a NJ tube, under fluoroscopic guidance, represents the most critical step in terms of patient compliance and also requires an expert operator, particularly in children. A small amount of high-viscosity barium sulphate is administered through the NJ tube, followed by a continuous and high-flow enema with a negative, nonabsorbable agent, such as hydroxymethylcellulose (or room air). The negative contrast

facilitates the rapid progression of barium sulphate, provides an excellent and homogeneous dilatation of the entire small intestine, and offers an optimal evaluation of the mucosal surface.

Obviously, SBE is more invasive compared to SBFT, although it is one of the most sensitive imaging modalities for the assessment of tiny mucosal abnormalities. However, both SBFT and SBE, with different accuracies, allow an evaluation of mucosal abnormalities as well as an excellent detection of luminal strictures and fistulas. However, only inadequate and indirect information is available on the small bowel wall [12].

Since inflammatory diseases that affect the small bowel are typically characterized by a transmural inflammatory process, the evaluation of the mucosal surface only, as in conventional barium studies (SBFT and SBE), is sometimes not satisfactory at all.

On the other hand, using cross-sectional imaging methods, an accurate assessment of the bowel wall and the surrounding fat tissue is possible. This is the major reason for the choice of cross-sectional imaging rather than conventional barium studies for the evaluation of IBD [13].

Ultrasound

With US, two different approaches are available: study of the bowel loops with no intestinal distension or administration of oral contrast agents for bowel distension. The first approach, also called trans-abdominal US (TUS), is obviously less sensitive, especially for the evaluation of jejuneal loops, although a good assessment of the terminal ileum is often possible [14]. The other approach is represented by the so-called small intestine contrast US (SICUS) [15]. With SICUS, an oral contrast agent, such as polyethylene glycol, is administered orally in order to distend the bowel loops; then, a manual retrograde small bowel loop tracking is performed, moving from the cecum to the jejunum. This approach offers clearly detailed information on the wall and lumen of the small bowel loops. However, the expertise of the sonographer is important to achieve optimal results.

Moreover, SICUS is a time-consuming examination and reflects some of the general limits of a US examination, such as the poor comparability of examinations and the poor panoramic view of images. Some authors have proposed the use of an intravenous microbubble US contrast agent for the definition of bowel wall vascularization in the adult population; however, poor experiences with this technique have been reported in children.

Computed Tomography

With CT, both approaches have benefitted from the recent development of MDCT.

Thanks to the isotropic acquisition afforded by the latest MDCT scanner generation (16-, 32- and 64-rowMDCT), excellent image quality of coronal reformations is achievable.

The use of intravenous iodinated contrast medium is necessary to better delineate the small bowel mucosa with respect to the bowel lumen, and to assess the degree of disease activity [16].

The high quality of coronal reformations is quite an advantage for bowel studies because it enables excellent demonstration of the complex bowel anatomy.

Indeed, since the bowel wall has an unpredictable orientation through the space, the chance to reformat native axial images in the desired plane with the same image quality, enables radiologists to easily evaluate the entire small bowel.

However, the cost of the excellent spatial resolution of MDCT is somewhat offset by the high radiation dose delivered to patients.

Therefore, the ionizing radiation hazard related to CT enterography and CT enteroclysis should be considered too high a risk, especially in the pediatric population.

Magnetic Resonance Imaging

MRI of the small bowel presents several benefits with regard to the other techniques.

First, MRI is a safe, ionizing radiation-free, repeatable, and reproducible test. MRI is definitely less operator-dependent than US.

The most important issue is that MRI provides multiplanar images with high contrast resolution for soft tissue, thus enabling differential diagnosis between edema and fibrosis that represents a key issue in patients who suffer from CD.

However, MRI also carries some limitations. First, MRI of the small bowel requires optimal MRI scanners with 'fast imaging' capabilities and a certain degree of operator experience. Moreover, a rigorous technical approach should be used to obtain satisfactory results [17, 18].

A crucial issue for MR imaging of the small bowel is the intestinal distension that can be obtained either by means of oral administration (MR enterography study) or by using a nasojejuneal tube (MR enteroclysis).

Obviously, the degree of intestinal distension with enteroclysis is superior with regard to the oral approach, and the true benefit of this excellent distension in CD patients should be considered in a cost-benefit analysis.

Therefore, for IBD, when inflamed loops aid in the intestinal distension, the oral approach may be considered satisfactory for most patients. In pediatric patients, the relative noninvasiveness of MR enterography is an important issue compared to MR enteroclysis.

Therefore, a reasonable approach is to use MR enterography in children whose symptoms are suspicious for ileal CD and in their follow-up, while in adult patients

with suspected nonocclusive small bowel lesions, MR enteroclysis or CT enteroclysis is the preferred method.

Among the choice of oral contrast agents to be used for MR enterography in children, most authors agree that biphasic agents, such PEG4000 or other unresorbable water solutions [19–20], are preferred.

The use of intravenous gadolinium chelates is necessary to evaluate the degree of disease activity.

The main limitation of small bowel MRI in children is poor patient cooperation. Therefore, it seems reasonable to use this test only in children of school-age or older, avoiding this approach in patients under 5 years old.

Imaging of Ileal Crohn's Disease

For ileal CD in children, imaging methods should be able to answer the following questions arising from the clinical arena:

Is there any ileal localization of CD? Can the affected segment(s) be localized? Are there any complicating lesions such as strictures, abscesses, or fistulas? What is the inflammatory disease activity?

Not all imaging tests are able to answer all the above-mentioned questions. For instance, conventional barium studies may answer the localization and extension of ileal disease questions, and also questions about the presence of strictures or fistulating CD, but little information is available about disease activity and abscesses.

The imaging test that can answer these questions without invasiveness or ionizing radiation exposure is MR enterography [21].

Considering the pathological and biological characteristics of ileal CD, we will describe the appearance of ileal CD with the different imaging techniques.

Conventional Barium Studies

Conventional barium studies, especially using a double-contrast approach, allow a high spatial resolution able to detect tiny aphthous abnormalities of the mucosa (fig. 1). The classic appearance of deep longitudinal ulcers and hypertrophic mucosa leads to the well-known cobblestone appearance on the mucosal profile at X-ray studies (fig. 2).

The early stages of chronic ileal inflammation in CD are characterized by thickening and a slight nodularity of the circumferential folds on conventional barium studies, due to submucosal edema and hypertrophy of the intramural lymphoid tissue (fig. 3) [22]. Although this may represent an early finding in patients with CD, this nodular appearance of the mucosal layer at the level of the terminal ileum due

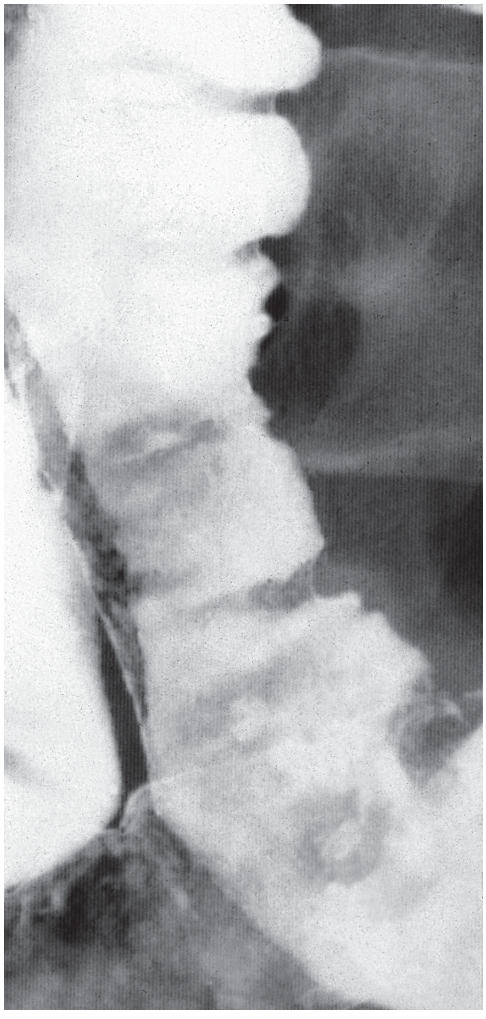

Fig. 1. Conventional X-ray with small bowel follow through. Image shows typical mucosal alterations with a target appearance consistent with multiple aphtoid lesions in the early stage of ileal CD.

to enlargement of the submucosal lymphoid follicles may also be present in healthy children.

Therefore, the lymphoid follicular pattern of the terminal ileum on barium studies should not be used as a specific early marker of CD.

More specific signs are represented by the presence of mucosal barium collections, up to 5 mm, that represent aphtoid ulcers.

The presence of early inflammatory changes of the terminal ileum, such as the presence of a few aphthoid lesions, is not a specific sign of CD.

The differential diagnosis in such cases during childhood comprises the so-called backwash ileitis, a nonspecific form of mild inflammation of the terminal ileum due to incompetence of the ileocecal valve and the reflux of cecal material into the small bowel.

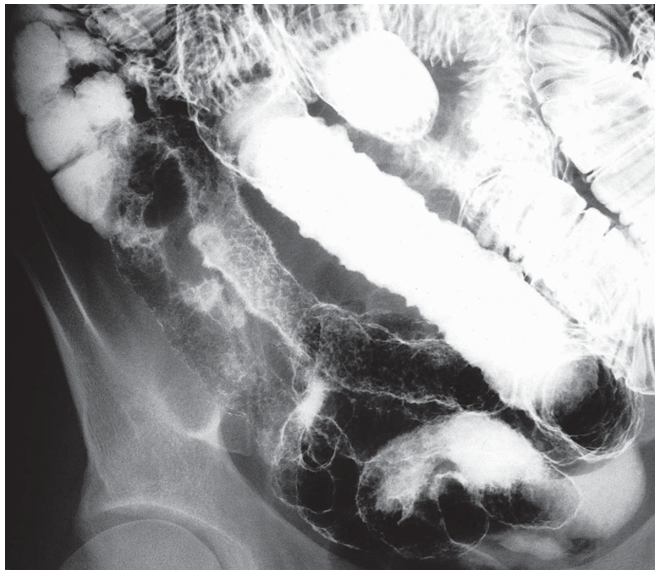

Fig. 2. Double-contrast enteroclysis. Image shows the classic cobblestone appearance of the mucosa due to the presence of deep longitudinal and transversal ulcers and hypertrophic mucosa.

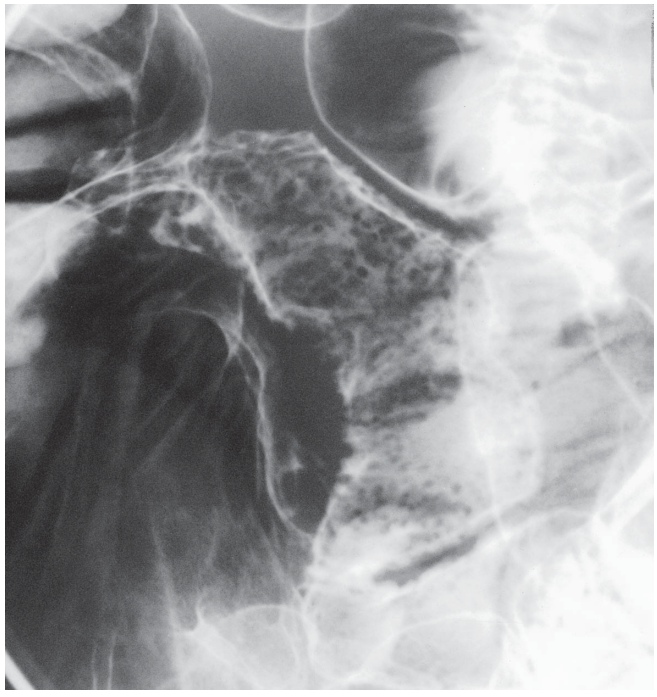

Fig. 3. Double-contrast enteroclysis. Image shows multiple nodules of the mucosal profile, indicative of hypertrophy of the submucosal lymphoid tissue. This kind of nodular pattern of the mucosa is also known as a lymphoid pattern and may also be observed in healthy children.

For jejuneal localization of CD, early findings on barium studies are characterized by blunting, flattening, and distortion of the valvulae conniventes and 'string sign' appearance.

In the more advanced phase of the disease, the transmural inflammatory changes in the bowel wall may result in more specific findings on barium studies.

These findings are represented by the presence of serpiginous longitudinal and transverse ulcers separated by an area of edema that leads to the classic cobblestone appearance of the mucosal profile.

Rigidity and straitened loop with luminal narrowing are the unique indirect signs of bowel wall thickening detectable with X-rays.

However, the separation and displacement of loops may represent the indirect signs of the so-called fibrofatty proliferation of mesenteric fat. Of course, localization of the affected loops represents one of the most important characteristics of ileal inflammation with discontinuous bowel involvement and intervening normal areas.

The presence of strictures is very-well-depicted on conventional barium studies thanks to the 'string sign'. This sign is an expression of marked irritability and spasm. The area of narrowing relaxes when a peristaltic wave approaches the affected loop and it is useful in differentiating it from a stricture. The 'string sign' is usually found in the terminal ileum and represents the intense spasm associated with ulceration.

Tiny linear images with barium density in the extraintestinal space represent the direct visualization of a fistulous track, while the presence of abscesses is sometimes challenging with conventional barium studies (fig. 4).

Cross-Sectional Imaging

Although cross-sectional imaging does not have adequate spatial resolution to depict tiny mucosal alterations such as aphtoid lesions, deep ulcers and cobblestoning may be easily recognized. Moreover, the presence of ulcers is a criterion for the definition of the activity status of CD.

One of the major pathological characteristics of CD is transmural chronic inflammation of the bowel wall. This pathological feature corresponds in cross-sectional imaging techniques to an increased bowel wall thickness. US, CT and MRI can easily reveal the exact bowel wall thickness. The threshold for normal bowel when a correct distension is obtained is 3 mm.

Cross-sectional imaging also allows the definition of the internal structure of the bowel wall. In other words, sonography and MRI, in particular, are able to distinguish several layers within the thickened bowel wall that correspond to mucosa and submucosa and the muscular layer. A modification of the normal pattern of bowel wall stratification may be used to identify inflammatory changes.

Sonography

The classic appearance of an intestinal loop affected by CD at sonography is a thickened, circumferential diffusely hypoechoic bowel wall with loss of normal layering due to intramural edema and/or fibrosis (fig. 5).

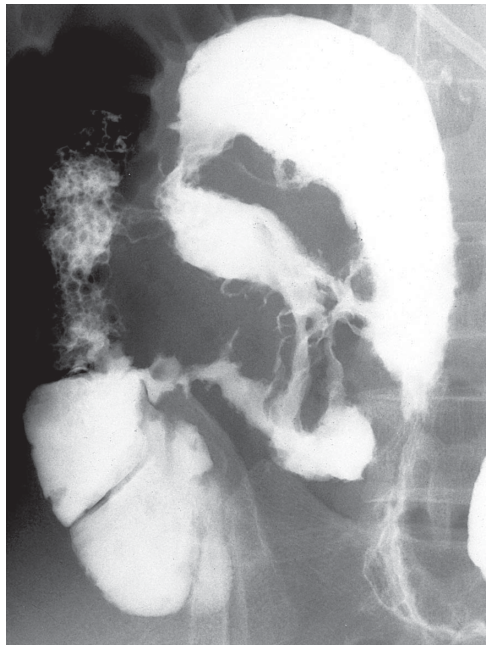

Fig. 4. Conventional small bowel follow through. Multiple barium-filled sinus tracts are visible as a direct sign of entero-enteric fistulas.

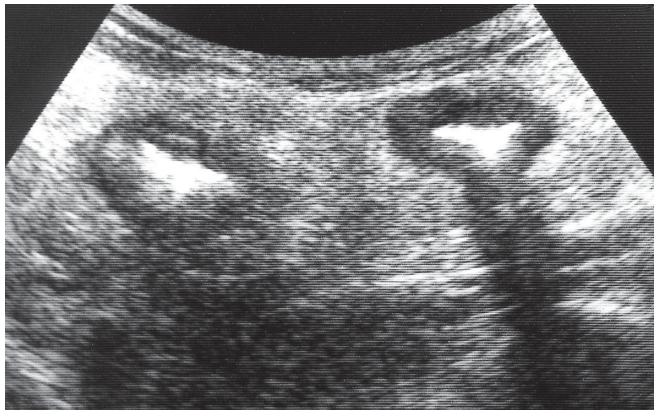

Fig. 5. Sonography. Image shows wall thickening of bowel loops with loss of the normal stratification of the bowel wall in a patient with active CD. Echogenic gas with some acoustic posterior artifacts fill the bowel lumen.

Sonography is able to dynamically analyze intestinal peristalsis along the affected loops. Therefore, one of the sonography criteria by which to distinguish an organic stricture from a functional lumen reduction is the observation of bowel peristalsis and the evaluation of bowel wall compliance. The evaluation of mesenteric tissue using sonography is not always satisfactory due to poor sonographic windows that limit the evaluation of the deep abdominal structures. However, in case of abscesses, the presence of an abdominal fluid collection may be easily detected with US (fig. 6) [23]. The evaluation of fistulas using sonography does not present satisfactory results with regard to the evaluation of disease activity.

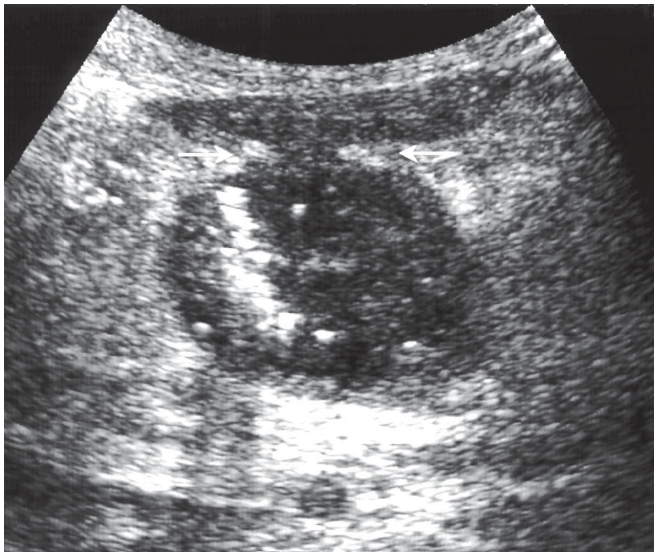

Fig. 6. Sonography. Abdominal abscess in a child suffering from CD. A short and wide sinus tract (arrows) originates from an inflamed loop and penetrates a large abscess collection, which presents well-defined margins, a heterogeneous hypoechoic structure, and numerous gas bubbles.

Initial and encouraging results have been described in this field using power Doppler and intravenous administration of ultrasonography contrast agents that allow the detection of different patterns of bowel wall enhancement during the arrival of microbubbles; however, the experience in this method is very limited, especially in children. Another limitation of sonography in the evaluation of the small bowel is that US does not allow a panoramic visualization of the jejuneo-ileal loops, and an accurate and panoramic demonstration of affected segments is crucial, especially for surgical planning.

Computed Tomography

The need to obtain a panoramic visualization of the small bowel loops is completely accomplished by CT, especially using the last generation of MDCT, which allows excellent quality of coronal reformations (fig. 7). However, the use of CT in children is strongly limited by the ionizing radiation dose delivered to patients. Therefore, dedicated CT studies of the small bowel, such us CT enterography and CT enteroclysis, are not suitable for pediatric patients. In any case, CT permits excellent evaluation of the bowel lumen and bowel wall thickness and provides excellent resolution for the identification of mucosal ulcers. CT also enables evaluation of the mesenteric tissue and the mesenteric vessels and lymph nodes with excellent results. The creeping fat sign and the comb sign, together with the presence of enlarged mesenteric nodes, are all markers of active intestinal disease. Abscesses and fluid collection are easily detected with CT. The evaluation of abscesses is also possible without the use of dedicated bowel distension. Moreover, CT has several benefits, especially in the acute

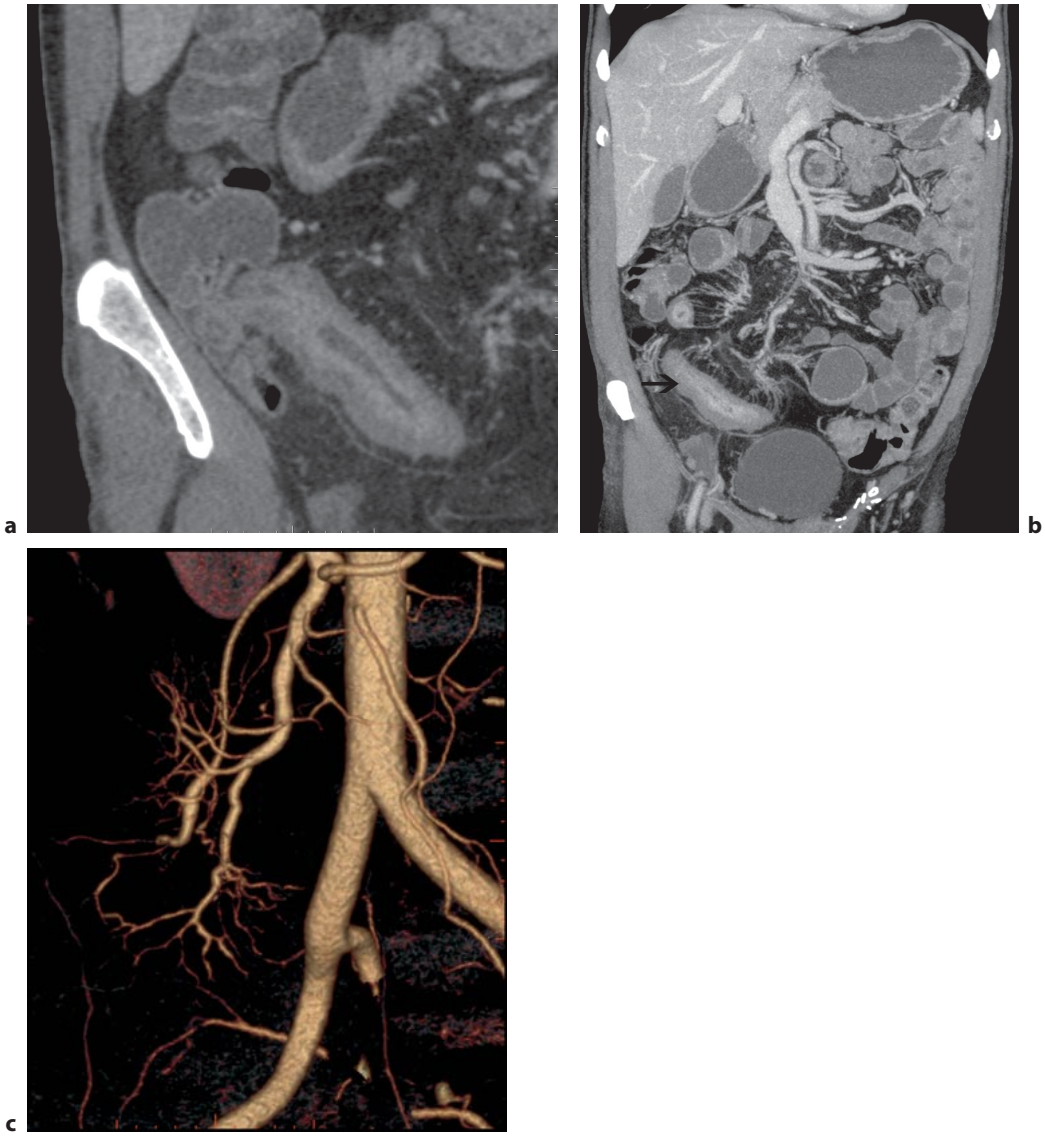

Fig. 7. Adult patient with ileal CD at CT enterography (coronal reformation, **a**, **b**). The high spatial resolution provided by the newest generation of scanners offers excellent image quality of the coronal reformations. The image shows clearly a thickened segment of the terminal ileum, with strongly enhancing mucosa and submucosa. **c** 3D volume-rendering reconstruction showing, in an angiographic view, the engorged vasa recta feeding the affected loop.

clinical setting, which provide an accurate differential diagnosis of acute abdominal pain in adults as well as children.

However, the use of CT scanning in the elective evaluation of children affected by CD should be discouraged unless the superior performance, accuracy, and benefit to the patient in an acute clinical situation far outweigh the radiation dose exposure.

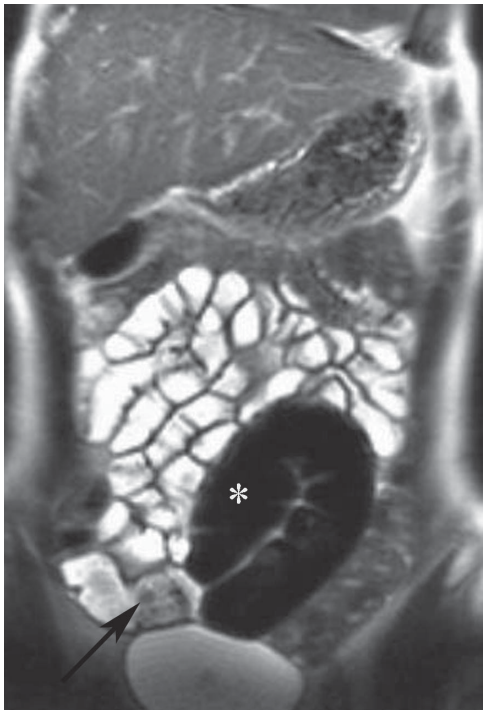

Fig. 8. Normal appearance of the small bowel in a 6-year-old healthy child at MR enterography. Image shows normal caliber and bowel wall thickness on a T_2-weighted coronal image. Oral contrast agent distending the bowel lumen shows a high signal intensity, while the bowel wall has a low signal intensity and a very sharp appearance.

MRI

The most sensitive imaging tool for the assessment of ileal inflammation is MRI.

In patients with proven or suspected CD, cross-sectional images should be analyzed specifically for identification and characterization of pathologically altered bowel segment [24].

Most MR information about the small bowel concerns evaluation of the bowel wall.

The normal wall thickness of the small intestine is between 1 and 3 mm when the lumen is distended (fig. 8). Any portion of the bowel wall that exceeds 4–5 mm is considered abnormal. An adequate intestinal distension is mandatory because collapsed loops or spastic intestinal segments may mimic wall thickening.

Small bowel wall thickening is a very sensitive, but not pathognomonic sign of CD, since it is also observed in several other intestinal diseases, such as infections, ischemic disorders, and graft-vs.-host disease.

Although superficial mucosal lesions are easily missed due to inadequate spatial resolution, MRI can detect early inflammatory changes of the bowel wall, based on enhancement following the intravenous injection of contrast medium [25, 26].

There are two patterns of enhancement in a pathologic bowel segment: 'homogeneous' and 'stratified'. Homogeneous enhancement is a diffuse transmural enhancement with no recognition of different bowel layers. A stratification of the bowel wall

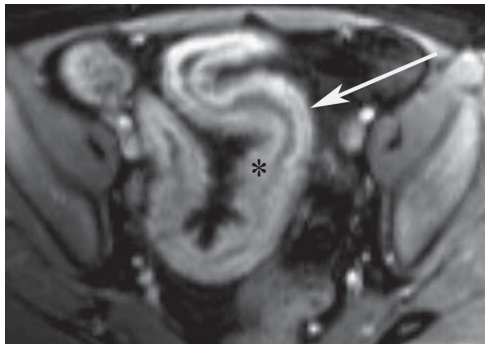

Fig. 9. Axial, Gd-enhanced, T_1-weighted MR image in a 7-year-old child with active CD. The high signal intensity of the entire bowel wall (arrow) without signs of stratification is indicative of transmural inflammation.

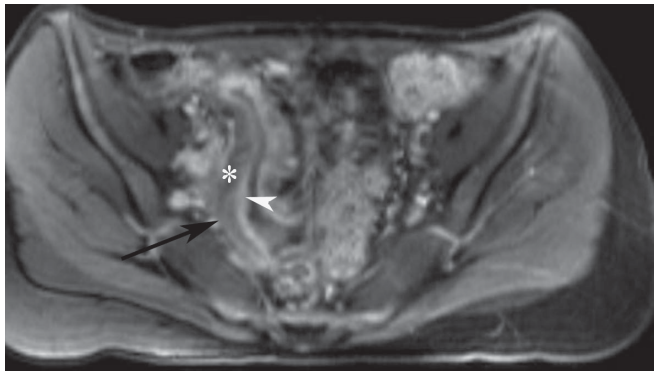

Fig. 10. Gd-enhanced, T_1-weighted image showing layered enhancement of a thickened bowel wall due to hypoenhancing fibrous tissue in the outer layer, and a hyperenhancing inner layer.

(the so-called 'target' or 'double halo' appearance) is related to mucosal enhancement, with a hypoenhancing outer layer.

On contrast-enhanced T_1-weighted images, two different patterns can be recognized:

(1) Transmural enhancement (no stratification) on T_1-weighted images. This pattern is more frequently associated with the early stages of CD and is very common in pediatric patients and in young adults (fig. 9).

(2) Stratified enhancement pattern on T_1-weighted images. This is typical of long-standing CD, with fibrosis, or of patients following intense medical treatment (fig. 10).

The recognition of a stricture is easy, considering that the normal lumen of the small intestine is around 2.5 cm in diameter (fig. 11). The presence of a prestenotic dilatation may help in the diagnosis. MR is able to identify long-standing fibrotic strictures (with a thick hypointense bowel wall and no significant contrast enhancement) that would not benefit from medical treatment, although in most cases, the choice between surgery or medical therapy is mainly related to the number and the severity of episodes of intestinal occlusions or sub-occlusions.

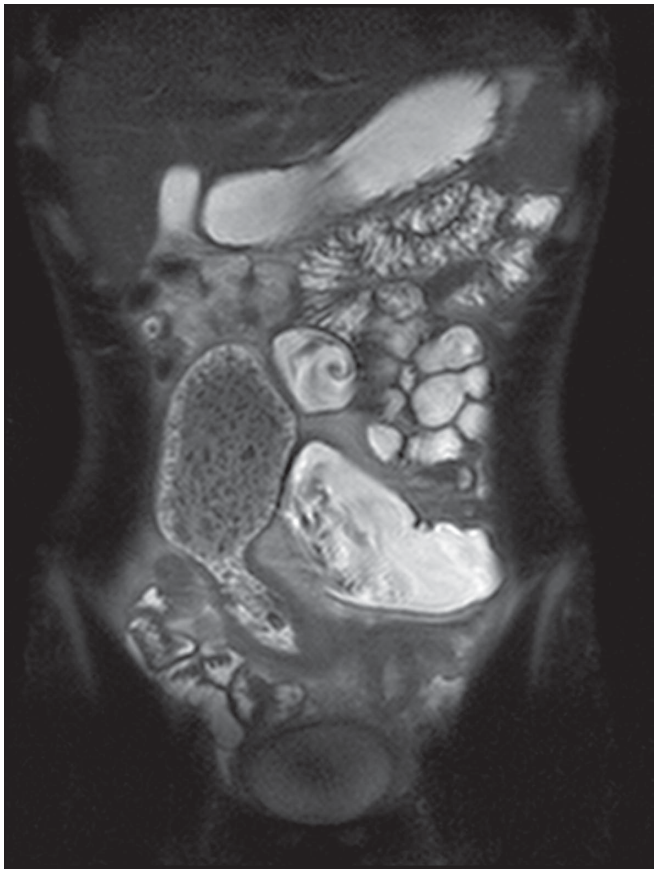

Fig. 11. A thickened ileal loop with severe lumen reduction and large dilatation of the proximal segment, indicative of intestinal stricture in a child with CD.

Extramural abnormalities include fibrofatty proliferation, vascular engorgement on the mesenteric side of the bowel, and mesenteric lymphadenopathy. CD, from a pathological point of view, is a chronic granulomatous inflammation that affects the bowel wall and extends to the perivisceral mesenteric fatty tissue. The chronic inflammation of the mesenteric fatty tissue also induces a proliferation of the fat tissue itself, together with a fibrotic component. This is the so-called fibrofatty proliferation and MR imaging may demonstrate a pseudomass with prevalent fibrous or fatty components (fig. 12).

The 'comb sign,' a sign of active inflammation, arises from the combination of vascular engorgement of the vasa recta and fibrofatty proliferation, and it is demonstrated as multiple tubular, tortuous opacities on the mesenteric side of the ileum, aligned like the teeth of a comb.

Other typical findings of active CD are the presence of deep ulcers that penetrate the small bowel wall, leading to the cobblestone appearance of the mucosal profile (fig. 13).

Mesenteric lymphadenopathies, ranging in size between 3 and 8 mm, are well-depicted using true FISP or T_2-weighted turbo spin-echo sequences. When lymph nodes are multiple, and larger than 10 mm, lymphoma or carcinoma should be excluded.

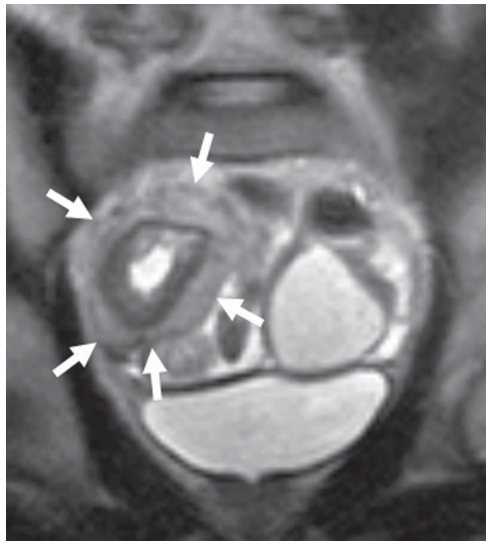

Fig. 12. A large fat-content pseudomass (arrows) is visible surrounding a thickened ileal loop, indicative of fibrofatty proliferation.

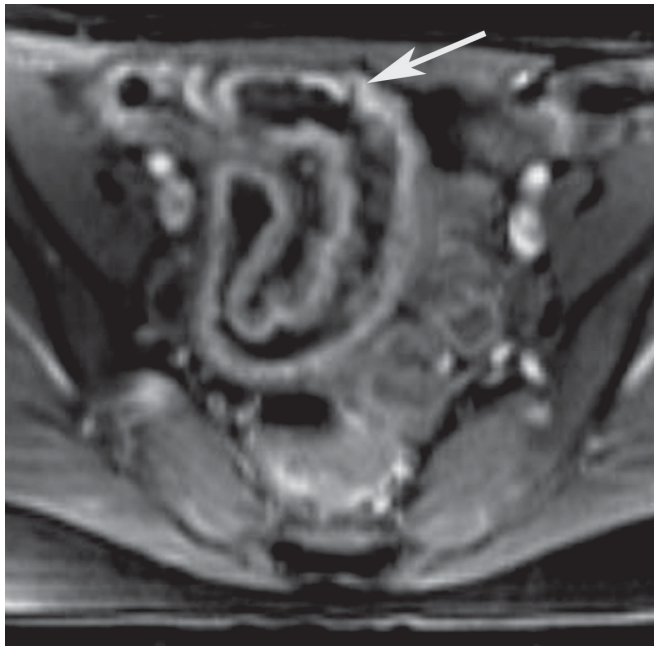

Fig. 13. Gd-enhanced, T_1-weighted axial image showing a long inflamed intestinal segment in a child with CD. A deep transversal ulcer is clearly visible as a sign of active inflammation (arrow).

Common complications of CD include fistulas, abscesses, and phlegmons. The reported sensitivity of MR imaging for depicting fistulous sinus tracts is 50–75% when compared with conventional enteroclysis [25]. Even if direct visualization of fistulous tracts is not always possible with MR, indirect signs can be recognized. This finding is often associated with inhomogeneity and enhancement of the mesenteric fat around the sinus tract. MR is also a suitable technique in the evaluation of patients after surgery to determine the recurrence of CD (fig. 14).

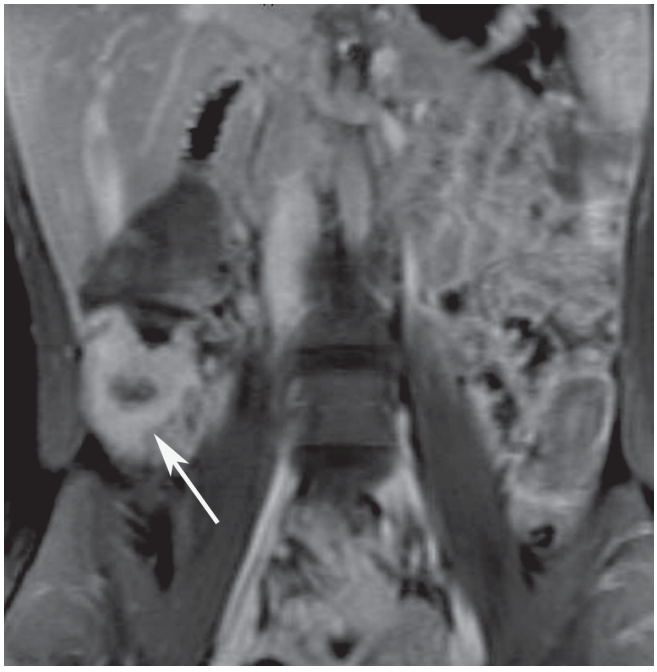

Fig. 14. Mural thickening and hyperenhancement of the cecal apex (arrow) after surgery, indicative of local resurgence of CD.

The assessment of disease activity is extremely important, given its influence on the choice of therapy (choice of drug and adequate dose) and its ability to provide an assessment of the patient's clinical course. In a number of studies, MR was used to evaluate disease activity. Based on different experiences, contrast-enhanced, fat-suppressed, T_1-weighted images offer the best correlation between MR findings and the CD Activity Index (CDAI), although a correlation using fat-suppressed T_2-weighted images has also been demonstrated.

A correlation not only between contrast-enhanced MR and CDAI, but also with the findings from distal ileoscopy was demonstrated in our study on a pediatric population of patients.

In summary, MRI is able to identify different forms of intestinal wall inflammatory changes that correlate with different levels of disease activity during CD. Complicating lesions of CD, strictures, and abscesses are also easily depicted by MRI.

Colon Imaging: Technical Approaches

Conventional Barium Studies

Imaging of the colon represents a controversial issue in radiology.

Several techniques have been optimized in the process of going from conventional barium studies to cross-sectional imaging.

These technical approaches are represented mainly by barium enema and double-contrast barium enema using conventional radiology.

A conventional barium study of the colon has been, for many years, the unique imaging method available for the evaluation of the colon. Therefore, patient preparation, technique, and also indications of the findings of IBD at conventional barium studies are very well defined.

The double-contrast approach is definitely preferable to conventional barium enema since it provides greater diagnostic power. A common technical requirement for both barium and double-contrast barium enema is a colonic preparation provided by the administration of cathartic agents.

In the evaluation of the complicating lesions of ulcerative colitis, such as toxic megacolon, plain film of the abdomen is also a crucial test that enables a quick and safe method for monitoring colonic distension.

If the working diagnosis suggest toxic megacolon both colonic enema and double contrast colonic enema are contraindicated due to the high risk of perforation.

Computed Tomography and CT Colonography

Much experience has been gained in the last decade on the optimization of a dedicated CT study of the colon, the so-called virtual colonoscopy (VC) or CT colonography (CTC) [27, 28]. This approach is based on the acquisition of a volumetric CT dataset after colonic cleansing and colonic air filling. VC was tested extensively in an adult population and for the detection of neoplastic lesions, diverticular disease, and colonic polyp detection, with some experience on IBD. Therefore, CT colonography is not currently indicated for the evaluation of IBD in adults. VC is also not recommended in children because the radiation dose exposure is considered much too high.

Therefore, VC should not be performed in children with known or suspected IBD.

Although the use of VC is not recommended in children, CT may be extremely useful using a conventional scan of the abdomen and pelvis, especially in the acute clinical presentation of colonic IBD.

Magnetic Resonance

Magnetic resonance colonography (MRC) provides an interesting perspective in the study of colonic diseases [29, 30]. Potential clinical indications for MRC are under debate; however, similar to small bowel imaging, MRC seems to offer great potential for the assessment of colonic inflammation in patients with IBD [31, 32].

Techniques for MRC need to be optimized and tested on large series of patients. In the past few years, several authors have proposed different technical approaches to MRC using conventional patient preparation with cathartic agents and colonic

distension obtained by a colonic enema. Two different approaches can be performed: bright lumen MRC and dark lumen MRC. These two approaches differ in the contrast agent used to distend the colonic lumen. If a bright lumen approach is preferred, a gadolinium chelate enema is performed in order to obtain a positive signal intensity on T_1-weighted images. The other approach (dark lumen MRC) consists of the administration of a water enema that produces a low signal intensity on T_1-weighted images. This approach is preferred for the evaluation of IBD because it permits a better evaluation of the bowel wall.

Dark lumen MRC is based on the use of a heavily T_1-weighted, three-dimensional, gradient-echo sequence after the rectal administration of a water enema and intravenous injection of paramagnetic contrast material. The low signal intensity produced by a water enema into the colonic lumen provides an excellent evaluation of the enhancing colonic wall after intravenous gadolinium administration.

Recently, in order to increase patient compliance, some authors have proposed the use of the so-called fecal tagging approach to MRC, which avoids large bowel cleansing and modulates the signal intensity of fecal material by adding contrast compounds to regular meals. The barium-based approach to fecal tagging has been successfully assessed in an adult population [33, 34]. By ingesting barium before the MR examination, stool is rendered virtually indistinguishable from the administered water enema on heavily T1w GRE images, generating a high contrast resolution between a brightly enhancing colonic wall after i.v. Gd-DOTA injection and the homogeneously dark colonic lumen.

Imaging Features of Colonic Localization of IBD

The role of imaging in the colonic localization of IBD is to determine the site and extent of disease, detect of complications, and assess therapeutic response.

The differential diagnosis between CD, ulcerative colitis, and indeterminant colitis is not always possible on the basis of imaging alone, and often requires optical colonoscopy with biopsy and histology.

However, imaging may show some useful findings, indicative of one form of IBD or another.

Ulcerative Colitis on Conventional Barium Studies

Ulcerative colitis presents some distinctive findings on conventional barium studies. Loss of colonic folds, with a tubular appearance of the colonic surface, may represent a common finding during the inactive phase of disease. The constant involvement of the rectum and the continuous progression of colitis are distinctive findings for the differential diagnosis between UC and CD.

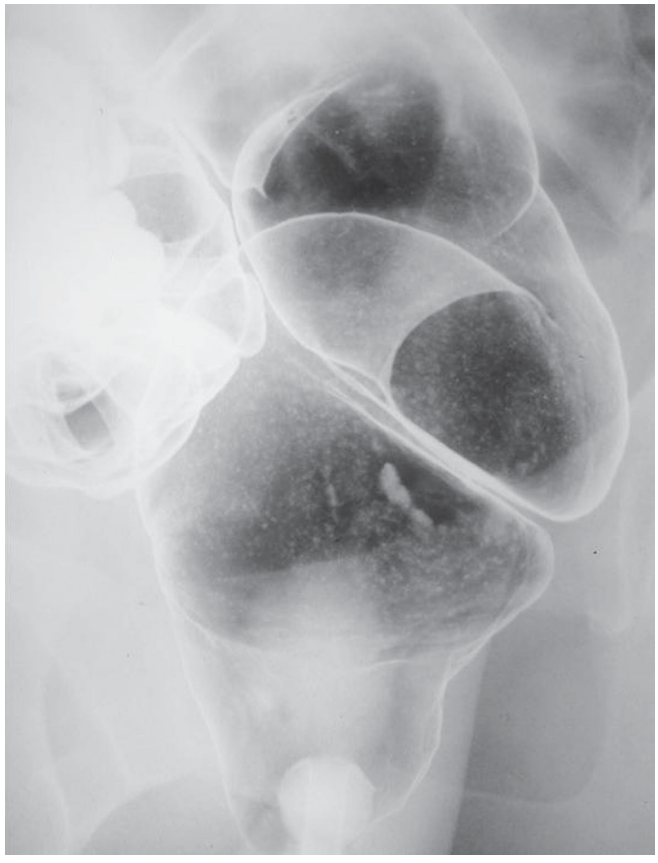

Fig. 15. Double-contrast barium enema showing the granular pattern of the rectal mucosa in an early stage of ulcerative colitis.

During the active phase of disease, mucosal abnormalities are the most relevant findings of UC on barium studies. These abnormalities are characterized by a granular pattern, mucosal stippling, and collar-button ulcers. These findings reflect the intense edema and infiltration of the mucosa and submucosa with crypt abscesses eroding into the lumen (fig. 15).

In cases of severe UC, the combination of extensive mucosal and submucosal ulceration and the inflamed edematous mucosa produce the numerous inflammatory pseudopolyps, which are the expression of an exuberant reparation process (fig. 16).

UC is commonly associated with a backwash ileitis due to reflux of colonic content into the terminal ileum, with an associated granular pattern at the level of the terminal ileum.

Colitis at CT and MRI

Early mucosal changes are not seen on CT or MRI, although large pseudopolyps may be seen.

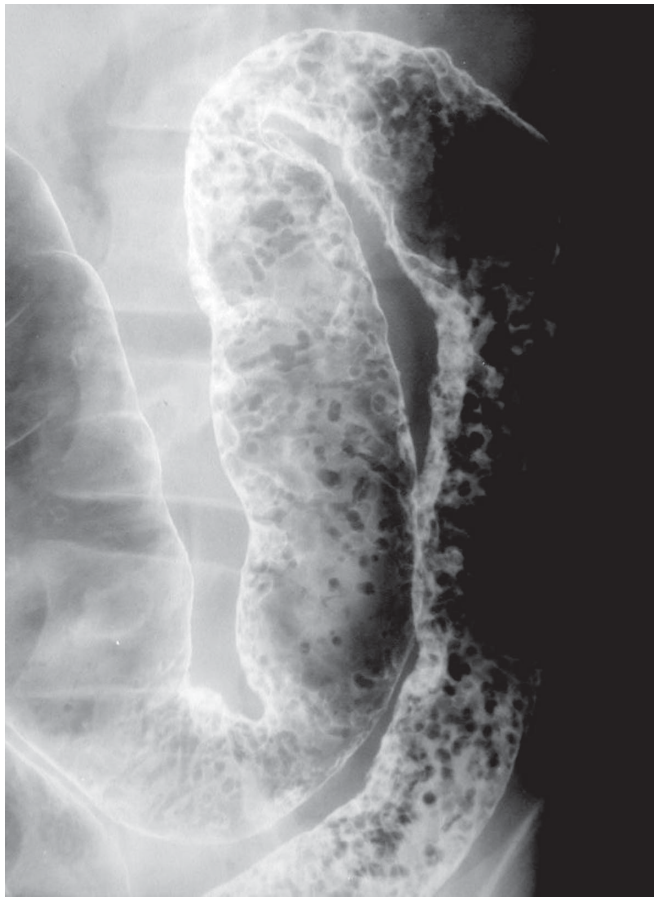

Fig. 16. Many pseudopolyps are clearly visible at the level of the colonic splenic flexure in a patient with ulcerative colitis.

A common finding of UC at CT and MRI is mural thickening due to edema or fatty infiltration of the submucosa and hypertrophy of the muscularis mucosae (fig. 17).

During UC, inflammation does not involve the entire colonic wall, but is usually limited to the mucosa and submucosa. Those inflammatory changes may be evident as mild thickening of the colonic wall at cross-sectional imaging. Moreover, even if the muscularis propria is usually spared from inflammation, there is frequently a reactive hypertrophy of this layer that contributes to the thickened appearance of the colonic wall on CT and MRI.

The experience with CT and MRI in the evaluation of UC is very poor at the moment and these studies are not used in routine practice in the non-acute clinical setting.

On the other hand, CT scans of the abdomen present several benefits over other imaging tests for evaluation in the acute clinical setting of gastrointestinal disorders in adults as well as in children. First of all, CT scans in the acute clinical setting are safe tests for the evaluation of intestinal occlusion or perforation. Moreover, CT scans of the abdomen may help in the differential diagnosis of acute abdominal pain, offering detailed information about intestinal occlusion or perforation, intestinal intussusception, and

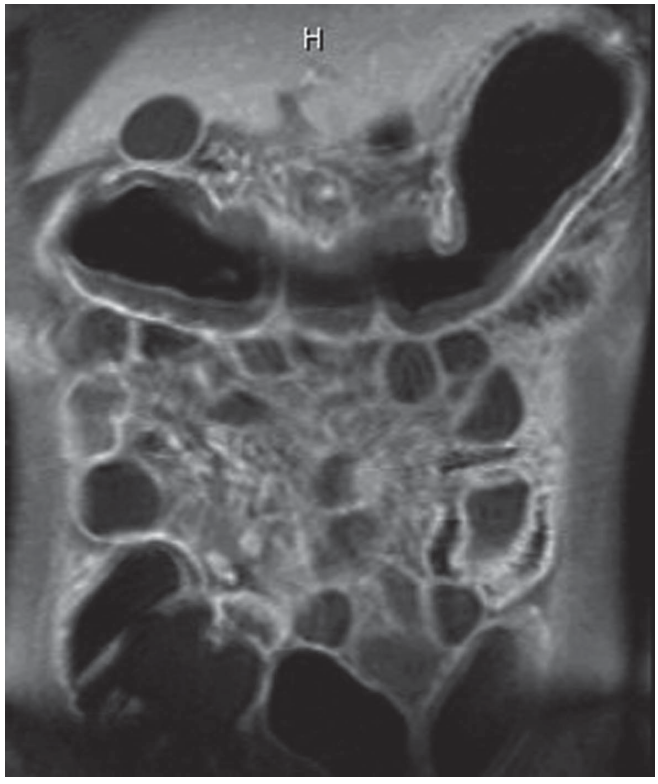

Fig. 17. MR colonography in a child with ulcerative colitis showing diffuse mural thickening of the transverse colon.

also in cases of acute presentation of IBD or other entities that affect the gastrointestinal system, such as vasculitis and/or ischemic disorders and infectious disease.

UC may present in a minority of patients in the acute clinical setting of toxic megacolon with transmural inflammation, vasculitis of small arterioles, destruction of the myoenteric and submucosal plexus, and myocytosis in the muscularis propria.

Those pathologic features lead to colonic dilatation as a major finding in toxic megacolon, with mean diameters ranging between 8 and 9 cm. This huge colonic dilatation may also be easily depicted on a conventional plain film of the abdomen. This test is also useful for monitoring colonic dilatation.

CD of the Colon and Indeterminant-Type Colitis

CD isolated to the colon is a relatively rare entity. The distribution of lesions isolated to the colon is reportedly 20% in CD.

Moreover, in case of isolated colitis, a definite differential diagnosis may be challenging, especially in children.

In the classic presentation, CD, especially in adult patients, presents some peculiarities with respect to UC in terms of lesion distribution. Lesion distribution typically

appears continuous in UC and patchy and discontinuous in CD. In this crucial differential diagnosis, the presence of ileal inflammation is sometimes distinctive for CD.

However, in children, the two forms of IBD that affect the colon may greatly overlap at clinical presentation, i.e. endoscopic and radiologic features, and histologic findings. For these reasons, a new form of chronic colon inflammation was recently categorized: the so-called indeterminant-type colitis type. This last form of chronic colitis is more common in children than in the adult population and represents an immature form of a more definite IBD that will develop in adult life.

Concluding Remarks

Imaging of the gastrointestinal tract can be performed using several technical approaches. Conventional barium studies that were, for long time, the unique imaging opportunity to evaluate the GI tract now has a strong competitor in the emerging techniques of sonography, CT and MRI.

The ionizing radiation hazard related to the use of CT limits the CT approach in the acute clinical setting in pediatric patients.

In the nonacute clinical setting, particularly, US and MRI are the most beneficial techniques for evaluation of the small bowel.

However, a rigorous technique should be followed for both US and MRI to ensure excellent results. MRI of the bowel overcomes some of the limitations of sonography for the evaluation of the bowel and offers a great opportunity to study the small bowel, with the ability to look directly at small bowel wall abnormalities and not only at mucosal changes. MR enterography is a noninvasive alternative for use in the pediatric population and its use will likely increase in the next few years.

MRI offers detailed information about the localization of CD, an assessment of the disease activity index, and an identification of disease complications.

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Endoscopic Modalities in Pediatric Inflammatory Bowel Disease

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Abstract

Endoscopy plays an important role in the management of IBD from initial diagonosis to performing endo-therapeutic procedures. With the modern endoscope the duodenum and ileocolon can be accessed and biopsies taken. Advances in endoscopy including the development of sonde enteroscopy, intra-operative enteroscopy, wireless capsule endoscopy and double balloon enteroscopy has made it possible to visualise, biopsy and perform interventional endo-therapy in the whole of the small bowel. Proper patient preparation including a preparatory visit, screening to identify potential sedation and anesthetic risks, antibiotic prophylaxis where necessary, good bowel preparation, adequate sedation and where possible a general anesthetic are important prerequisites for a successful endoscopic procedure. Complications through rare, do occur and need to be kept in mind. Further in this chapter, the importance of upper gastrointestinal endoscopy and terminal ileal intubation have been highlighted and newer endo-diagnostic methods such as high magnification chromo-endoscopy and confocal endomicroscopy discussed.

Safe, informative, and effective endoscopy performed in a child-friendly situation with the minimum of distress to child and parent alike is a sine qua non of a unit adhering to best-practice in the care of children and adolescents with inflammatory bowel disease. The care of children and adolescents differs in important ways from that of adults. This is reflected in the emphasis placed on various aspects of endoscopy especially ileocolonoscopy, such as the frequent use of general anesthesia, the number and location of mucosal biopsies, and the routine inclusion of ileal intubation during a complete examination. The question of who should conduct the procedure continues to receive attention among pediatric gastroenterologists. It is generally accepted that a pediatrician, preferably with experience in pediatric gastroenterology, should be involved in the care of the child or adolescent and, ideally, should carry out the procedure. There can be few more satisfying experiences in medicine than making a clinical judgment and diagnosis in a child, confirming the nature and extent of

the disease oneself by endoscopy, treating appropriately, and then visually demonstrating the success of such endeavors to child and parent by a follow-up procedure.

Endoscopy plays an important role in the initial diagnosis of inflammatory bowel disease (IBD), differentiation of IBD into Crohn's disease (CD) and ulcerative colitis (UC), assessment of disease extent, monitoring of response to therapy, surveillance of cancer, and to perform endo-therapeutic procedures such as stricture dilation [1].

Endoscopy – Background History

Rigid esophagoscopes and sigmoidoscopes were introduced in the late 19th century and semi-flexible scopes in the 1930s. The invention of fiber optics in the 1950s led to the development of the first flexible sigmoidoscope in 1963 and colonoscope in 1966. This made it possible to visualize, take biopsies and perform endo-therapeutic procedures and reach the duodenum and ileo-colon. Incorporation of video-chip technology in the 1980s, allowed digital images to be displayed on a monitor, stored, analyzed and transmitted as necessary. Further advances have seen the development of Sonde enteroscopy [2] limited by lack of therapeutic potential, and then push enteroscopy, allowing the therapeutic endoscopist access up to 70–100 cm small bowel beyond the pylorus. Intra-operative endoscopy appeared to be the only means available to access the whole of the small bowel at the turn of the century until the development of Wireless capsule endoscopy (WCE). This technological breakthrough allowed the direct visualization of the entire small bowel without the need of external wires, fiberoptic bundles or cables but as yet is limited to diagnostic input alone. Double balloon enteroscopy (DBE) is a more recent modality, which enables high-resolution endoscopic imaging of the entire small bowel, with the advantage over WCE of potential for mucosal biopsies and interventional endo-therapy.

Patient Preparation

Ideally, both the child and the parents should be offered a preparatory visit to the endoscopy unit to answer questions and defuse any potential concerns and anxieties regarding the procedure and admission. Children with greater knowledge of the procedure exhibit less distress and report less anxiety toward the procedure [3]. Younger children undoubtedly benefit from preadmission visits and the involvement of a play therapist to enable some understanding of what is to take place and why [4]. Diagrams may help in explanations to older children. Preparatory videotapes are also useful for informing the patient and parent regarding what to expect.

A full screening is important to identify potential sedation or anesthetic risks. Although there is little correlation of mildly deranged peripheral coagulation indices with hemorrhage after mucosal biopsies, more pronounced bleeding diatheses may

require forethought and appropriate blood product backup [5]. Properly informed consent should be obtained with an information sheet detailing potential complications and their incidence, and a separate consent should be signed in the event of research biopsies being requested.

Guidelines concerning antibiotic prophylaxis in children with lesions susceptible to endocarditis or in the immuno-compromised child are available in the literature [6]. A combination of intravenous or intramuscular ampicillin (50 mg/kg, maximum 2 g) and gentamicin (2 mg/kg, maximum 120 mg) 30 min before and 6 h after the ileocolonoscopy is generally recommended. Vancomycin (20 mg/kg slow intravenous infusion 1 hour before) can be substituted for ampicillin in those with documented penicillin allergy.

Bowel Preparation

Poor bowel preparation is a major factor that may prevent or impede successful ileocolonoscopy. Although administration of regimens is not always easy, modern protocols can be remarkably effective in clearing the colon and ileum. Use of sodium phosphate preparations was associated with a transient rise in mean serum sodium and phosphate, but with no change in serum calcium [7]. Low-volume non-absorbable polyethylene glycol preparations are becoming increasingly popular in pediatric units and are well tolerated, with no observable electrolytic disturbance [8]. Table 1 outlines several low-volume regimens that have been used successfully in children [7–10]. The regimen employed in our unit, shown in table 2, combines the beneficial effects of oral low-volume administration with the backup of an enema 1–2 h beforehand if no clear fecal effluent is observed. No clinically significant fluid shifts or electrolyte imbalances have been observed in over 2,000 colonoscopies over a 5-year period in our unit.

Monitoring and Sedation

The aims of adequate sedation include patient safety, anxiolysis, analgesia, amnesia as well as adequate endoscopic examination, time and cost efficiency [11]. Debate has surrounded the relative merits and safety of sedation and general anesthesia for upper gastrointestinal endoscopy and ileocolonoscopy in children for several years [12].

The risks of general anaesthesia include those associated with intubation and administration of an anesthetic, which can be minimized by proper preparation and good intubation technique. However, the benefits include complete amnesia and total avoidance of pain to the patient and as well as freeing the endoscopist from managing airway, monitoring vital signs and recovering the patient [11].

Intravenous sedation (IV-S) usually consists of a narcotic (meperidine or fentanyl) and a benzodiazepine (diazepam or midazolam), the former for analgesia and the

Table 1. Successful recent low-volume regimens for the preparation of the bowel for colonoscopy

Study	Regimen	Diet	Success rate
Gremse et al. [9], 1996	oral sodium phosphate (45 ml/1.7 m^2) 6 p.m. and 6 a.m. for a.m. procedure	clear liquid 24 h	18/19
da Silva et al. [7], 1997	oral sodium phosphate (22.5 ml if <30 kg, 45 ml if >30 kg) 7 p.m. and 5 a.m. for a.m. procedure	clear liquid after first dose	10/14
Pinfield et al. [10], 1999	sodium picosulphate with magnesium citrate (2.5 g <2 years, 5 g 2–5 years, 10 g >5 years per dose) 24 and 18 h before procedure	clear liquid for 24 h	32/32 (3 vomited)
Dahshan et al. [8], 1999	magnesium citrate and X-prep	clear liquid for 48 h	

Table 2. Bowel preparation for children undergoing colonoscopy

Clear fluids for preceding 24 h (12 h for infants receiving no solid intake)	
5 p.m.	
Senokot	1–2 mg/kg (max 30 mg)
Sodium picosulphate	2.5 g if <1 year 5 g if 1–4 years 10 g if >4 years
6 a.m.	
Repeat sodium picosulphate dose 1 h before procedure	phosphate enema (1/2 if <1 year)

latter for anxiolysis and amnesia. Ketamine and midazolam has been used with reportedly lesser side effects [13]. IV-S has been argued to be safe, effective and less costly in comparison to general anesthesia with successful sedation achieved in more than 95% of elective procedures [14]. In spite of the advantages of IV-S pediatric gastrointestinal endoscopy has moved towards general anesthesia since it is now acknowledged that to get the requisite cooperation, and therefore a properly conducted procedure with minimum distress to the child, deep sedation is usually necessary. With deep sedation, it is clear that the risks are significant, including hypotension, respiratory compromise, and even respiratory arrest.

Pre-procedural medication with a benzodiazepine have been found to be useful in reducing patient anxiety and improve patient and parent acceptance of the procedure without any adverse effects [15].

While it is generally accepted that ileocolonoscopy and biopsy has a central role in the initial diagnosis and differentiation of inflammatory bowel disease [16], it is now widely recognised that esophagogastroduodenoscopy (EGD) also has a definitive place in the initial diagnostic work up [17]. Typically described upper gastrointestinal symptoms include dysphagia, pain when eating, nausea and/or vomiting, and aphthous lesions of the mouth. However, several studies have shown a higher incidence of microscopic mucosal disease in the upper GI tract [18, 19] then previously thought even in the absence of any upper GI symptoms [20]. Histological abnormalities including granulomas are seen even when the gross appearance of the tissue is normal [17, 18]. Therefore it is important to take biopsies from several sites in the upper gastrointestinal tract even if they appear normal endoscopically.

Esophageal disease in CD (fig. 1) can vary from small erosions to transmural involvement resulting in perforation and fistulization into adjacent organs [21]. Granulomas are reported in 20–39% of esophageal biopsies in patients with CD [22]. Other findings include erythema, ulceration, polypoid lesions, pseudomembranous formations, strictures and mucosal bridges [22]. Endoscopic findings in the stomach and duodenum include linear and serpigenous ulcers, diffuse superficial ulcers, aphthous ulcers, nodularity, cobblestone appearance, rigidity of the GI wall and narrowing of the lumen [23].

Focal enhanced gastritis as is an important feature of CD [23] (fig. 2). Further several studies confirmed this finding with a positive predictive value of 71–94% [19, 24]. Focal antral gastritis is more frequently seen in *Helicobacter pylori*-negative adults with CD then in those with UC or in non inflammatory bowel conditions [24].

The presence of non-caseating granuloma is characteristic of CD. Granulomas are found in 7–68% of patients with CD in the upper GI tract [17, 18, 22, 23] and often help in making a definitive diagnosis when none are found at other sites. Non-caseating granuloma in the upper gastrointestinal tract tends to occur in the superficial mucosa then in the muscularis or the serosal layers in comparison to ileal Crohn's disease.

UC conventionally was thought to involve only the colon and possibly ileum (backwash ileitis). However, it is increasingly recognized that features of inflammation in the upper GI tract are seen in UC and have been found in 50–75% of patients with UC in various studies [20, 25, 26].

Ileocolonoscopy

Equipment

Most modern units employ adult and pediatric videocolonoscopes, and the general technical specifications for the pediatric instruments differ little between

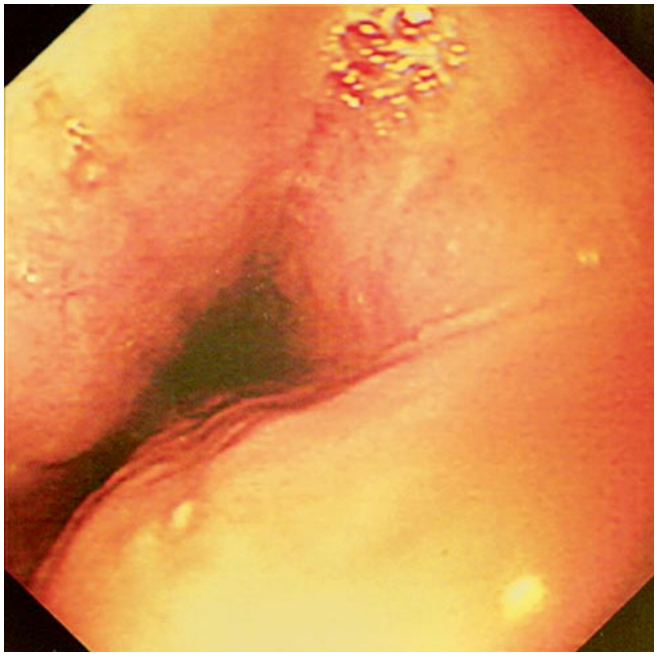

Fig. 1. CD of the oesophagus showing discrete ulcers.

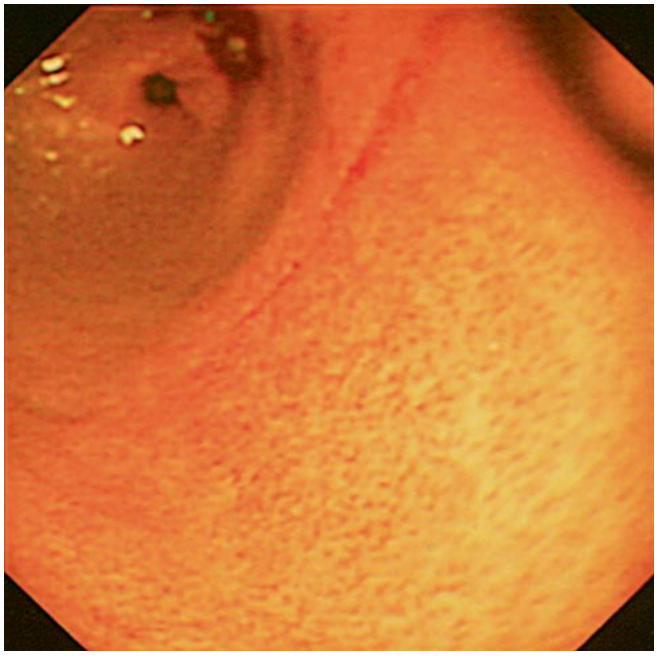

Fig. 2. Focal enhanced gastritis in CD.

Table 3. Technical specifications of various pediatric colonoscopes

Parameter	FUJINON (EC-410 MP15)	OLYMPUS (PCF 240L/I)	OLYMPUS Variable Stiffness (CF 240AL/I)	PENTAX (EC-3440PK)
Angle of vision	140°	140°	140°	140°
Depth of field	6–100 mm	4–100 mm	3–100 mm	6–100 mm
Distal end	11 mm	11.3 mm	12.2 mm	11.5 mm
Insertion tube	11.1 mm	11.3 mm	12.0 mm	11.4 mm
Channel	2.8 mm	3.2 mm	3.2 mm	3.8 mm
Angle up/down	180°/180°	180°/180°	180°/180°	180°/180°
Angle right/left	160°/160°	160°/160°	160°/160°	160°/160°
Working length	1,520 mm	1,330 mm (I) 1,680 m (L)	1,330 mm (I) 1,680 mm (L)	1,500 mm

manufacturers (table 3). When and in whom to use a pediatric colonoscope, is mainly a matter of personal preference. We use personal judgment based on age and/or body weight. In general terms, the lower limit for the adult colonoscope is 3–4 years of age and/or 12–15 kg. The extra stiffness of the adult versions diminishes the likelihood of forming sigmoid loops, but extra care must then be taken, especially in younger children and with general anesthesia, not to advance against undue resistance, to avoid the unlikely complication of colonic perforation. The variable stiffness colonoscope (table 3) may negotiate some of these problems. A control dial on the upper shaft of this small-diameter colonoscope (Olympus XCF-240AL/I) allows an increase in the stiffness of the insertion tube when passing through the sigmoid and transverse colon to avoid looping [27].

Ileocolonoscopy Basic Technique

Getting Started and Patient Positioning

The patient is usually positioned in the left lateral knee to chest position, although some operators prefer the right lateral position, citing easier sigmoid negotiation. Certainly, if the procedure is not subsequently allowing easy access to the splenic flexure, then patient repositioning from one side to the supine and then to the other side may be advantageous. In general, frequent turning of the patient is conducive to easier ileocolonoscopy as a whole and is to be advocated. An assistant stands on the operator's left to administer any abdominal pressure that may subsequently be deemed necessary to control, or try to prevent, loop formation in the sigmoid or transverse colon.

Practical Tips in Ileocolonoscopy

One important 'trick' in learning ileocolonoscopy is to grasp the concept of the lumen and the positions of a clock face. For instance, if the lumen is at 9 o'clock, then to enter this requires anticlockwise rotation combined with upward deflection of the scope tip from the 'neutral' position of 12 o'clock. Similarly, a combination of upward deflection of the tip with clockwise rotation of the colonoscope will allow entry of the lumen, suggested by a dark crescent, if seen at anywhere clockwise from 12 to 6 o'clock. Obviously, one may equally use downward tip deflection combined with the opposite rotatory control to that with upward tip deflection, and the execution and teaching of this concept are at personal discretion. With either approach, this is the most important manoeuvre that can be learned to assist in three-dimensional spatial orientation in the colon. Prolonged 'side viewing' of the bowel wall as it slides by should be avoided. Generally, in ileocolonoscopy, gentle scope advancement with clear lumen visualization is desirable, and, usually, only the forefinger and thumb will be required to advance the colonoscope. If greater pressure is required, then the operator is not performing an optimum procedure, and loop formation is likely to have occurred.

Rectal Intubation

Prior to any colonoscopy, it is considered good practice to perform an anal and then a rectal digital examination, the latter to avoid missing, by colonoscopy, very low-lying rectal polyps. Adequate water-soluble lubrication, avoiding the tip of the instrument, allows easy passage into the rectum. Posterior positioning of the tip and air insufflation will allow visualization of the rectal mucosa and the three semilunar folds, or valves of Houston, occurring on alternating sides of the lumen. Subsequently, direct visualization of the bowel lumen is mandatory, except in some circumstances at the splenic flexure.

Sigmoid and Descending Colon

Gentle torquing of the shaft clockwise and anticlockwise combined with upward or downward tip deflection and scope advancement is ideal for negotiating the sigmoid colon – the so-called 'torque-steering' technique. The initial sigmoid fold or valve can usually be passed by 90–120 of anticlockwise torsion. The different loops encountered in the sigmoid are demonstrated in figure 3. A so-called N loop may be overcome by trans-abdominal pressure by an assistant on the apex of the loop pushing toward the feet (fig. 3a). This often allows a so-called α loop to form, which can usually be tolerated as the instrument advances toward the splenic flexure (fig. 3b). Reducing an α loop is accomplished by initial clockwise rotation and then slow removal of the colonoscope, keeping the lumen in the centre of the field of vision.

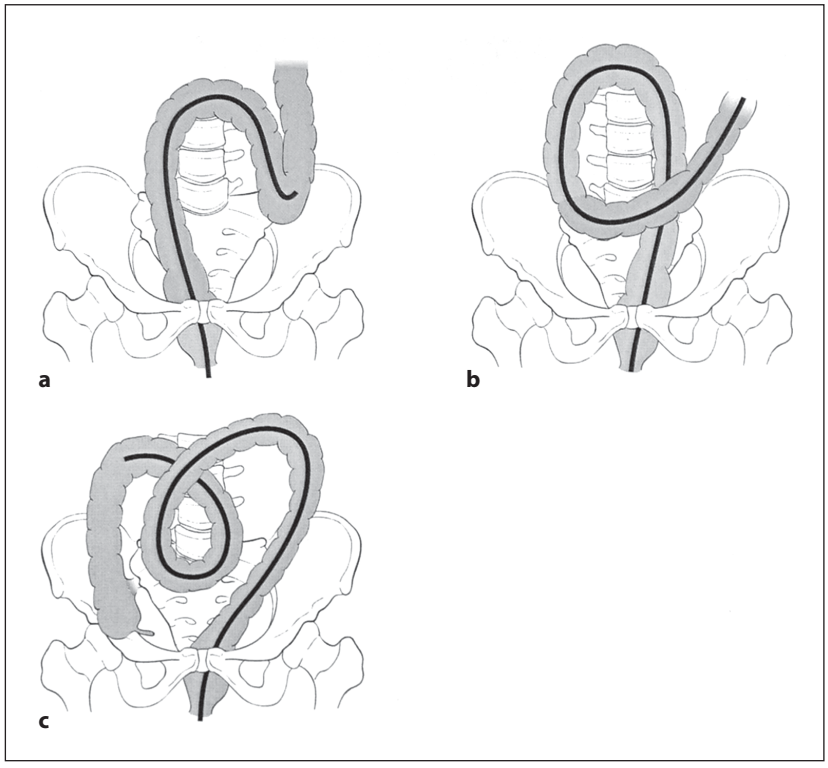

Fig. 3. Diagram of colonoscope sigmoid loops that may from: an N loop in the sigmoid colon (**a**); an α loop in the sigmoid colon (**b**), and a γ loop in a redundant transverse colon (**c**).

Splenic Flexure and Transverse Colon

Non-looped colonoscope length used at his point might be 40 cm in older children and even 20–25 cm in those under the age of 3–4 years. This is valuable in determining whether a loop is present. At the splenic flexure, the spleen may then be seen as a dark blue transmural discoloration. The transverse colon is recognized by the triangular haustral folds and is usually easily passed (fig. 4). Supine or right decubitus positioning may ease this. The more difficult γ loop may occur in a redundant transverse colon (fig. 3c). In addition, a good bit of advice is to apply gentle suction as the tip is advanced again in an attempt to concertina a potentially long dependent transverse colon over the colonoscope, thus maintaining a relatively short colonoscope and, hence, good control and maneuverability.

Hepatic Flexure and Ascending Colon

Non-looped colonoscope length used at this point might be 60 cm in older children and even 40 cm in those under the age of 3–4 years. The hepatic flexure is also recognized by the dark, usually blue, discoloration seen through the bowel wall, and positional

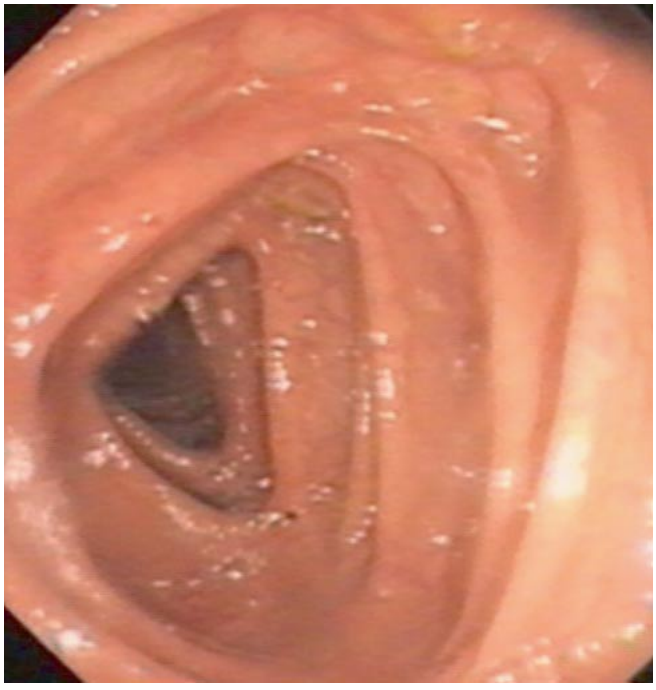

Fig. 4. Normal triangular appearance of transverse colon.

change to the supine or right decubitus may again facilitate identification of the lumen. The combination of right, up, and clockwise followed by anticlockwise rotation and suction down into the ascending colon once around the sharply angled hepatic flexure is usually the most effective maneuver, but various combinations, including position change and scope withdrawal, may be required. Once the hepatic flexure is negotiated, the transverse colonic γ loop may be reduced with anticlockwise or clockwise rotation followed by withdrawal of the colonoscope and suction. It is important to remember that the ascending colon, may be as short as 5 cm in some younger patients.

Cecum

Three useful ways to ensure that one has reached the cecum are as follows:

1 Observing the colonoscopic illumination in the right iliac fossa (using the specific high-intensity light transillumination application available with some colonoscopes is not usually necessary in children, excepting with some obese adolescents, for whom it can be helpful when applied in a dark environment).
2 Digitally indenting the abdominal wall over the right iliac fossa and observing the corresponding effect on the colonic wall with the colonoscope.
3 Identifying the triradiate fold, appendicele orifice, and (especially if gas bubbles or ileal effluent are being excreted from it) the typical two-lips-like appearance of the ileocecal valve.

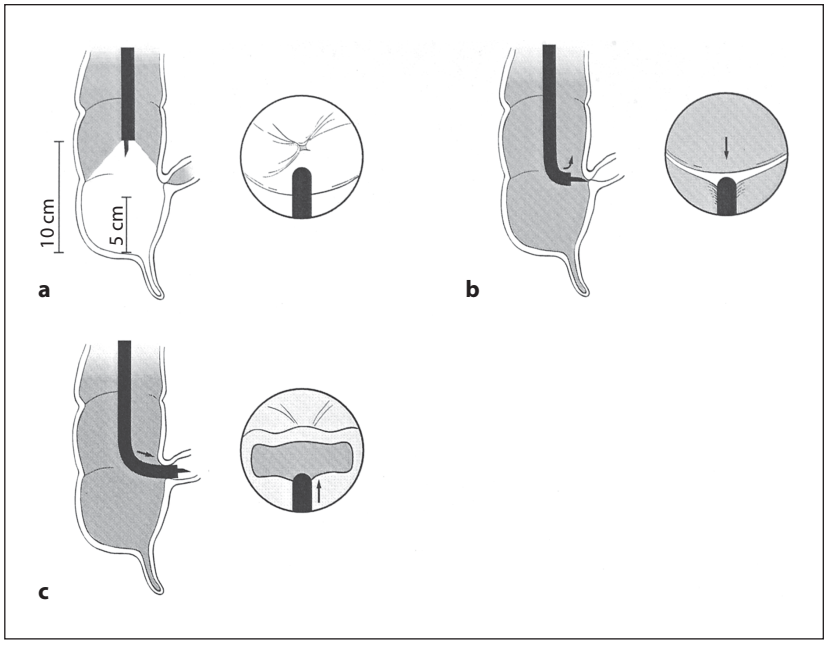

Fig. 5. **a** Identification of cecum with triradiate fold, appendicele orifice and ileocecal valve. **b** Ileocecal valve at the 6 o'clock position. **c** Forceps opening up ileocecal valve with downward defection of colonoscope tip.

Ileal Intubation and Its Importance

The ileocecal valve is present approximately 1–4 cm distal to the appendiceal orifice opening into a smooth asymmetric fold and opens perpendicular to the axis of the colon. Figures 5 show the steps of the easiest technique for ileal intubation. Removal of any colonic loops is important to allow for a responsive scope with no paradoxical movement. Figures 5b and 6 show the valve maneuvered to the 6 o'clock position and figures 5c and 7 show the insertion of the biopsy forceps such that just the tip or the first few millimeters are visibly exposed beyond the end of the scope. Once the valve is opened, the scope may be passed into the ileum with further downward deflection. In the absence of ileocecal valve strictures, and with practice, this technique will allow an ileal intubation rate of 100%. Perforation of the cecum or ileum with this technique is a theoretical concern raised by some observers unfamiliar with this technique, but this has not occurred in our experience of over 5,000 ileocolonoscopies and is extremely unlikely.

An alternative technique is 'blind' intubation of the ileocecal valve. This involves the same positioning of the valve at 6 or 9 o'clock and then slowly withdrawing the scope back from just beyond the valve's fold while insufflating with air and deflecting the scope tip downward. The disadvantage of this technique is that it is not under direct vision.

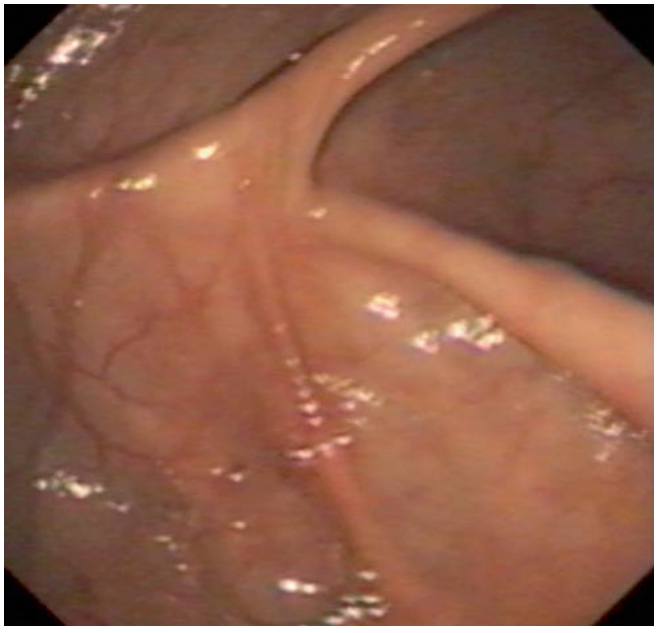

Fig. 6. Ileocecal valve at 6 o'clock.

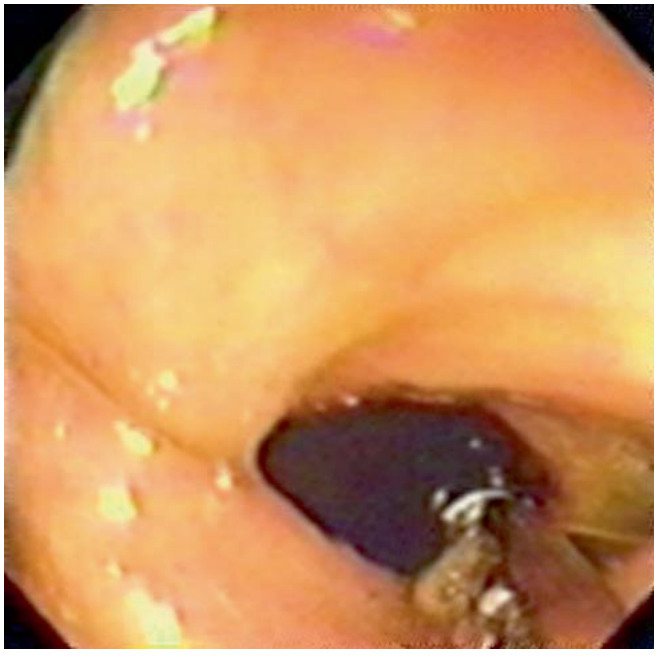

Fig. 7. Ileocecal entry using forceps.

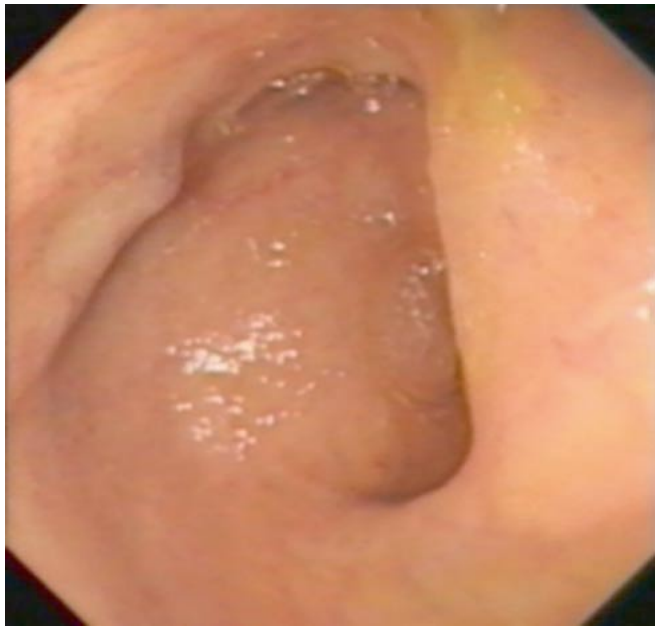

Fig. 8. Normal appearance of terminal ileum.

Ileum

The ileal mucosa will have the typical velvet-like appearance of small bowel (fig. 8), with the presence of smoother raised areas, which are Peyer's patches, and, occasionally, lymphonodular hyperplasia of varying degrees. Villi are more easily seen if the lumen is flooded with water. It is pertinent here to discuss the diagnostic need for entering the ileum in children suspected of inflammatory bowel disease. Several studies have demonstrated ileitis with granulomata detected by ileocolonoscopy may be the sole finding of CD [28, 29]. There are, of course, other reasons apart from the principal one, that is, diagnosis of chronic inflammatory bowel disease, for entering the ileum in children. For instance, ileoscopy will facilitate diagnoses of other causes of ileitis such as infection with tuberculosis or *Yersinia*. In addition, therapeutic dilation of short-terminal ileal strictures by endoscopic balloon catheter may be attempted.

Complications of Ileocolonoscopy

Complications, excluding those due to sedation, are summarized in table 4. Complications are more common following therapeutic procedures. The literature to date reveals over 3,000 colonoscopies under 20 years of age reported, with 5 perforations – 4 post-polypectomy and 1 in a patient with severe UC. Ten procedure-related

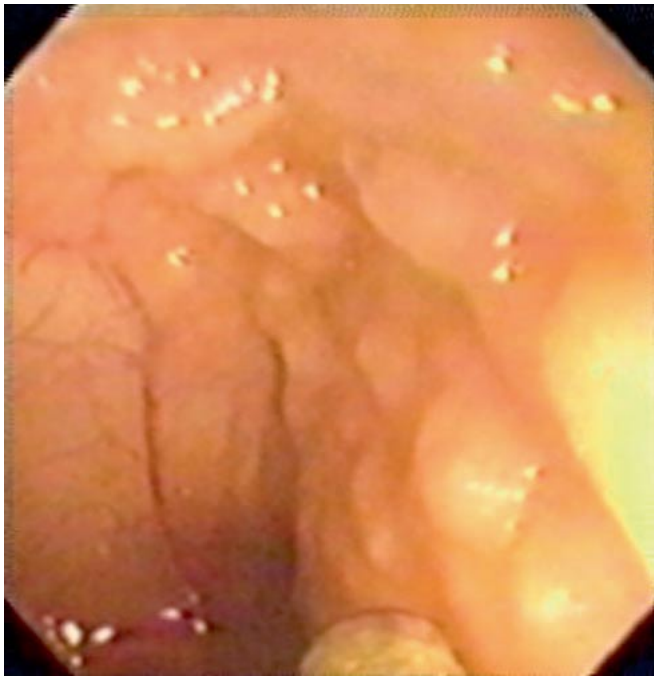

Fig. 9. Lymphonodular hyperplasia of the terminal ileum.

minor complications are noted, including four small post-polypectomy hemorrhages, 3 cases of post-procedure abdominal pain with spontaneous resolution, one common peroneal nerve palsy secondary to periprocedure positioning, and two with a post-procedure fever for more than 24 h [16, 30, 31]. This equates to a complication rate owing to the procedure itself of approximately 0.3% and, without polypectomy, of about 0.05%.

The merits of conservative therapy of selected cases of colonic perforation have been discussed [32], and it would seem reasonable to adopt conservative management, for instance, in the case of silent asymptomatic perforations and those with localized peritonitis without signs of sepsis who continue to improve clinically without intervention [33].

In contradistinction to adults, bacteremia has not been detected in children after ileocolonoscopy [34]. In addition, modern cleaning machines seem to largely prevent the glutaraldehyde-associated colitis reported in the past [35].

Endoscopic Findings in Inflammatory Bowel Disease

It is important to recognize the normal appearance of the bowel macroscopically and histologically. The colonic mucosa when seen through an endoscope appears glistening salmon-pink in color with a visible network of branching vessels seen beneath the

Table 4. Procedure-related and post-procedure complications in paediatric colonoscopy

Diagnostic procedure-related
Vasovagal reactions
Hemorrhage
Perforation – traction serosal; direct transmural
Pancreatitis
Splenic trauma
Therapeutic procedure-related
Perforation
Hemorrhage
Thermal injury – transmural
Post-procedure
Distension and discomfort (less if CO_2 insufflation used)
Delayed evidence of perforation or hemorrhage

mucosa. The smoothness of the mucosal surface is the hallmark of a healthy colon and there is a lack of contact bleeding, friability or exudates [36]. Microscopically, the mucosa appears flat with normal crypt density, undistorted crypt architecture, intact surface epithelium, normal mucin content and without any neutrophil infiltration [37].

The earliest changes seen in UC are the presence of diffuse erythema and dull appearance of the vascular architecture consequent to the vascular congestion and edema. The engorged mucosa leads to contact bleeding and friability when touched with an endoscope. Progressively minute ulcers appear which coalesce to form large ulcers within a background of diffuse colonic inflammation [37]. The colonic mucosa is involved in a continuous fashion from the rectum extending further up the colon. Long-standing UC leads to development of pseudopolyps (fig. 10). Earliest changes in CD are the development of focal ulcers (aphthous lesions). These ulcers gradually enlarge and become deeper leading to development of linear (fig. 11) and transverse ulcers. Characteristically the ulcers are focal with normal intervening mucosa, the so-called skip lesions (fig. 12). More severe disease can cause nodularity giving the typical cobblestone appearance (fig. 13), strictures (fig. 14) and stenosis. Terminal ileum is the most common site to be involved in CD (fig. 15) hence, as has been stressed earlier; it is imperative that every attempt should be made to reach the terminal ileum at colonoscopy.

Follow-Up and Surveillance Ileocolonoscopy

It is the practice in many units to perform a follow-up ileocolonoscopy 2–3 months after the start of treatment in a newly diagnosed case of inflammatory bowel disease since Modigliani and colleagues showed that only 29% of adults with CD in clinical and

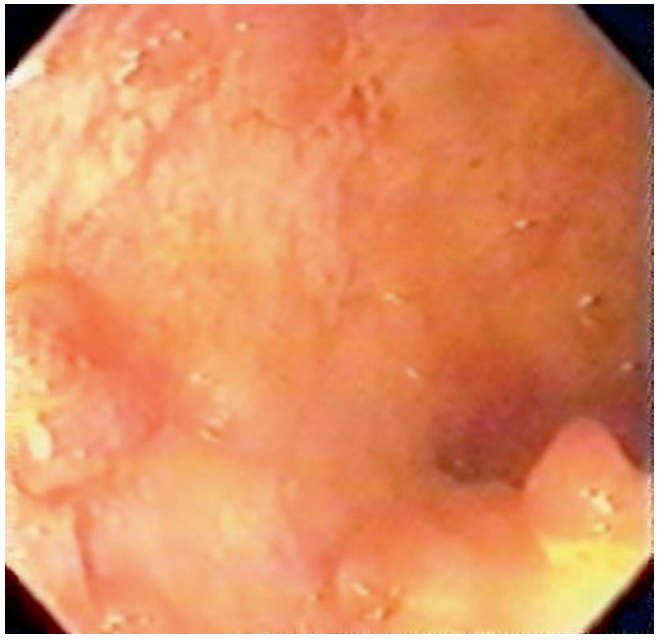

Fig. 10. Pseudopolyps in ulcerative colitis.

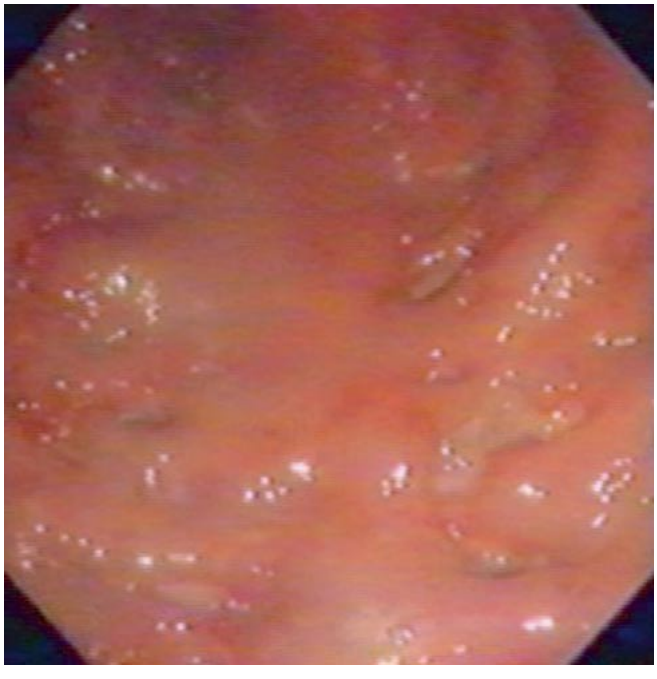

Fig. 11. Deep aphthous ulcer in CD.

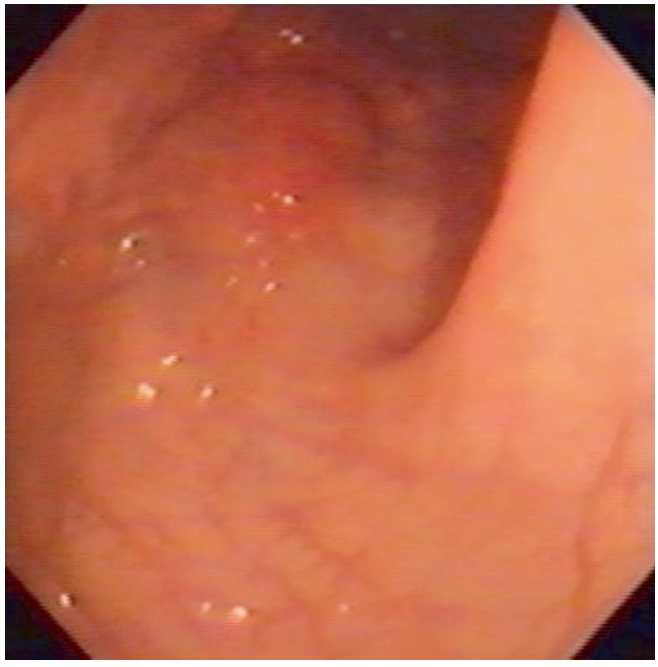

Fig. 12. Skip lesions in CD.

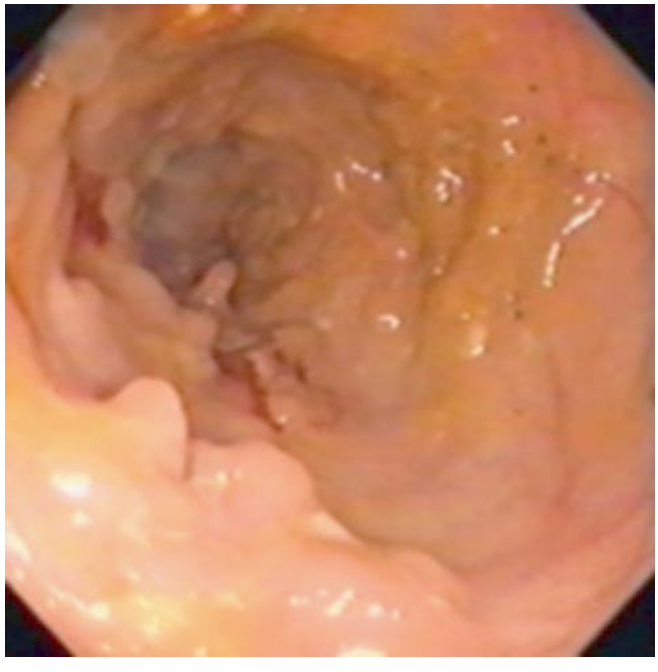

Fig. 13. Typical cobblestone appearance in CD.

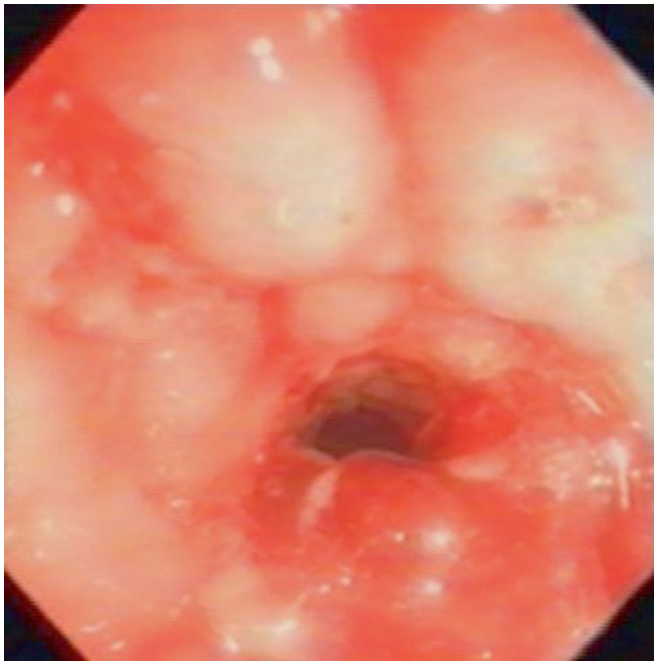

Fig. 14. Colonic stricture in CD.

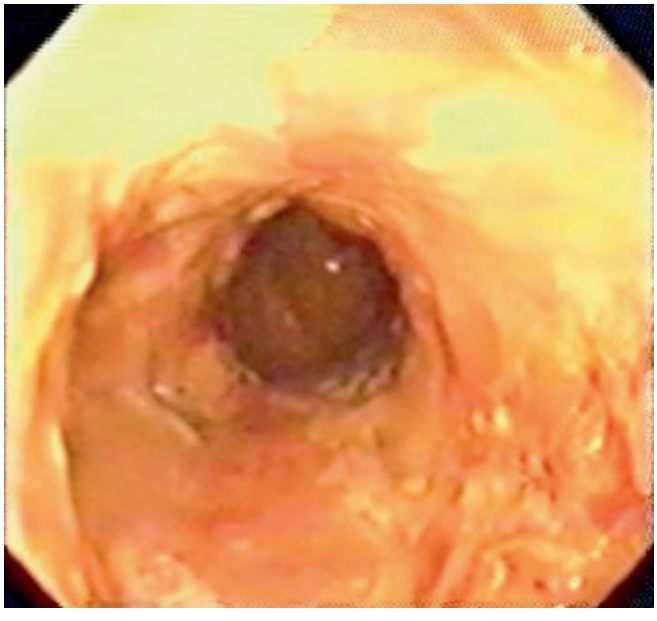

Fig. 15. Terminal ileal CD.

biochemical remission actually achieved endoscopic remission [38]. This has a number of advantages. It allows the physician to observe the mucosal efficacy of the therapy, because, in many instances, such as steroid use in colitis, the clinical improvement of the patient may not be mirrored by the mucosal improvement, which is regarded by most as the most important meter of a successful treatment regimen [39].

Enteroscopy

Enteroscopy, now a standard endoscopic procedure in adult medicine and recently reviewed [40], came of age because of the realization that the small bowel did indeed have specific pathology requiring not only diagnostic but also therapeutic expertise. Sonde-type, intra-operative-assisted push enteroscopy [41, 42] and more recently non-surgical push enteroscopy [43] has been described in children. Sonde enteroscopy has largely been abandoned in favor of push enteroscopy, given the desire for therapeutic capability. The techniques of per oral push enteroscopy and laparoscopy-assisted enteroscopy continue to evolve, and have been superseded by double balloon enteroscopy (DBE).

Double Balloon Enteroscopy

DBE is a recent development, which enables high-resolution endoscopic imaging of the entire small bowel [44]. While push enteroscopy can aid in visualization of the proximal jejunum, DBE goes a step further making it possible to examine, take biopsies and perform therapeutic procedures such as haemostasis and balloon dilatation through out the entire small bowel. This potential for mucosal biopsies and interventional endo-therapy provides significant advantage over WCE [45].

DBE has been extensively evaluated in adults with obscure GI bleeding and to a lesser extent in CD. Since CD can be confined to the small bowel alone DBE has a definite role in the evaluation of patients with suspected CD with negative ileocolonoscopy and radiological investigations. In a recent study comparing DBE to BMFT [46], DBE was able to detect early or faint lesions like aphthoid ulcers, erosions and small ulcers which were not found by BMFT. Also DBE was better in differentiating open and healed ulcers thus helpful in evaluation of response to treatment in CD. However small strictures are difficult to detect with DBE since they may be mistaken for an intestinal band.

Endosonography

Endoluminal ultrasonography of the rectum has been an established technique for years; however, more recently, an echocolonoscope has allowed combined examination

of the mucosa and the bowel wall. This is a forward-viewing colonoscope with the transducer (7.5 MHz) situated in the rigid tip of the scope [47]. Alternatively, an ultrasound miniprobe can be introduced via the biopsy channel (7.5 or 12.5 MHz). A fluid interface is necessary for all endosonography, and this can be achieved either with a fluid-filled balloon or filling the relevant colonic segment with water.

Inflammatory bowel disease appears as wall thickening and subsequent loss of the normal layer structure of the colon with progressive inflammation. Although theoretical differentiation between UC and CD is possible owing to the transmural nature of CD, it has been shown recently that active UC can have echo-texture changes extending into the submucosa and that these changes correlate with disease activity [48]. Perirectal and pericolonic fistulae and abscesses have been seen using the rigid rectal ultrasound probe, and this is a potential application for endoscopic ultrasonography [49].

New Endo-Diagnostic Methods

High Magnification Chromoscopic Colonoscopy (HMCC)

Recent improvements in technology have led to the development of a generation of endoscopes with the ability to magnify endoscopic images. The high magnification endoscope allows conventional video imaging with the facility to increase magnification instantaneously up to 100 times by a thumb activated lever. By pushing the lever downwards the magnified picture is obtained immediately and by reverting back to the normal position the image is returned to normal [50]. A topical dye like indigo carmine 0.2–2% is sprayed on the mucosa helping further to delineate the pathology. During magnification chromoscopic colonoscopy, pit patterns are observed. These pit patterns are classified according to the modified Kudos' criteria and based on the pit patterns it is possible to predict the histology as well as take targeted biopsies [51].

This technique has been extensively used in cancer surveillance in adults. HMCC has been used to evaluate UC in predicting the severity of the disease as well as in predicting relapses in those who were in a quiescent state [52].

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is an exciting new technology developed in the last 5 years. It is an adaptation of light microscopy, whereby a low power laser illumination is focused to a single point in a microscopic field of view. Light emanating from that specific point is focused to a pinhole detector. Light emanating from outside the focally illuminated spot is not focused to the pinhole and, therefore, is geometrically rejected from detection. The beam path is scanned in a raster pattern and measurements of light returning to the detector from successive points are digitized

to produce two dimensional images. Each such image thus is an optical section representing one focal plane within the specimen [53, 54].

The components of the laser confocal endomicroscope are based on the integration of a confocal laser microscope mounted in the tip of a conventional colonoscope (EC3870K; Pentax, Tokyo, Japan), which enables confocal microscopy in addition to standard videoendoscopy. The diameter of the distal tip and insertion tube is 12.8 mm. The distal tip contains an air and water jet nozzle, two light guides, a 2.8-mm working channel and an auxiliary water jet channel. The water jet channel is used for the topical application of the contrast agent. During CLE, an argon ion laser delivers an excitation wavelength of 488 nm with a maximum laser output of <1 mW at the surface mucosa. Confocal images can then be collected at a scan rate of 0.8 frames/s (1,024 × 1,024 pixels) or 1.6 frames/s (1,024 × 512 pixels). The optical slice thickness is 7 μm with a lateral resolution of 0.7 μm and z-axis range of 0–250 μm below the surface layer. Sodium fluorescein is given intravenously at the time of the procedure as a contrast agent. Thus it is possible to get cellular and sub-cellular microscopic images at the time of endoscopic procedure.

The advantages of using CLE are that as it is less invasive, there are potentially significant time, histopathological, materials, man-power and consequent financial savings to institutions conducting paediatric endoscopic services. There is no doubt that this new technique will be useful in taking targeted biopsies in patients with IBD and reduce the need to take biopsies.

Conclusions

Pediatric endoscopy results differ significantly from their adult parallels in nearly every aspect, including patient and parent management and preparation, selection criteria for sedation and general anesthetic, bowel preparation, expected diagnoses, instrument selection, imperative for terminal ileal intubation, and requirement for biopsies from macroscopically normal mucosa. The chapter has highlighted the importance of endoscopy in general and ileocolonoscopy in particular in the diagnostic and therapeutic management of IBD. Also the role of other advanced diagnostic techniques like DBE has been discussed, while wireless capsule endoscopy is discussed in a separate chapter. Endoscopy is a necessary and important investigation in the various stages of management of inflammatory bowel disease from diagnosis to surveillance of cancer. There is no dispute in the use of ileocolonoscopy in the initial assessment of patients with IBD. Recent data has shown that upper GI endoscopy also has an important role in the initial diagnosis and differentiation of IBD and hence is recommended as a part of initial investigation of all cases presenting with symptoms suggestive of IBD. Other endoscopic investigative modalities like WCE, DBE, HMCC, confocal endomicroscopy and endosonography aid in further management of IBD. Apart from diagnosis, endoscopy also has an important role in the therapeutic management of IBD.

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Approach to Clinical Diagnosis of Inflammatory Bowel Disease

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Abstract

The clinical diagnosis of inflammatory bowel disease in a child requires a high degree of suspicion. Once suspected, the primary tests that establish the diagnosis include upper endoscopy, colonoscopy, endoscopic biopsies, and radiographic imaging of the small intestine. The latter can be performed either by contrast radiography with barium, abdominal computed tomography scan, or magnetic resonance imaging of the small bowel. The differentiation of Crohn's disease from ulcerative colitis can be challenging in some patients. However, the findings of macroscopic small bowel inflammation, granulomas on endoscopic biopsy, or significant perianal disease strongly suggest the diagnosis of Crohn's disease. Newer modalities, such as serologic testing and video capsule endoscopy, may provide additional useful information in challenging patients.

Inflammatory bowel disease (IBD) in children is a once-rare condition that is becoming more prevalent. The precise reason that pediatric IBD is increasing in prevalence is unknown. However, it most likely involves a combination of genetic factors and environmental risk factors. A recent Finnish study documented the doubling in instance in pediatric IBD in a 15-year period [1]. The disease is more prevalent in Northern latitudes than in latitudes closer to the Equator [2–4]. Nevertheless, IBD can be seen in any country, in any race, and in any nationality.

The diagnosis of IBD in a child or adolescent requires a high index of clinical suspicion, and involves five steps. The first and most important step is to perform a careful history and physical examination. If IBD is suspected, relatively straightforward blood testing (including complete blood count, sedimentation rate, and albumin level) will provide additional information as to whether or not the patient should undergo further investigation. The second step is to exclude other conditions that may cause intestinal inflammation, particularly enteric infections. The third step involves performing upper endoscopy with biopsies, colonoscopy with biopsies, and radiographic

imaging of the small bowel; these interventions will formally establish the diagnosis, and allow the clinician to differentiate Crohn's disease (CD) from ulcerative colitis (UC). The fourth step is to further delineate the precise location and extent of the CD or UC, which will in turn guide therapy. The fifth step is to evaluate for extra-intestinal manifestations, including liver disease, skin disease, and eye disease. This chapter will provide an overview as to the proper approach to diagnose IBD in the child.

Diagnosing IBD is tricky, and classifying it correctly is even trickier [5, 6]. Nevertheless, the choice of the proper therapy depends completely on making a correct diagnosis. This chapter will provide an overview into how to correctly diagnosis pediatric IBD, utilizing the technologies available in 2008. As our technologies improve, the precise choice of surrogate markers and imaging studies used to diagnose IBD will undoubtedly change. However, a proper and accurate diagnosis (which includes the determination of disease type, disease location, and disease behavior) will always be used to determine the best therapy.

Suspicion of Disease

IBD can present at any age. However, in the pediatric age group it most commonly presents in late childhood and adolescence [7]. IBD is far less common under the age of 5 years. There is some evidence that IBD that starts under the age of 5 may in fact have a slightly different phenotype and natural history [8]. Presenting symptoms of both conditions are shown in table 1.

IBD is classically categorized into two types: UC and CD. UC is classically limited to the large intestine, though a number of recent studies suggest that microscopic ileitis and gastritis can also be seen in patients with UC [9, 10]. Because UC is limited to the large intestine, the most common symptoms are diarrhea and rectal bleeding. According to some recent studies of large pediatric consortia, greater than 80% of patients with UC present with blood in the stool at time of diagnosis [7, 11]. Chronic diarrhea without rectal bleeding is a much less common presentation of UC. Classically, the pain seen in UC is peri-defecatory, meaning that it occurs around the time of bowel movements, and is typically relieved after the passage of a bowel movement. Less common presenting features can include arthritis, arthralgia, erythema nodosum, or liver disease (primary sclerosing cholangitis). Malnutrition, growth failure, pubertal delay, and significant perianal disease are rarely seen in UC, and the presence should make the clinician suspect CD [12, 13].

In contrast to UC, CD can involve every region of the small bowel, from the mouth to the anus. The most common presentation is Crohn's involving the distal (terminal) ileum and the cecum or ascending colon. The other common presentations include disease limited to the terminal ileum, disease involving the ileum and different regions of the colon, or disease limited to the colon. Crohn's of the colon is more common in younger children (under age 8) than in older children [11]. CD primarily involving

Table 1. Common presenting symptoms in patients with IBD

Symptom	Comment
Rectal bleeding	more common in UC (80% vs. 40% in CD)
Diarrhea	more common in UC (98% vs. 30% in CD)
Abdominal pain	
Weight loss	
Fatigue	more common in CD
Growth failure	30–50% of CD patients, 10% of UC
Perianal disease	fistulae and large skin tags are only seen in CD
Erythema nodosum	<10% in both UC and CD
Family history of IBD	10% in first-degree relatives

Concurrent laboratory features: anemia, microcytosis, hypoalbuminemia, thrombocytosis, increased erythrocyte sedimentation rate.

the mid-jejunum, duodenum, or stomach are much less common presenting locations in children [14].

Because CD frequently involves the small bowel, rather than the large bowel, the symptoms are different from UC. Specifically, a patient with CD is more likely to present with chronic abdominal pain, often in the right lower quadrant, because the ileum is inflamed. Diarrhea without blood is more commonly seen in CD of the small bowel. However if Crohn's colitis is present, rectal bleeding is seen as in UC. Growth failure and pubertal delay are seen in between 30–50% of patients [15, 16]. The growth delay most likely occurs because the inflamed intestine produces cytokines that suppress the hypothalamic pituitary axis. In addition decreased caloric intake of patients occurs in patients with CD due to chronic anorexia, and this in turn produces pubertal delay [16].

Perianal disease is also seen in approximately 30% of children with CD at presentation, while small perianal fissures can occur both in patients with constipation and in patients with UC. CD typically presents with large perianal fissures, 'elephant ear' skin tags, or perianal fistulizing disease (fig. 1). The presence of such significant perianal disease should automatically prompt investigation for CD, though some of these patients may have simple recurrent perianal abscess [17]. Other extraintestinal manifestations (including erythema nodosum, mouth ulcers, and liver disease) can be seen in both CD and UC. Rarer presentations may include nausea and vomiting (particularly if there is ileal obstruction), chronic constipation, encopresis, and anorexia without obvious GI symptoms [18]. Therefore, CD should be considered in the differential diagnosis of the adolescent with anorexia nervosa.

A history and examination suspicious for CD should prompt inquiries about the family history. In patients with IBD, approximately 10% will have a first-degree

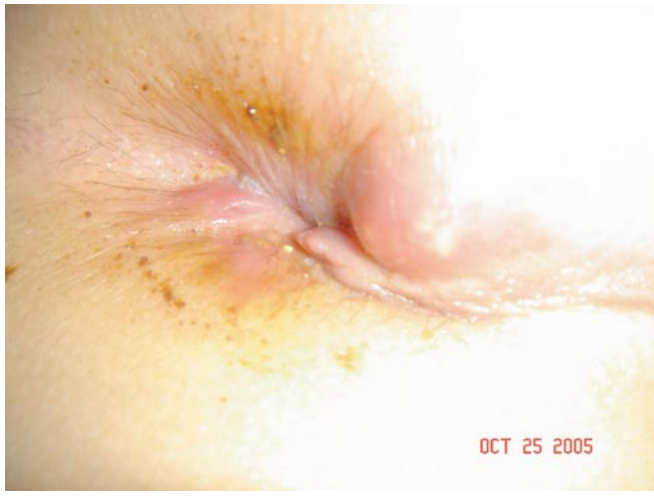

Fig. 1. Perianal abscess in a patient with CD.

relative with either CD or UC. However, approximately 90% of patients will not have a family history in a first-degree relative, so the absence of a family history should not preclude the diagnosis of CD. In general, if a first degree relative has CD, the proband is more likely to also have CD. However, UC also can be seen in relatives of patients with CD, emphasizing that CD is not strictly a genetic disease, but the product of gene-environment interactions. In addition to disease tracking by family history, disease PHENOTYPE also tracks by family history (ie a patient with terminal ileal CD is more likely to have a relative with terminal ileal CD than other types of CD) [19].

If the history and examination suggest IBD, the next step is typically laboratory studies. The most useful laboratory studies in pediatric IBD are the complete blood count, the sedimentation rate, C-reactive protein, and the serum albumin. A patient with UC will often have signs of anemia. More severe colitis will be characterized by leukocytosis, with a white blood count ranging from 15,000 to 25,000. In patients with moderate to severe CD or UC, the inflammatory response will produce an elevated sedimentation rate, elevated C-reactive protein level, elevated platelet count and decreased albumin level. It must be remembered, however, that in milder cases of IBD, 20% of Crohn's patients and 50% of UC patients will have laboratory studies that are completely normal at the time of diagnosis [20]. These patients often have more limited disease (i.e. ulcerative proctitis).

Recently, a panel of serum antibodies has been utilized by some investigators to facilitate the diagnosis of IBD [21]. The published studies suggest that the perinuclear anti-neutrophil cytoplasmic antibody (pANCA) has a sensitivity of approximately 70–80% for UC, approximately 20–30% for CD, and a 5–10% false positive rate in healthy controls [22, 23]. The anti-*Saccharomyces cerevisiae* antibody (ASCA) is highly specific for CD, primarily CD involving the ileum and cecum. However, its sensitivity is not as good, ranging from 40–60% [22]. The antiflagellin antibody (anti-CBir) may also be positive in some cases of CD [24]. While this antibody panel

may provide some additional diagnostic information, its utility in the diagnosis of IBD remains controversial. Specifically, most patients with IBD have enough clinical symptomatology to warrant their definitive evaluation irregardless of what the antibodies show [25]. In addition, if the antibody panel is used to screen patients with irritable bowel syndrome, the false-positive rate of antibodies may prompt the clinician to undertake unneeded endoscopic evaluations. Therefore, the role of the serology study in routine clinical practice remains controversial. There are some data, however, to suggest that serologic markers may be useful in predicting disease outcome, including the likelihood of requiring surgery in the future. Ongoing research will hopefully clarify these issues.

Exclusion of Other Conditions

Most patients with UC and with Crohn's colitis present with bloody diarrhea. Depending on the geographic location where the disease presents, the specific evaluation for infectious pathogens may differ. For instance, in Boston, Massachusetts, amebic infection is quite rare, and so parasitic analysis is not always routinely performed in patients with suspected IBD. In contrast, in those areas where amoeba may be more prevalent, a full evaluation for *Entamoeba histiolytica* may be necessary. At a minimum, however, the evaluation of the infectious evaluation of the patient presenting with colitis should include common bacterial pathogens, and stool for *Clostridium difficile* (table 2). In immunocompromised hosts, such as patients who have undergone renal or bone marrow transplants, graft-versus-host disease, cryptosporidiosis, and cytomegalovirus infection should be excluded. It should also be remembered that Henoch-Schonlein purpura can cause bloody diarrhea secondary to colonic vasculitis. Bowel ischemia is rare as a cause of colitis, but should be considered in patients with a compromised circulation, including patients with lupus vasculitis and congenital heart disease with impaired circulation.

As mentioned previously, CD presents with granulomatous inflammation primarily involving the ileum and/or cecum. The most common mimic of CD causing granulomatous ileitis is tuberculosis [26]. Thus, a patient with ileitis should be evaluated with a purified protein derivative skin test or chest X-ray to evaluate for tuberculosis. For patients coming from areas where tuberculosis is highly prevalent, extra care should be taken to exclude this condition before starting corticosteroid therapy. Yersinia infection can also have similar presenting features as Crohn's enterocolitis in young children [27].

It should be noted that *Clostridium difficile* can be detected at time of the disease onset in patients with IBD, and that *C. difficile* may trigger exacerbations of IBD [28]. Therefore, the positive test for *C. difficile* toxin does not exclude a diagnosis of IBD, and the decision to proceed with endoscopic investigations should be made based on the clinical presentation.

Table 2. Infectious evaluation of the patient with suspected new IBD

Stool for enteric pathogens
Salmonella
Shigella
Yersinia
Campylobacter
C. difficile toxins A and B
Stool for amebiasis in endemic areas
If watery diarrhea, consider rotavirus, adenovirus, giardia
In immunocompromized hosts
Stool and blood for cytomegalovirus
Stool AFB stain for *Cryptosporidium*
Ideally, tuberculin skin test or chest X-ray should be performed prior to corticosteroid treatment. Evaluation for tuberculosis is mandatory prior to treatment with infliximab or adalimumab.

Many patients with infectious or acute self-limited colitis (ASLC) will have negative cultures. The poor sensitivity of stool cultures probably reflects the limitations of our current culture based techniques, and implies that we have yet to discover all the pathogens that cause colitis. According to one study comparing ASLC to IBD, the sensitivity of culture in self-limited (presumed infectious) colitis was probably about 50% [29]. In patients with bloody diarrhea where there is uncertainty about the diagnosis, colonoscopy may help differentiate IBD from UC. Specifically, IBD typically has a more severe endoscopic appearance of inflammation, and histologic signs of chronic change (crypt branching, crypt distortion, basal plasmacytosis) are seen on biopsy [5, 30].

Differentiating Crohn's Disease from Ulcerative Colitis

Assuming that the IBD is suspected on the basis of chronic diarrhea or rectal bleeding, and that other conditions have been excluded, the next appropriate step is to perform a detailed investigation of the bowel. This is typically done with three tests: upper endoscopy, colonoscopy, and contrast imaging of the small intestine.

Upper Endoscopy

In 2008, the formal diagnosis of IBD is typically made by the endoscopist. In children, assistance by an anesthesiologist to allow for either general anesthesia or deep

sedation allows for a more careful and thorough endoscopic examination. Therefore, in many large centers, the initial endoscopic evaluation of a child with IBD is done either under general anesthesia or with propofol administered by an anesthesiologist. Therefore, even though colonoscopy is the most important part of the endoscopic examination in patients with IBD, upper endoscopy is often performed at the the initial diagnostic evaluation, since the child is already under anesthesia.

There have been a number of prospective studies of upper endoscopy that have been performed on patients with IBD, and all of these demonstrate the diagnostic value of upper endoscopy. Upper endoscopy will identify gastritis in between 50 and 70% of patients with IBD, whether that disease is either UC or CD. In approximately 10–20% of patients, however, the upper endoscopic findings may assist in the differentiation of CD from UC, because they will identify granulomatous inflammation either in the duodenum, stomach or esophagus [9, 10, 31]. The finding of such upper GI tract disease may also change therapy, in that CD limited to the ileum or colon may sometimes be treated only with salicylates, but more systemic inflammation may require immunosuppressive therapy.

Given the additional information provided by upper endoscopy in children with suspected IBD, the IBD Working Group of ESPGHAN (Porto Group) has recommended that upper endoscopy be a routine part of the initial diagnostic evaluation in children with IBD [32]. During this evaluation, it is recommended that photographs be taken of any pertinent endoscopic findings and that routine sampling be performed with the duodenum, the antrum, the corpus and the esophagus (fig. 2).

Colonoscopy

Colonoscopy remains the most valuable diagnostic test in the evaluation of a child with known or suspected IBD. The colonoscopy must be performed on a child that is adequately comfortable and has received an adequate bowel prep so that all walls of the colon can be adequately visualized. In a well-sedated or anesthetized child over two years of age, the colonoscope can generally advanced to the cecum, the ileo-cecal valve can be identified, and the terminal ileum can be intubated. From that point, the pattern, region and distribution of endoscopic inflammation should be charted in the ileum, cecum, the ascending colon, the transverse colon, the descending colon, sigmoid colon, and rectum. A flow sheet to identify features on the colonoscopy that suggest CD was recently published by the IBD working group of NASPGHAN [5].

The endoscopic features of UC include granularity (sandpaper appearance, friability (contact hemorrhage), erythema, and mucopus (mucopurulent exudates) [29]. UC involves the entire circumference of the bowel (diffuse inflammation) (fig. 3). The inflammatory changes in UC typically begin at the anus; the inflammation extends proximally up to some point where there is a transition zone between abnormal inflamed mucosa and normal mucosa. This transition point is frequently referred

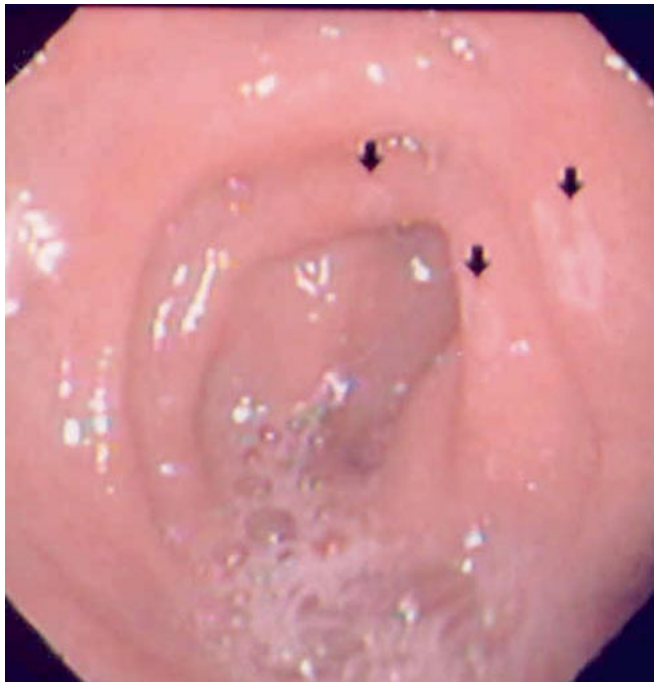

Fig. 2. Duodenal aphthae in a patient with CD.

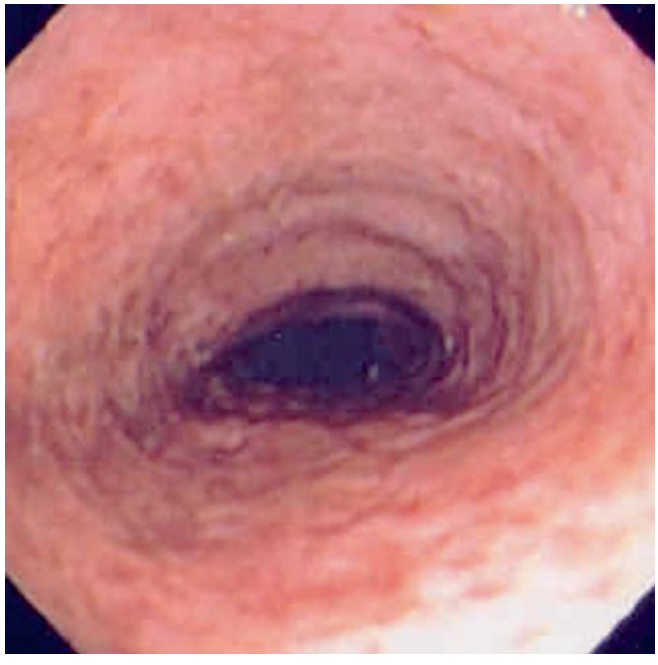

Fig. 3. Colonoscopy in moderately active UC – note granularity and loss of vascular pattern in the colon.

to as the line of demarcation. In approximately 80% of children, UC is pan-colonic, meaning the inflammation extends from the rectum all the way to the cecum. In most patients with pan-colonic UC, the ileo-cecal value is usually widely patent, and the

terminal ileum is well visualized. The ileum will frequently look normal, but it may have a somewhat granular appearance with some mild erythema. This appearance is termed 'backwash ileitis,' and should not necessarily be confused with CD, which causes ileal stenosis and ulceration.

Approximately 20–25% of children with UC will have more limited disease. The most common presentation is 'left-sided colitis', where inflammation extends to the rectum to some point more proximal into the descending colon, usually up to the splenic flexure. At that point there is a line of demarcation, and the transverse colon and ascending colon are usually normal. It's important to note, however, that in patients with left-sided UC, a small amount of peri-appendiceal or cecal inflammation can be seen. This inflammation is referred to as 'the cecal patch,' and should not be confused with CD [33, 34]. In patients with left-sided UC, there is usually no backwash ileitis [35].

A small subset of children (approximately 5–10%) will have disease limited to the rectum (ulcerative proctitis). In this disorder, the inflammation only extends up about 15 cm, and then there is a line of demarcation with the remainder of the colon being normal [36]. In proctitis a 'cecal patch' can be seen, but the terminal ileum is normal.

Most patients with CD, even those involving the colon, have a dramatically different appearance. The most common type of CD seen is CD in the ileum, cecum and ascending colon. In these patients there is minimal inflammation of the rectum, sigmoid, descending and transverse colon; very often these areas appear completely normal. When one extends to the ascending colon, however, one will see a thickened, 'cobblestoned' ascending colon with a thickened and stenotic ileocecal valve (fig. 4) [37]. If the endoscopist can traverse the stenotic ileocecal valve, findngs that suggest Crohn's ileitis include 'cobblestoning' of the ileum, deep lineal ulcers or ileal stenosis. The finding of granulomatous inflammation in the ileum or colon suggests CD rather than UC.

In more extensive CD involving the colon, there is frequently sparing of the rectum. However, the morphological appearance of the colon demonstrates a patchy colitis with areas of profoundly thick and ulcerated mucosa and intervening normal areas (skip areas). Careful biopsy of both the inflamed and more normal appearing areas of the colon may demonstrate granulomas in approximately 25% of patients with CD. Therefore, this author and others suggest the endoscopist to take at least two biopsies from the ileum, and two biopsies from each segment of the colon (ascending, transverse, descending, sigmoid colon, rectum).

Contrast Imaging of the Small Intestine

The last remaining routine test to assess a patient with IBD is contrast imaging of the small intestine. The traditional way of performing this is by barium upper GI with small bowel follow-through [38]. A well conducted barium study typically shows exquisite mucosal detail, and in the hands of a skilled radiologist can identify stenosis,

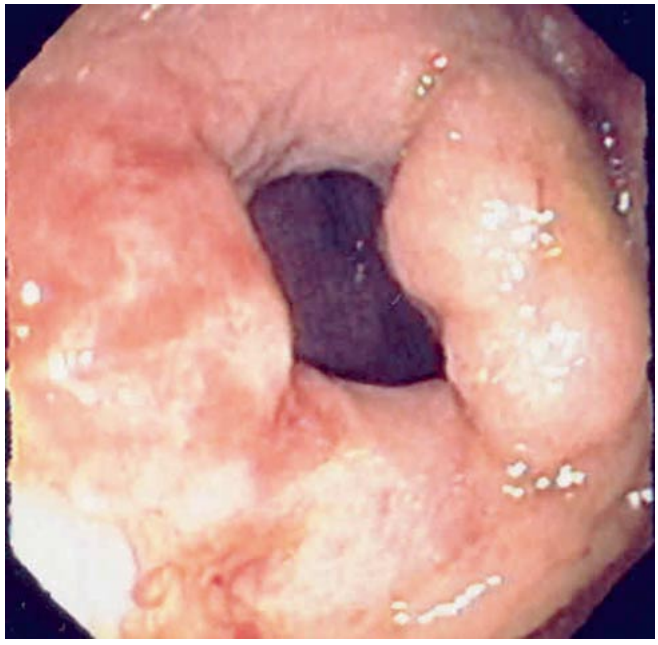

Fig. 4. Ileocecal valve in CD – edema and narrowing.

thickening and/or narrowing of the jejunum and/or ileum. Recently, however, additional techniques have been developed to increase the sensitivity of small bowel imaging. A study of 46 children undergoing both barium studies and ileoscopy suggest the sensitivity of an upper GI with small bowel follow through is about 85–90% that of the 'gold standard' of ileoscopy [39]. In patients where the ileocecal valve is strictured and the terminal ileum cannot be intubated, radiographic imaging of the ileum may be the only way to assess the extent and severity of the disease.

Computer tomography of the small intestine is frequently used, particularly in the patient with a suspected abdominal abscess. In some cases a patient with CD may present for the first time to the emergency room with right lower quadrant pain. In this case, the computed tomography study will both evaluate the terminal ileum to look for signs of CD, evaluate for the presence or absence of small bowel lymphoma, and exclude appendicitis (fig. 5) [40]. Therefore, in a patient presenting with new onset right lower quadrant pain, and in whom the differential diagnosis is unclear, CT scan is a very useful test.

Other modalities used to evaluate the small bowel in IBD include magnetic resonance imaging (MRI) and ultrasound. MRI requires a patient to ingest large volumes of contrast material and remain in a scanner for up to one hour, so it is not feasible in young children. The advantages of MRI include the test's sensitivity for demonstrating bowel wall thickening, and that MRI readily identifies fistulae and strictures. In addition, MRI does not involve any radiation exposure [41]. However, the MRI technique is highly operator-dependent. Some centers have also utilized ultrasound imaging to carefully evaluate the small bowel, but this study is once again highly

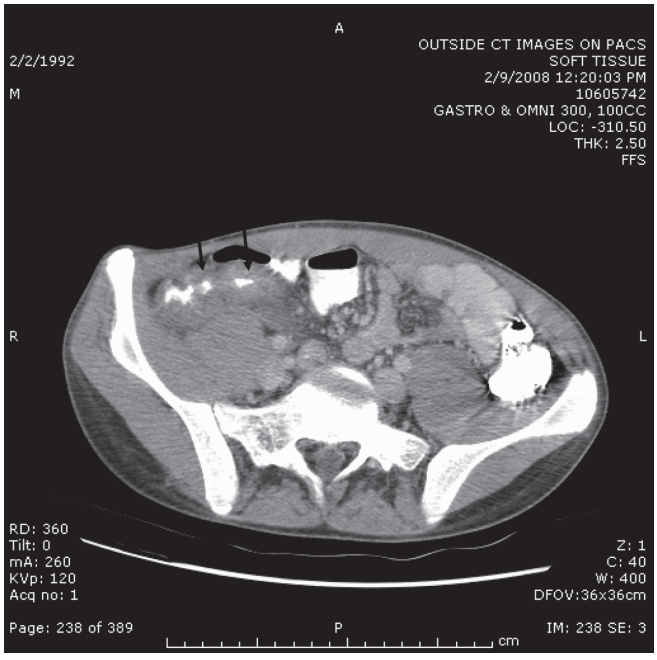

Fig. 5. Abdominal CT scan in CD, demonstrating marked thickening of the ileum (arrows).

operator-dependent [42]. Given that small bowel imaging is a collaboration between the physician ordering the test and the radiologist performing the study, the clinician should discuss the case with the radiologist and jointly determine the optimal test.

The most recent technique develop to image the small bowel is the video capsule endoscopy. In this study, a small 'pill camera' is either swallowed or placed into the stomach with an endoscope. The pill camera gradually peristalses through the small intestine and is ultimately excreted in the stool. During its one-day travel down the intestine, the camera can take 10,000 or more pictures of the small intestine and beam them to a computerized digital camera. This test has been shown to be highly sensitive in the diagnosis of subtle CD lesions, and therefore if the clinician has a high index of suspicion and other testing is negative, a pill camera should be considered [43, 44]. One major disadvantage of the pill camera, however, is that if the small bowel has a stricture, the metal capsule can become impacted in the region of the stricture and may require surgical removal. Therefore, a contrast study of some sort to exclude a small bowel stricture is needed before having a patient undergo a pill camera study.

Utilizing the 'Montreal Classification' to Classify Crohn's Disease and Ulcerative Colitis

The literature on IBD is filled with multiple different terms to describe of disease location, including 'ileitis', 'ileocecal disease', 'ileo-ascending colon disease', 'subtotal

Table 3. Summary of 'Montreal Classification for IBD' [6]

Crohn's disease
Age
A1 – age less than 17 years
A2 – age 17–40 years
A3 – age over 40 years
Location
L1 – terminal ileal disease
L2 – colonic disease
L3 – terminal ileal and colonic disease
L4 – upper GI disease more than 90 cm proximal to terminal ileum
Behavior
B1 – nonstricturing, nonpenetrating
B2 – stricturing (causing stenoses with obstruction)
B3 – penetrating (causing intestinal perforation with fistulae or abscesses)
For patients with perianal disease, the modifier 'p' is added (e.g. A1L1B1p)
Ulcerative colitis
E1 – ulcerative proctitis (disease limited to the rectum).
E2 – left-sided UC (inflammation distal to the splenic flexure)
E3 – subtotal or pancolitis (inflammation extending proximal to the splenic flexure)

colitis', 'jejunoileitis', etc. All these terms make it difficult for a physician reviewing the literature to accurately phenotype patients. In an attempt to standardize medical descriptions in the literature for both patient care and research studies, working groups have developed terminology to classify disease behavior and disease location. The first of these working groups met in Vienna approximately 10 years ago, and the second World Congress working group met in Montreal in 2005 [6, 45]. Silverberg et al. [6] have now published a detailed paper with the 'Montreal Classification' of the Crohn's Disease and Ulcerative Colitis. They classify patients with CD according to three criteria: age at diagnosis, disease location, and disease behavior. This information is summarized in table 3. In addition, they have developed standard terminology for UC. It is recommended that after a definitive diagnosis of IBD has been made, that the 'Montreal Classification' be utilized to characterize CD into various subtypes.

However, it should be noted that disease behavior can change over time. For example, a patient characterized as behavior B1 (nonstricture nonpenetrating disease) can either develop an abdominal abscess, thus changing disease behavior from B1 to B3, or develop an ileal stricture, thus changing behavior from B1 to B2 [46]. Additional work on phenotyping will no doubt work to improve standardization and additionally classify patients with IBD.

Extraintestinal Manifestations

Patients with IBD can develop a large number of extraintestinal manifestations, including primary sclerosisng cholangitis, pulmonary disease, uveitis, or arthritis. After a diagnosis of IBD is made, it is important that the physician caring for these patients have a high degree of suspicion for these conditions. It's recommended that a liver function test be screened twice a year at the minimum to check for any signs of hepatitis or increased gammaglutamyl transpeptidase [47]. We also routinely recommend an eye exam once a year to screen for patients for uveitis. Patients on chronic corticosteroid therapy also benefit from yearly eye exams, because corticosteroids elevate interocular pressure and cause glaucoma. In addition to 'routine' extraintestinal manifestations, patients with active disease are susceptible to complications from inflammation (hypercoagulable state, thrombosis, osteopenia, micronutrient deficiency), and also from medical therapy (e.g. corticosteroid-induced mood alterations) [48, 49].

Conclusion

The most important aspect to properly diagnosing a patient with IBD is having a high index of suspicion for the diagnosis. Features such as weight loss, bloody diarrhea or positive family history of IBD should prompt an initial screening investigation with CBC, sedimentation rate and albumin level. While these tests do not definitively diagnosis or exclude IBD, they can suggest a diagnosis. It should be noted, however, that these laboratory tests can be normal, so in patients with a high index of suspicion, upper endoscopy, colonoscopy and small bowel imaging should be performed. If the IBD is demonstrated, use of the Montreal Classification will help classify Crohn's and UC into various subtypes. The correct diagnosis will then facilitate proper therapy according to disease location.

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Growth and Puberty in Inflammatory Bowel Disease

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Abstract

Growth failure and delayed puberty are important features of many patients with inflammatory bowel disease, particularly those with Crohn's disease. In Crohn's disease growth may be abnormal before diagnosis and height is inversely proportional to the length of delay in diagnosis. Height is particularly abnormal in patients with jejunal disease. During the course of the illness growth rate is often low, although only 25% of patients develop short stature. Final adult height is decreased, but shows improvement compared with height at diagnosis. The inflammatory process appears to contribute to abnormal growth, through cytokine-induced disturbance of the IGF system. This can be corrected by regimens of enteral nutrition. Genetic factors may influence height as shown by the effect of a polymorphism of the IL-6 gene which was linked to shortness at diagnosis. Therapy for growth failure should aim to induce remission in the primary disease. In prepubertal patients with localized colonic disease intestinal resection has been followed by excellent catch-up growth. Delayed puberty is common and may be treated in boys by short-term testosterone replacement which can induce catch-up growth and improve confidence significantly.

Disturbances of linear growth and the normal onset and progression of puberty are common features in a number of chronic childhood diseases. These disturbances are particularly seen in disorders, such as Crohn's disease, cystic fibrosis and juvenile chronic arthritis, where chronic inflammation is a major pathogenetic feature. The addition of a nutritional insult, as for example in coeliac disease, to the inflammatory process is likely to exacerbate the clinical problems. Chronic illness places major physical and psychological burdens on the growing child and adolescent. If in addition to the primary disorder, which may be difficult to cure or control satisfactorily, linear growth is disturbed and the onset of puberty is delayed, additional stress is imposed. This chapter will discuss the epidemiology, pathogenesis and management of disturbances of growth and puberty in childhood inflammatory bowel disease.

Linear Growth

Crohn's Disease

At Diagnosis

Abnormalities of linear growth have long been documented as complications of paediatric Crohn's disease [1, 2]. A damaging effect of Crohn's disease on growth can be seen even before the diagnosis is made and growth velocity has been reported to be abnormally decreased with a significant percentage of cases being underweight and having abnormal height at diagnosis [3]. The degrees of these abnormalities have recently been documented in a large UK epidemiology study, with mean weight in 605 children being –1.1 SD (95% CI –1.2 to –0.9) and mean height in 539 patients being –0.5 SD (–0.7 to –0.4) [4]. A negative relationship has also been demonstrated between the duration of pre-diagnosis symptoms and height standard deviation score (SDS) at diagnosis [4].

Consequently, earlier diagnosis and treatment can beneficially influence the growth prognosis during the course of the disease. Awareness of the early, frequently non-specific, symptoms of Crohn's disease by family doctors and general paediatricians is particularly important. Growth failure may be the presenting symptom of Crohn's disease (fig. 1) [4] and screening for the presence of occult inflammation by measuring ESR and C-reactive protein forms part of the baseline investigations of children and adolescents with short stature.

The influence of jejunal disease on growth, being present at diagnosis in 20% of new cases, was suggested [5], but this association has now been clearly demonstrated [4].

During the Course of the Illness

Longitudinal studies have demonstrated impaired growth rate [6] and, on cross-sectional analysis, height is abnormally low in approximately 25% of patients [7]. Growth velocity is frequently decreased without the patient becoming short [8]. Collaboration between paediatric endocrinology and gastroenterology services and the introduction of formal auxological assessment to the gastroenterology clinic will assist in identifying children with subnormal growth velocity. Puberty is frequently delayed and a late adolescent growth spurt can contribute to relative short stature during the immediate pre-pubertal period [8].

Final Adult Height

There are only a small number of reports which have analysed final adult height in patients diagnosed with paediatric Crohn's disease [6, 9]. A number of factors may affect adult height including age at diagnosis, severity and distribution of inflammation, puberty status and different treatment modalities. A recent study has analysed all of these variables in a large cohort of patients [10]. The findings in 123 patients

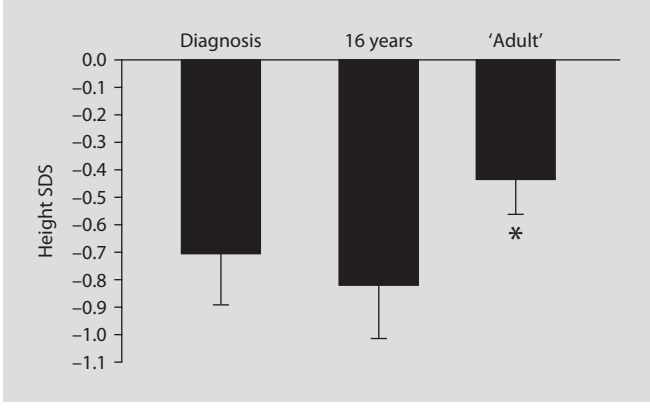

Fig. 1. Mean height SDS at diagnosis, at age 16 years and at final adult height in 91 patients with pediatric-onset Crohn's disease. Mean final height was greater at final adult height than at diagnosis (* p = <0.05) [10].

under 16 years of age showed that mean height at diagnosis was –0.5 SDS, which improved to –0.29 SDS at adult height, indicating a benefit of therapy on growth potential (fig. 1). However, a significant proportion of the patients (19%) achieved an adult height which was >8.0 cm below their mid-parental target height. As the length of symptoms before the diagnosis correlated negatively with height SDS at diagnosis [4], which itself was related to adult height SDS, earlier diagnosis of paediatric Crohn's disease can beneficially influence long-term growth. The use of corticosteroids in patients treated in specialist clinics in the UK is largely limited to those failing treatment with enteral nutrition. Although long-term steroid use may suppress growth, the use of short courses did not appear to have a negative impact on height [10].

Pathogenesis of Growth Failure

Nutritional Status and Inflammation

The pathogenesis of abnormal growth in Crohn's disease is almost certainly multifactorial. Nutritional deficit associated with abdominal pain, weight loss and diarrhoea are important presenting features. In the UK epidemiological study, weight loss was a feature at diagnosis in 58% of children [4]. Growth failure has traditionally been attributed chiefly to undernutrition [3, 11]. Reversal of deficiency of serum IGF-I levels following oral nutritional supplementation also emphasized the likely impact of nutrition on the biochemical indices of growth [12]. The same endocrine changes were also seen during a regimen of enteral nutrition [13].

However, more recent data has demonstrated that inflammation per se appears to suppress growth through secretion of cytokines [14]. Elevation of serum interleukin (IL)-6 and IL-1β were demonstrated in Crohn's disease patients in relapse and these levels correlated negatively with serum IGF-1 [15]. A longitudinal study in children and adolescents of IL-6, C-reactive protein (CRP) and IGF-I during enteral nutrition,

showed clearly that IL-6 and CRP decreased significantly and IGF-I increased after 7 days, whereas no changes in nutritional variables were seen until day 14 [16]. These data indicate that inflammation alone, through the action of cytokines, can suppress physiological mechanisms linked to growth. Studies from the Gastroenterology Unit at Queen Mary School of Medicine, University of London have shown that in prepubertal rats, chemically induced colitis induced growth retardation which accounted for approximately 40% of their growth deficit [17]. The same group has now taken this hypothesis further by administering anti-IL-6 antibodies to rats with colitis. These antibodies did not improve nutrient intake but significantly restored linear growth ($p = 0.023$) and increased serum IGF-I ($p = 0.05$) [18].

Genetic Influences

Expression of IL-6 is increased in Crohn's disease and circulating levels parallel disease activity [14, 19]. IL-6 expression, induced by using transgenic techniques in mice without inflammation results in growth failure and reduced circulating IGF-I [20]. The human IL-6 gene is located on chromosome 7p15–7p21 and a functional G→C single nucleotide polymorphism of the IL-6 gene has been demonstrated at position –174 of the promoter [21]. The GG allele was associated with greater induction of IL-6 compared to the GC or CC alleles. In children with Crohn's disease, it has been demonstrated that at the time of diagnosis, the presence of the IL-6 GG genotype was associated with significantly decreased stature ($p = 0.031$) (fig. 2) and higher CRP levels ($p = 0.027$) compared with the GC and CC genotypes [18]. Investigation of the NOD2 gene in patients with Crohn's disease has shown no association between the NOD2 genotype and growth failure [22].

Treatment of Growth Failure

Enteral Nutrition

Regimens of enteral nutrition, usually consisting of a palatable polymeric (whole protein based) formulae, are widely used in the management of paediatric Crohn's disease. Reversal of growth failure was reported in response to this form of therapy [12] and superiority of height velocity compared to steroid therapy was also established [23]. The diet is usually given as sole therapy with other nutrients being excluded and the relatively short term nature of this treatment makes changes in linear growth difficult to detect. However, normalization of CRP, ESR, PCDAI and IGF-I have been clearly demonstrated [13, 16].

Medical Therapy

Successful treatment and induction of remission is the primary aim of the management of Crohn's disease and will provide the most favorable environment for improvement in growth and puberty [24]. Steroid treatment has long been the mainstay of

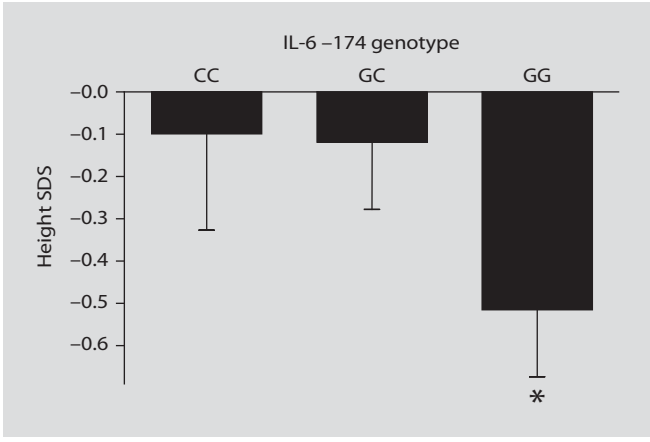

Fig. 2. Height at diagnosis varies by IL-6 genotype in children with Crohn's disease. Height SDS was more reduced in children with the GG genotype at diagnosis (n = 153). * p = 0.031 for GG vs. GC/CC [18].

medical therapy and alternate day corticosteroid administration can induce catch-up growth in Crohn's disease. Other immunosuppressive therapies such as azathioprine, 6-mercaptopurine, cyclosporine and more recently biological agents such as infliximab have also been reported to be associated with improved growth [25]; however, few randomized clinical trials to assess their effect on longer term growth as a primary end-point have been performed.

Surgical Therapy

The use of intestinal resection to remove inflamed intestine is not widely practiced, unless under emergency circumstances. As an elective procedure, in carefully selected patients with localized disease, colectomy or hemi-colectomy can result in dramatic improvement of linear growth [26, 27]. This improvement is far greater when the procedure is performed before or during early puberty [8]. If remission can be induced by removal of all inflamed bowel, catch-up growth will occur followed by the patient's own puberty growth spurt. If inflammation is widespread throughout both small and large intestines, this therapy will probably not significantly improve growth.

Ulcerative Colitis

There are very few studies looking specifically at linear growth in ulcerative colitis. It has been reported that in patients diagnosed under the age of 5 years, 11% had failure to thrive [28]. Cytokine levels are, however, elevated in paediatric ulcerative colitis [15]. However growth suppression is less marked than in Crohn's disease possibly because nutritional deficiency is less prominent [4]. Catch-up growth was reported after colectomy in ulcerative colitis [29] and long-term steroid therapy is likely to contribute to growth suppression [30].

Puberty Development

Chronic inflammatory diseases such as Crohn's disease and systemic juvenile arthritis may be associated with significantly delayed puberty [31]. Delayed puberty frequently complicates the clinical course of young patients with inflammatory bowel disease, more so in Crohn's disease than in ulcerative colitis. In Crohn's disease puberty is most often delayed in patients in whom a remission has never been achieved or who had frequent relapses in the pre-pubertal period, In a study of young patients with Crohn's disease, menarche occurred at the age of 16 years or later in 73% of female patients in whom disease onset preceded puberty. Menarche occurred at 14 years of age or younger in all patients with ulcerative colitis. Onset of puberty was also delayed in boys and girls with active Crohn's disease and the duration of puberty was longer, related to frequent episodes of relapse [8].

Aetiology and Pathogenesis of Pubertal Delay

Undernutrition, being very common in Crohn's disease and less so in ulcerative colitis, has been thought to be the main reason for delayed puberty [4]. Nutritional supplementation has been reported to induce onset of puberty in Crohn's disease patients [12] although the response to nutritional support will depend on the underlying disease activity. Dramatic catch-up of puberty development has been seen when remission of Crohn's disease has been induced by successful intestinal resection [8].

Observations in Experimental Animals

Rats with chemically induced colitis also have delayed puberty [32]. It is likely from studies described above on the different effects of inflammation and undernutrition on linear growth [16, 17] that inflammation, mediated by cytokine secretion, also has an effect on puberty. It has been our clinical experience that male patients with Crohn's disease, who have active disease may be resistant to the clinical effects of testosterone replacement therapy, possible due to cytokine-induced impairment of androgen receptor function. There have been no studies that have set out to determine which specific cytokines impact on puberty.

Management of Delayed Puberty

Sex steroid therapy has a place in the management of delayed puberty in chronic illness. Many patients, particularly boys, are psychologically disturbed by their failure to enter or progress through puberty. Few studies on the effects of testosterone replacement on puberty and linear growth in Crohn's disease have been performed. It is likely that depot testosterone administration for 3–6 months, using doses of 100–200 mg monthly of testosterone esters or ethinylestradiol 4–6 μg/day in girls can be beneficial in advancing pubertal development. The attainment of adult height will not be compromised using such regimens.

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Treatment by Enteral Nutrition in Inflammatory Bowel Disease

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Abstract

Exclusive enteral nutrition remains an important therapy in children and adolescents with Crohn's disease. Despite the lack of large randomised trials, a number of prospective cohort studies document the efficacy of this therapy. In addition, the evidence that exclusive enteral nutrition as therapy is able to achieve mucosal healing is well established. However, to achieve a clinical remission in around 80% of children requires a multi-disciplinary team of committed dieticians, nurses and physicians to support the child and family. It is also clear that poor compliance or partial enteral nutrition does not lead to the anti-inflammatory effects seen with exclusive enteral nutrition. The ability to offer an effective alternative to corticosteroids for remission induction in acute Crohn's disease also minimises a further negative impact on growth. The use of immunosuppressants (i.e. thiopurines) earlier in the course of disease provides an ideal opportunity for a course of exclusive enteral nutrition to induce remission while awaiting the delayed benefits of thiopurine activity. Until it is possible to better predict which patients will have a severe disease course and therefore might warrant a 'top-down' approach, exclusive enteral nutrition remains an effective, efficacious and side-effect-free therapy to induce mucosal healing and clinical remission in patients with active Crohn's disease.

Nutritional impairment and delay of growth and puberty are common clinical manifestations of Crohn's disease (CD) in children and adolescents. Although undernutrition and short stature may also be a feature of chronic ulcerative colitis (UC), they are much less frequently encountered. Loss of appetite, impaired absorption and increased caloric requirements are held responsible for the malnutrition associated with inflammatory bowel disease (IBD), which is present in up to three quarters of patients with active disease. Enteral nutrition – defined as the provision of a liquid formula diet by mouth or nasogastric tube [1] – has been used in the treatment of IBD for over 30 years. In addition to its ability to restore nutritional status in CD, nutritional therapy has a specific anti-inflammatory action. Unfortunately, there is no such firm evidence in paediatric patients with UC although the provision of adequate

nutrition still remains important. The development of a range of complete formula diets of varying compositions has now made enteral nutrition a highly desirable and practical alternative to parenteral nutrition.

In 1973, Georgina et al. [2] first suggested that treatment of malnutrition could lead to resolution of inflammation in a child with CD. Logan et al. [3] produced evidence that intestinal protein and lymphocyte loss decreased in adult Crohn's patients who were fed with an elemental diet. In Quebec, Moran et al. [4] described 4 children with Crohn's whose growth failure responded to an elemental diet. Larger studies confirmed this observation [5, 6]. At St. Bartholomew's Hospital in London, a small study using a semi-elemental diet was shown to be as effective as conventional steroids in the induction of a clinical remission [7]. Most importantly though this study showed there was no short-term growth whilst on steroid therapy, whereas enteral nutrition led to temporary growth acceleration. In some children growth was increased for a sustained period of time even after the discontinuation of enteral feeding [8].

Indications for Nutritional Treatment

Adequate nutritional support is an essential part of the long-term management of IBD. In most cases this involves the provision of nutritional supplements to complement an otherwise inadequate intake. For UC, no exclusively nutritional therapy has been shown to be therapeutically effective. In contrast, over many years patients with active CD have responded well to exclusive enteral nutrition (EEN). There have only been anecdotal reports of patients with indeterminate colitis responding to EEN, although the responders are likely to be those with a more Crohn's-like phenotype.

Although often not as severe as in patients with CD, malnutrition does occur in children with UC [9]. Whilst exclusive nutritional therapies are of no benefit in treating acute UC, nutritional support plays a vital role in minimising further morbidity. Although the concept of continuing enteral feeds during an episode of acute colitis may raise concerns in some, the evidence clearly suggests that equal nutritional improvement occurs with total parenteral nutrition and total enteral nutrition in active colitis [10]. Not only does the latter lead to fewer complications, it is less costly, more physiological and much simpler to provide.

Enteral Nutrition

Exclusive Enteral Nutrition

EEN has been shown in several paediatric studies to be a safe and effective first-line therapy for children with CD [11, 12]. A paediatric meta-analysis of all available data

suggested no significant difference in efficacy between corticosteroids and EEN at inducing a remission in acute CD [13]. However, almost all larger meta-analyses that apply more stringent inclusion criteria (and hence select almost exclusively adult studies) suggest that corticosteroids are more effective than EEN [14]. It may be that poor compliance and more advanced disease makes nutritional therapy less effective in adult patients. Given the potential benefits on growth and nutrition, EEN is therefore still an ideal primary therapy in a child with newly diagnosed CD. Large adult studies [15], as well as some of the smaller paediatric studies [12], suggest that disease distribution does not effect the efficacy of the treatment. However, randomised paediatric data have confirmed that partial enteral nutrition (50% of recommended daily requirements) is much less effective at achieving a clinical remission than an exclusive enteral diet (15 vs. 40%, respectively) [16]. More recent retrospective data, however, have shown that clinical remission with isolated colonic disease may only be about 50%, compared to 75–80% in the presence of any macroscopic ileal involvement [17]. Although there is only anecdotal evidence on the response of oral and perianal CD to EEN [18], the authors have only made use of EEN as an adjunct to immunosuppressive therapy in treating perianal CD.

Adverse effects to using EEN in CD are very rare. However, we reported a case of refeeding syndrome in a child following her presentation with severe Crohn's colitis. A rapid loss of weight over the preceding 4 weeks, followed by treatment with exclusive polymeric nutrition, led to a dramatic fall in serum phosphate and signs of hypervolaemia in the first few days of treatment [19]. Adequate supplementation of phosphate and magnesium in the first few days of therapy in severely malnourished children is therefore advisable.

Elemental Diet

An elemental formula is an extensively hydrolysed feed whose protein source consists of amino acids or short chain peptides, with short chain carbohydrates and added fat, minerals and vitamins. The National Aeronautics and Space Administration (NASA) had initially designed elemental diets for astronauts [20], with the intention of providing a nutritionally complete diet of which as much as possible would be absorbed. However, whilst absorption was limited mainly to the upper small bowel, the diet did not prevent the production of stool as had been hoped.

Nutritional therapy was initially used in IBD as an adjunct in malnourished patients with growth failure. Elemental diets were developed and first used as sole therapy for IBD in adults in the 1970s [21]. It became apparent that nutrition had a beneficial effect on disease by reducing the increased gut permeability characteristic of CD [3]. Logan et al. [3] studied 7 adults with extensive jejuno-ileal CD who showed a reduction in both intestinal protein and lymphocyte loss during a period of elemental feeding.

In 1973, Giorgini et al. [2] reported the first successful use of enteral nutrition in a child with acute CD. The same group later showed that exclusive constant rate elemental nutrition (CREN) was as effective as steroid therapy at inducing a remission [22]. While both these studies had few patients, they gave the first insights into the possible benefits of nutritional therapy as a treatment for childhood CD. In addition to achieving disease remission, nutritional therapy was also found to have beneficial effects on inflammatory masses and fistulae [22]. Simultaneously, both Morin et al. [4] and O'Morain et al. [23] documented that an elemental diet improved linear growth in several children with active CD.

In the beginning continuous feeding [5, 6] and then overnight feeds predominated [7] for the induction of remission. Supplementation of an elemental diet with glutamine, a gut-specific metabolic fuel, did not further improve efficacy, although the small numbers in this study make conclusions difficult [24].

Semi-Elemental Diet

Following the successful use of elemental diets, feeds containing short chain peptides were suggested to be a better nitrogen source than amino acids [25]. Silk et al. [25] refuted previous evidence that free amino acids were better absorbed than di- and tripeptides. By using an intestinal perfusion technique in adults, he was able to demonstrate better absorption of amino acids from both casein and lactalbumin hydrolysates than from an equimolar feed of free amino acids. Not only was there a more uniform absorption of amino acids, but the hydrolysates had a beneficial effect on jejunal uptake of water and electrolytes.

The first small randomised paediatric study comparing overnight naso-gastric feeding of a semi-elemental diet with prednisolone treatment followed shortly afterwards in children with predominant small bowel CD [7]. A 4- to 5-chain amino acid based diet was as effective as steroids at achieving remission in active CD. A clear acceleration in growth in the group not taking steroids was also shown.

Polymeric Diet

Several adult studies reported similar efficacy in the induction of remission when comparing whole protein diets to both elemental feeds and to steroids. Ruuska et al. [12] and Beattie et al. [26] demonstrated that polymeric diets induced remission as effectively as steroids in children. Whilst almost all paediatric patients previously required feeding by naso-gastric tube, whole protein formulae such as AL110 (Nestlé-Clintec) used by Beattie et al. [26] and Nutrison Standard (Nutricia) used by Ruuska et al. [12] were palatable enough for daily oral consumption. This considerable improvement in the quality of life made EEN an acceptable form of first-line therapy.

Fell et al. [11] showed that a whole casein, polymeric diet (Modulen IBD, Nestlé Clinical Nutrition) rich in transforming growth factor-β (TGFβ) is well tolerated and able to achieve both a clinical and histological remission. Twenty-nine consecutive patients were treated with this form of exclusive enteral diet for an 8-week period. Although over half had mild disease, 12 had moderate-to-severe disease with a paediatric CD activity index (PCDAI) >30 [27]. A nasogastric tube was only required in one patient for the first 2 weeks of treatment. Only 2 of 29 patients failed to show any clinical response, 1 with severe colonic disease, the other with an inflammatory mass requiring surgery. Twenty-three of 29 patients achieved complete remission on PCDAI scoring. The PCDAI fell dramatically within 2 weeks of starting the diet, but continued to fall until 8 weeks of treatment. There was significant macroscopic and histological improvement after treatment, with mucosal healing occurring in the terminal ileum and colon of 8 and 2 patients respectively. Serum TNFα and mucosal mRNA for IL-1 and IL-8 were significantly reduced in both the terminal ileum and the colon after treatment. IFN-γ was significantly reduced and TGFβ was elevated in the terminal ileum alone. There is no direct evidence that the TGF in the enteral formula is responsible for the up-regulation of mucosal TGFβ. Nonetheless, this study strengthens the findings by Breese at al. [28] that polymeric enteral nutrition alone can achieve an improvement in histology and a complete normalisation of some of the mucosal messenger RNA of pro-inflammatory cytokines involved in tissue damage. Bannerjee et al. [29] documented the most rapid reduction in pro-inflammatory cytokines to date, in children receiving EEN for active CD. Within 3 days of starting an exclusive polymeric diet, there was a significant reduction in IL-6 and ESR. This, together with improvements in CRP, IGF-1 and PCDAI by day 7, predated any measures of nutritional restitution (mid-upper arm circumference/triceps skinfold thickness).

The lipid composition of some polymeric diets has been held responsible for some of the variability in their efficacy [30]. High long-chain triglyceride (LCT) concentrations have been associated with a poorer response in treating active CD, with suggestions that the high linoleic acid concentration may be responsible [31], although high concentrations of medium chain triglycerides (MCT) do not affect its short-term efficacy [32]. However, only two randomised studies have been unable to show a difference in efficacy between formulae containing either low or high amounts of LCTs [33]. Only one randomised study appeared to show a significant difference in remission rates depending on the fatty acid composition of the polymeric feeds. Another study reported a significantly better clinical remission rate in adults after 4 weeks of an exclusive enteral feed rich in n–6 fatty acids, compared to one high in monounsaturated fats (52 vs. 20%, respectively). Why this conflicts with previous evidence [34] remains unclear although the high percentage of synthetic oleate (79% of total fat) in this study may mask beneficial effects previously seen with formulae containing different fatty acid profiles.

There is limited evidence of milk intolerance in adults with active CD. True lactase deficiency is an unusual cause of symptoms in adults with active CD [35]; however, up

to 46% complained of gastrointestinal symptoms related to milk intake. In contrast, exclusive enteral feeding with lactose-free, whole casein diets has not been associated with intolerance in children with active disease.

Enteral Nutrition and Crohn's Colitis

Enteral nutrition appears less effective at treating Crohn's colitis than Crohn's ileitis. Early use of enteral feed was limited to children with predominantly small bowel disease [36], with a suggestion that colonic disease was unresponsive to nutritional management [37]. More recent data from Thomas et al. [38], Ruuska et al. [12] and Fell et al. [11], however, supports the value of nutritional therapy both in large bowel and small bowel disease. The improvement in colonic mucosal cytokine profiles after enteral nutrition [11] provides hard evidence that there is an effect on colonic disease. Larger studies in adults also confirm that disease location does not appear to influence the response to treatment [14, 15].

A more recent retrospective analysis of 60 children treated with EEN suggested that disease distribution may be relevant in the response to nutritional therapy. Children with any macroscopic ileal inflammation were significantly more likely to achieve a clinical remission than those children with colonic involvement alone (75 vs. 50%) [17]. Despite this, many individuals with Crohn's colitis continue to respond extremely well, still making EEN the first choice for most children with active CD, irrespective of their disease distribution.

Food Reintroduction

There has long been uncertainty as to the best way of re-introducing a 'normal' diet after a period of EEN.

The best-described reintroduction program is based on the stepwise introduction of foods, starting with the least allergenic [39]. One new food is introduced every 48 h and, if not tolerated, reintroduced at the end of the program. This systematic but quite laborious program not only allows individual foods to be identified if causing immediate symptoms, but also gives the patients several more weeks on reasonable quantities of enteral nutrition while their normal diet is re-established. The most frequently implicated foods causing discomfort in adults are cereals, dairy products and yeast [39], although in children only a very small minority require exclusion of specific items from their diet. Recent data confirm that less than 1 in 20 children successfully completing an 8-week course of EEN go on to have persistent food intolerances [own unpubl. data]. However, in a randomised controlled trial of an exclusion diet following a remission induced with an elemental diet, subsequent rechallenge and double-blinded challenges in adults with CD also proved that specific dietary

exclusions did not persist [40]. There is thus insufficient evidence to routinely suggest exclusion of specific food items in children with CD.

Other units use less evidence based but more practical reintroduction programs which range from the immediate introduction of a full diet, to a graded introduction over 3 weeks with the ad libitum diet increasing by 25% each week, along with the simultaneous reduction in enteral nutrition. It is clear that there is no evidence for a prolonged and systematic food introduction.

Enteral Nutrition as Maintenance Therapy in Crohn's Disease

There has been much interest in whether dietary modification may prolong a remission in CD.

Initial studies suggested intermittent use of EEN could not only reduce steroid requirement and disease activity, but also increase long-term growth rate in children [41]. Whilst it may have a role in managing patients with otherwise intractable disease and a previous good response to enteral nutrition, repeated and prolonged use of exclusive enteral diets in the majority of adolescents is difficult and mostly unnecessary. Symptomatic dependence on EEN simply reflects persistent disease activity that requires review of maintenance therapies. No adolescent in our experience will willingly continue EEN as maintenance therapy indefinitely, irrespective of their parental enthusiasm! It is highly likely, however, that a long-term nutritional supplement, in combination with a well-tolerated immunosuppressant, will provide the optimal maintenance therapy for most children with moderate-to-severe CD. Low-residue diets are helpful in the presence of fibrosing/stricturing disease, but have otherwise not been shown to prevent disease relapse [42].

Peri-Operative Nutritional Support

Although improvements in the medical management of children with IBD continue to delay the need for surgery [43], larger studies still suggest that almost 60% of adults with CD will require an operation [44]. Emergency surgery may be unavoidable in a small number of children who present with fulminant colitis; however, the majority will require surgery for treatment-resistant disease allowing the planning of surgery some weeks in advance.

Optimising nutrition over a period of 4–6 weeks is likely to result in a much better post-operative course. Several weeks of EEN in children with severe CD can lead to complete nutritional restitution prior to surgery. In isolated cases, the use of total parenteral nutrition for a several weeks may also be justified if enteral access is impossible or inappropriate.

Post-operatively enteral feeds should be started as soon as possible. Adults who received enteral nutrition within 48 h of colectomy had no increased postoperative complications [45]. Provision for total parenteral nutrition should still be made if enteral feeding is likely to be delayed for more than 5 days in any undernourished child who is likely to suffer a long convalescence without achieving full enteral requirements.

Nutritional Treatment of Growth Failure

Exclusive Enteral Nutrition: Impact on Growth

Downregulation of pro-inflammatory cytokines by EEN alone may partly improve growth by reducing IL-6, a potent inhibitor of IGF-1 [29]. There is a dramatic reduction in CRP, with concomitant increase in IGF-1 and IGFBP-3, within 14 days of commencing EEN [11]. This clearly demonstrates a more rapid, direct anti-inflammatory effect than can be expected from simple nutritional restitution.

There is limited evidence on the direct benefits of EEN on long-term growth; however, almost all the available clinical trials reach a similar conclusion. A meta-analysis showed equal efficacy between EEN and corticosteroids and suggested a statistically significant benefit on growth of EEN over corticosteroids [46].

Over 20 years ago several small studies confirmed the central role of nutrition in the long-term management of growth failure in children with IBD. Motil et al. [47, 48] concluded that neither low-grade chronic inflammation nor low-dose corticosteroid use reduced whole body protein synthesis, and that it was adequate dietary supplementation that led to a significant increase in growth velocity of children with growth failure. This was confirmed by others as nutritional therapies became more practical for the treatment of acute CD [4, 49]. Using EEN for 1 month in every 4 months over a period of 20 months showed a statistically significant benefit on growth compared to use of alternate day prednisolone [50]. Similar effects were shown by other authors [7, 51] who, within 12 months, noted better growth in children treated with EEN than those treated with steroids. Even supplementation in addition to a normal diet appeared to have a beneficial effect on growth compared to conventional treatment without supplementation in the retrospective study by Wilschanski et al. [52].

Mucosal Healing

Attention has focused on the ability of treatments to achieve mucosal healing [53]. Breese et al. [28] gave an initial indication that enteral nutrition was able to down-regulate intestinal mucosal inflammation. Enteral nutrition was as effective as cyclosporin and steroids in reducing the percentage of IL-2-secreting cells in the terminal ileum

after treatment, whilst it appeared more effective than steroids at reducing the percentage of IFN-γ-secreting cells. Furthermore, it was only the enterally fed group that showed significant histological improvement.

Despite being only a small study, Breese et al. [28] raised two important issues. Firstly, that enteral nutrition may be able to heal mucosa, and, secondly, that mucosal cytokine analysis following treatment did not necessarily correlate with either clinical or histological indices of remission.

The mucosal cytokine responses of a much larger cohort of children were reported by Fell et al. [11]. Whilst clear clinical and histological remission was achieved in over 70% of children, cytokine profiles also dramatically improved with a polymeric diet alone. The dramatic downregulation of the potent pro-inflammatory cytokines IL-1β, IFN-γ and IL-8 is the most concrete evidence to date that enteral nutrition acts at the mucosal level.

The issue of whether clinical, endoscopic, histological or immunological remission should be the gold standard remains a matter of personal practice [53]. If we are to believe that the presence of chronic inflammation predisposes to long-term complications and malignancy, it may be a state of immunological remission at the mucosal level that should be achieved in children with a life time of CD ahead of them.

Future Directions

From the above discussion, it is abundantly clear that nutrition still has a major role to play in the management of children with IBD, and in particular those with CD. Whilst EEN is clearly effective in many children with active CD, it remains difficult for some children and their families to complete prolonged courses. Work is continuing to assess whether long-term supplementation of a normal diet prolongs remission.

Palatable whole protein formulae are being modified to include higher percentages of n–3 fatty acids, whilst the addition of probiotics to feeds is also already underway.

Work also continues on isolating the specific factors within formulae that may act directly on mucosal inflammation. Further characterisation of the gut microflora in children receiving EEN for acute CD may provide insights into the mechanisms that drive persistent inflammation. This may in time allow factors to be identified that promote and maintain mucosal healing.

Conclusions

Despite the ever-increasing choice of therapies available to children with IBD, the role of nutrition remains central to their optimal management. The impact of bowel inflammation on growth and development cannot be underestimated. As final adult

height is determined during the pubertal growth spurt, it is crucial to minimise the impact that both the disease and its therapies may have on a child's growth potential.

Advances in identifying children at particular risk of growth failure may, in the future, allow specific interventions to maximise growth.

We strongly suggest that exclusive enteral nutrition remains the best primary therapy for the treatment of all children presenting with a new diagnosis of CD, apart from those with severe perianal disease. Thereafter, the challenge is to maintain a lasting remission, particularly during puberty. This is likely to be best achieved with early use of immunosuppressants such as azathioprine/6-mercaptopurine, hoping to minimise steroid use. Continued vigilance of undernutrition and appropriate use of dietary supplementation remains essential to an optimal outcome.

The consequences of developing a chronic inflammatory disease during childhood will be felt long after a child is handed over to our adult physician colleagues. Increased risks of osteoporotic fractures, high rates of surgery and a reduced final height are only some of the areas where nutritional therapy is vitally important. The ability of therapies to achieve healing of the gut mucosa is of utmost importance in children who have a lifetime ahead of them. Although dietary therapies do not yet play a significant therapeutic role in maintenance therapy for IBD, it is likely that evidence about potential disease-modifying dietary supplements will continue to appear. It is important that as more potent immunological agents become available to treat these diseases, we do not forget the therapeutic role of nutrition in CD, its absence of adverse effects, and its proven impact on growth and gut mucosa.

Whilst newer therapies may require less commitment from families and medical teams, their unknown long-term safety profile still makes enteral nutrition an excellent choice for children with CD for many years to come.

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Medical Therapy for Inflammatory Bowel Disease in Children and Adolescents

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Abstract

The management of IBD has changed tremendously over the past 25 years, with a significant increase in the number of available medications. Each of these medications has its own profile of varying potency, safety, and clinical indications. Because the balance between safety and efficacy is different for each clinical situation and may depend on various patient and family preferences, patient education and informed decision-making is a critical process in the care of these patients.

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are idiopathic and chronic inflammatory disorders of the gastrointestinal track. Approximately 25% of cases begin during childhood or adolescence, and the incidence of these disorders appears to be increasing. CD is characterized by transmural inflammation that can affect any region of the gastrointestinal track from the mouth to the anus and may be discontinuous. In contrast, the inflammation observed in UC is limited to the mucosa of the large intestine. Disease in patients with UC typically begins in the rectum and extends in a continuous fashion to include more proximal portions of the colon. While proctitis and left-sided colitis are common in adult patients with UC, children most often present with pan-colitis. Despite these and the other differences that have been discussed in previous chapters, both conditions share a common pathophysiology and many of the same clinical features including abdominal pain, diarrhea, rectal bleeding, and weight loss as well as other systemic and/or extraintestinal symptoms.

The key principles of therapy for patients with UC and CD are identical: induction and maintenance of remission, monitoring and correction of nutritional deficiencies, and prevention of complications. Physicians caring for children with IBD have the added tasks of restoring normal or near-normal linear growth, pubertal maturation,

Table 1. Therapeutic goals in IBD

Adult and pediatric
1 Induction of remission
2 Maintenance of remission
3 Improvement in health-related quality of life and functional status
Pediatric specific
1 Restoration of normal or near-normal linear growth
2 Assessing and facilitating pubertal maturation
3 Promoting psychosocial development

Table 2. Guiding principles in the management of pediatric IBD

1 The selection of therapy should be guided by available medical evidence and/or expert guidelines
2 The type of IBD is a critical factor in determining appropriate therapy
3 Weighing the risks and benefits of selected therapies, including the risk of under-treatment, is the cornerstone of disease management
4 Selection of appropriate therapy is based on severity of illness, disease location, and therapeutic goals
5 Evaluate and aggressively treat symptoms of functional bowel disease
6 Compliance is a major obstacle to the success of medical therapy
7 When two or more medically acceptable options exist, treatment decisions should involve collaboration between physicians, patients, and their families
8 Disease-modifying strategies, including 'step-up vs. top-down' therapy remain controversial

and psychosocial development (Table 1). This chapter provides an overview of the medical management of children with IBD. Nutritional, surgical, and psychosocial treatments are discussed elsewhere.

Principles of Therapy and Therapeutic Goals

IBD encompasses a heterogeneous group of disorders with variable severity, phenotype, and location. However, a number of general clinical principles, and limitations, should be considered when treating patients with these conditions (Table 2):

(1) *The selection of therapy should be guided by available medical evidence and/or expert guidelines*. However, due to the small number of pediatric clinical trials, and because many of these studies are either uncontrolled and/or suffer from small sample size, it is often necessary for pediatric gastroenterologists to make treatment decisions based on extrapolations from adult data.

(2) *The type of IBD is a critical factor in determining appropriate therapy*. Although many of the medications discussed in this chapter are effective in treating both CD and UC, some are more effective for one disease. For example, existing data indicate that the clinical efficacy of methotrexate is limited primarily to patients with CD.

(3) *Selection of therapy must always include a careful analysis of the risks and benefits of competing agents.* Treatment decisions are typically guided by a patient's clinical severity. More potent medications, which typically carry a higher risk of toxicity, are reserved for those patients with severe or refractory disease. Risks associated with medication toxicity must always be weighed against the risks of under-treatment, including ongoing intestinal inflammation and the development of disease complications.

(4) *Choice of medical therapy is based on therapeutic goals*. Some therapies (i.e. oral steroids) are more effective for induction rather than maintenance of remission. In contrast, the immunomodulators methotrexate, 6-mercaptopurine (6-MP), and azathioprine are primarily used as maintenance therapies. Many classes of agents (aminosalicylates, infliximab) can be used for both induction and maintenance of remission.

(5) *Location of disease is an important determinant of drug therapy*. Systemic therapy is often necessary to treat widespread or anatomically isolated or inaccessible disease (i.e. pancolitis or ileitis, respectively). Conversely, rectal disease can often be treated with topical agents (i.e. enemas or suppositories).

(6) *Symptoms manifest by patients with IBD may also be functional in nature*. Patients with IBD may also have concurrent symptoms of irritable bowel syndrome (IBS). Failure to recognize these symptoms may lead to the inappropriate use of escalating doses of immunosuppression and other IBD-directed therapies.

(7) *Compliance is a major obstacle to the success of medical therapy*. Other factors that must impact on a physician's decisions about medical therapy include cost, availability, insurance coverage, dosing schedule, and potential reluctance to use topical therapy, all of which may affect compliance. In pediatrics, taste and the availability of liquid preparations and/or capsules containing sprinkles are additional considerations.

(8) *When two or more medically acceptable options exist, treatment decisions should involve collaboration between physicians, patients, and their families.* The treatment of IBD involves significant trade-offs, and the current body of medical evidence is often insufficient to definitively guide physicians in choosing a specific course of therapy. In situations in which two or more medically acceptable treatment options exist, physicians should provide patients and their families with developmentally and cognitively appropriate information to permit them to play an active role in medical decision-making.

(9) *Whether to pursue a 'step-up' versus a 'top-down' approach remains controversial.* At the heart of this debate is the relative merit of utilizing a conventional 'step-up' approach, adding increasingly potent therapy in a step-wise fashion, versus pursuing a 'top-down' approach, initiating more potent therapies earlier in the course of disease in an effort to modify disease outcome and reduce long-term morbidity. This is particularly relevant in pediatrics, as patients diagnosed in childhood face a lifetime of potential disease-related complications. Potential 'disease-modifying' agents

include immunomodulators such as 6-MP and azathioprine and biologics such as infliximab and adalimumab. Indeed, available evidence suggests that initiation of immunomodulators at the time of diagnosis may prolong remission in children with CD [1]. Similarly, adult patients with moderate-to-severe CD that were treated with infliximab and azathioprine were more likely to achieve remission at 6 and 12 months than those treated with budesonide and/or prednisone [2]. Although the early introduction of more aggressive treatments may alter the course of these otherwise chronic and progressive illnesses, their benefit needs to be weighed against the potential for increased toxicity as well as increased medication related costs. Results of ongoing outcome research may identify potential disease subgroups who may benefit the most from early intensification of therapy. Ultimately, further studies are necessary to evaluate the safety and efficacy of treatment strategies aimed at 'inverting the therapeutic pyramid' before any definitive treatment algorithms can be generated.

The goals of therapy in the management of children and adults with IBD are aimed at inducing and maintaining disease remission as well as improving quality of life. Although clinical remission can be defined using pediatric and adult disease activity indices as an endpoint in clinical trials, a more pragmatic definition of remission for use in clinical practice would be the absence of IBD-related symptoms and normalization of laboratory parameters including albumin, hematocrit, and inflammatory markers. Controversy exists as to whether mucosal healing should also be a requisite to achieving remission [3]. Health-related quality of life (HRQOL) and functional status (including school/work attendance and participation in other age-appropriate activities) are also important therapeutic goals. Because these do not necessarily correlate with disease activity, effort to assess and improve HRQOL and functional status should be made at every patient encounter.

Physicians caring for children and adolescents must be aware of the ways in which the clinical symptoms of IBD can affect their patients as they move through different stages of physical and cognitive development, and every effort must be spent to minimize the impact of these symptoms on their patients' linear growth, pubertal maturation, and psychosocial development. At each clinical encounter, pediatric providers must assess the child and parent's understanding of, and adjustment to, their chronic illness and be aware of the family's ability to effectively implement the child's care plan.

Treatment of Ulcerative Colitis

Induction Therapy

Mild UC

The treatment of UC is based on disease severity and location (fig. 1). However, as the majority of children present with pancolitis [4], clinical severity is typically the

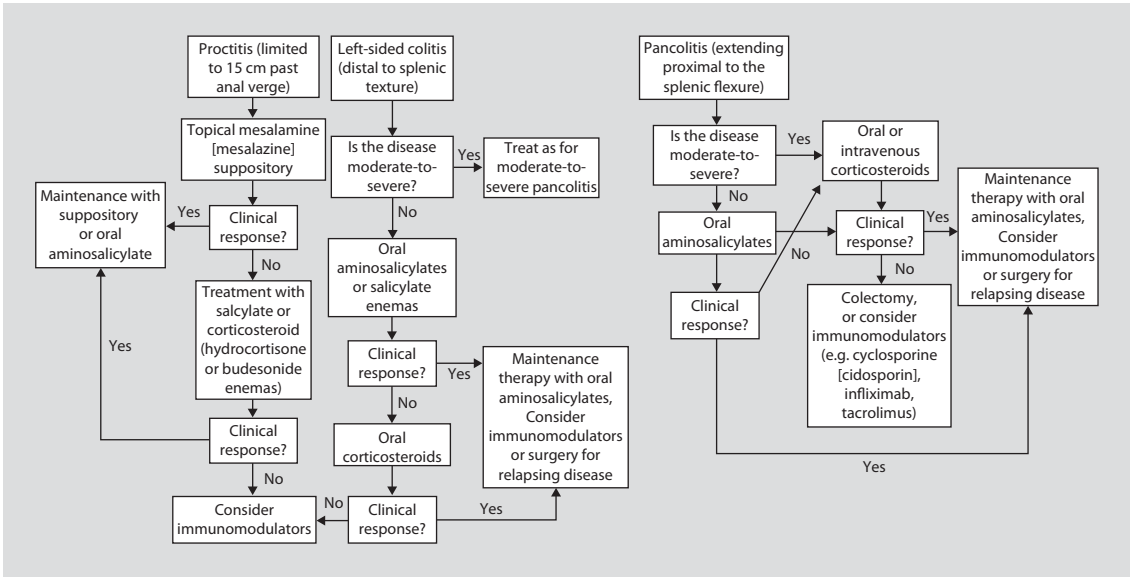

Fig. 1. Treatment algorithm for the management of ulcerative colitis.

primary therapeutic determinant in pediatric patients. Mild UC includes patients with fewer than four stools per day, diarrhea containing minimal or no blood, and no systemic symptoms such as fever [5]. Aminosalicylate therapy, including sulfasalazine and 5-aminosalicylates (5-ASA), is effective in approximately 80% of pediatric and adult patients with mild UC [6, 7]. Sulfasalazine utilizes a diazo bond to link the anti-inflammatory agent 5-aminosalicylate (mesalamine) to the inert carrier, sulfapyradine. When the diazo bond is cleaved by bacterial proteases in the large intestine, the 5-aminosalicylate component is released locally onto adjacent intestinal mucosa. Dose-dependent adverse effects of sulfapyridine therapy, including headache, flushing and rash, can be minimized by slowly escalating the dose from 25 mg/kg/day to a final dosage of 50–70 mg/kg/day. Additional idiosyncratic adverse effects associated with sulfasalazine therapy include rash, pancreatitis, leukopenia, and hepatitis [5]. Newer agents containing only the anti-inflammatory moiety, 5-ASA (mesalamine), have decreased toxicity and do not require gradual titration. The mesalamine products, Asacol® (Procter & Gamble, Cincinnati, Ohio, USA) and Pentasa® (Shire, Wayne, Pa., USA), encase 5-ASA in pH and time-dependent release vehicles, respectively. Olsalazine, available as Dipentum® (Pfizer, New York, N.Y., USA), links two 5-ASA molecules together by a diazo bond. Balsalazide or Colazal® (Salix, Morrisville, N.C., USA) uses a diazo bond to link 5-ASA to the much larger inert carrier, 4-aminobenzoyl-β-alanine. These medications all have similar efficacy. For younger children, Pentasa and balsalazide are available as sprinkle capsules that can be opened and delivered in food. Sulfasalazine and olsalazine can be compounded into suspension form.

Moderate-to-Severe UC

Pediatric patients with moderate-to-severe UC not responding to 5-ASA agents are typically next treated with glucocorticoids including prednisone and prednisolone (1–2 mg/kg/day). The majority of these patients will respond within 2–4 days. Treatment is continued at the starting dose for about 2 weeks, after which the steroid therapy can be slowly tapered over a period of 4–8 weeks. Patients not responding to oral corticosteroids may benefit from inpatient management and parenteral methylprednisolone, delivered at a dose of 1–2 mg/kg/day in two divided doses.

Fulminant and/or Steroid-Resistant UC

Severe colitis in children is defined by the modified Truelove and Witts score as patients with 4 of the 5 following criteria: 5 or more bloody stools per day, oral temperature of more than 100°F during the first hospital day, tachycardia, anemia (hematocrit of 30 or less), and low serum albumin (≤3 g/dl). The presence of toxic megacolon (dilation of transverse diameter of the colon in excess of 6 cm) alone is sufficient to warrant a diagnosis of severe colitis [8]. Initial management of these patients is aimed at rapid assessment and stabilization. This involves inpatient admission and the administration of parenteral corticosteroids, as well as intravenous antibiotics for febrile or acutely ill appearing patients. Bowel rest, though not shown to benefit patients in clinical studies, is often initiated due to the clinical impression that regular diets increase pain and diarrhea. Correction of any metabolic disturbances, as well as the provision of nutritional support, is imperative [9]. Despite these initial management strategies, up to 50% of patients may not respond to corticosteroids [8]. After excluding infection (*Salmonella, Shigella, Campylobacter*, *E. coli*, etc., *Clostridium difficile*, and cytomegalovirus), the therapeutic options for these patients include colectomy, treatment with more potent immunosuppressive therapy such as cyclosporine (CSA) or tacrolimus, and infliximab.

CSA is efficacious in inducing remission in approximately 80% of children and adults with refractory UC [10, 11]. Intravenous dosing begins at 4 mg/kg/day and is adjusted to maintain trough levels of 150–300 ng/ml. Patients usually respond within 6–7 days, and can be transitioned to oral CSA therapy. Though generally well tolerated, side effects of CSA therapy include hypertension, elevated serum creatinine, and seizures. Tacrolimus has the advantage of not requiring intravenous administration. Oral dosing for tacrolimus in children and adults starts at 0.1 mg/kg/dose, given twice a day, and is titrated to maintain a trough level of 10–15 ng/ml [12]. Response rates and adverse effect profiles are similar to those observed in patients treated with CSA [12, 13]. The toxicities associated with CSA and tacrolimus therapy make long-term administration of these agents undesirable. Instead, these agents are typically used to avoid emergent colectomy and are considered to be a 'bridge' to more effective maintenance therapy such as 6-MP or azathioprine (discussed later), or to provide additional time for a child and family to acclimate to the diagnosis before making a decision to undergo surgery.

A large randomized controlled trial in adults as well as open label experience in children have established that infliximab is effective in inducing and maintaining

remission in patients with corticosteroid-dependent UC. In the adult (ACT 1 and ACT 2) trials, approximately 65% of patients receiving infliximab responded by 8 weeks, compared to 35% in the placebo group [14]. It is important to note that the response to infliximab was lower, albeit slightly, than that reported in previous studies evaluating the efficacy of CSA or tacrolimus in more acutely ill patients. Therefore, although infliximab may have less short- and long-term toxicity, and can be effectively used as a maintenance regimen for patients with steroid-refractory UC, it may not be as effective as CSA or tacrolimus at inducing clinical remission in hospitalized children with fulminant or refractory colitis. No head-to-head trials to date have compared the clinical efficacy of infliximab to either CSA or tacrolimus in patients with UC. Furthermore, additional data are necessary to determine whether CSA or tacrolimus are safe and effective when used in patients that have failed infliximab therapy.

Proctitis and Left-Sided Disease

Pediatric and adult patients presenting with regional UC involving primarily the rectum (proctitis) or those with left-sided disease (not extending beyond the splenic flexure) may not require systemic therapy, and topical mesalamine and steroid agents are available for use in these patients. Well-administered steroid or mesalamine enemas can reach as far as the splenic flexure. Similarly, mesalamine or glucocorticoid suppositories or foam preparations can deliver high concentrations of agent to affected mucosa in patients with disease limited to the rectum. Many patients with limited left-sided colitis or proctitis can be managed with once or twice daily topical therapy [15].

Maintenance Therapy

Pediatric and adult studies have demonstrated that oral and topical 5-ASA agents are effective in maintaining disease remission in children and adults with pan and left-sided UC [7, 16]. Immunomodulatory agents, including azathioprine and 6-MP, are effective in maintaining remission in pediatric patients with UC who experience recurrent flares, do not tolerate 5-ASA agents, are corticosteroid dependent, or have had fulminant colitis requiring CSA or tacrolimus therapy [17, 18]. Because of their delayed onset of action (6–10 weeks), these agents are not useful for inducing remission in patients with active disease. Current dosing for azathioprine is 1.5–2.5 mg/kg/day, and for mercaptopurine 1–2 mg/kg/day. The major dose-dependent toxicities include bone marrow suppression, elevation of serum transaminases, and infectious complications. Commercially available assays can measure thiopurine methyltransferase capacity, the enzyme that converts 6-MP to its active metabolites 6TG and 6-methylmercaptopurine, and adjustments can be made in the starting dose in patients who are intermediate metabolizers [19, 20]. It should be noted that other adverse reactions of 6-MP therapy, including pancreatitis, appear to be idiosyncratic rather than dose related. Although some epidemiologic data suggests an increased risk of malignancy including

lymphoma in patients treated with 6-MP or azathioprine [21], most experts agree that the benefits of immunomodulatory therapy outweigh this potential risk [22].

In summary, the treatment of active UC is based on clinical severity. Aminosalicylates are usually effective in patients with mild-to-moderate UC. Corticosteroids can be used in patients with moderate-to-severe disease, or for whom aminosalicylate therapy fails. CSA, tacrolimus, and infliximab are reserved for steroid nonresponders. Both aminosalicylates and immunomodulatory agents can be employed to maintain remission in children and adults with UC. Selection of a maintenance regimen involves estimating the risk and severity of future recurrences as well as choosing a regimen that has the highest likelihood of compliance.

Treatment of Crohn's Disease

Induction Therapy

Mild-to-Moderate CD

Patients with mild-to-moderate CD are ambulatory and able to tolerate oral alimentation. These patients do not display dehydration, systemic toxicity, abdominal tenderness, painful mass, obstruction, or greater than a 10% weight loss on physical exam [23]. Patients with mild-to-moderate ileal, ileocolonic, or colonic CD can be treated with oral 5-aminosalicylates such as mesalamine at a dose of 50–75 mg/kg/day (fig. 2). However, the efficacy of these agents remains uncertain due to the high placebo response in clinical trials [24–26].

Existing data suggest that antibiotic therapy may be efficacious in treating patients with mild inflammatory or perianal CD. Metronidazole appears to be as effective as 5-ASA, particularly in patients with colonic disease [27, 28]. Ciprofloxicin, used alone or in combination with metronidazole, has been effective in adult patients with ileitis [29].

Budesonide, a corticosteroid with enhanced hepatic first-pass metabolism and potentially lower systemic corticosteroid exposure, appears to be effective in reducing disease activity in about 60% of pediatric patients with ileal or ileocolonic disease [30, 31]. The starting dose for oral budesonide is 9 mg/day, and it is weaned in 3-mg increments.

Enteral therapy, using either elemental or polymeric formulas, has been shown to be as efficacious as oral corticosteroid therapy in inducing clinical remission in children with mild Crohn's disease. Patients with mucosal disease affecting primarily the ileum or ileum/right colon appear to benefit most from this form of therapy [32].

Moderate-to-Severe CD

Patients who have failed to respond to treatment for mild disease or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness,

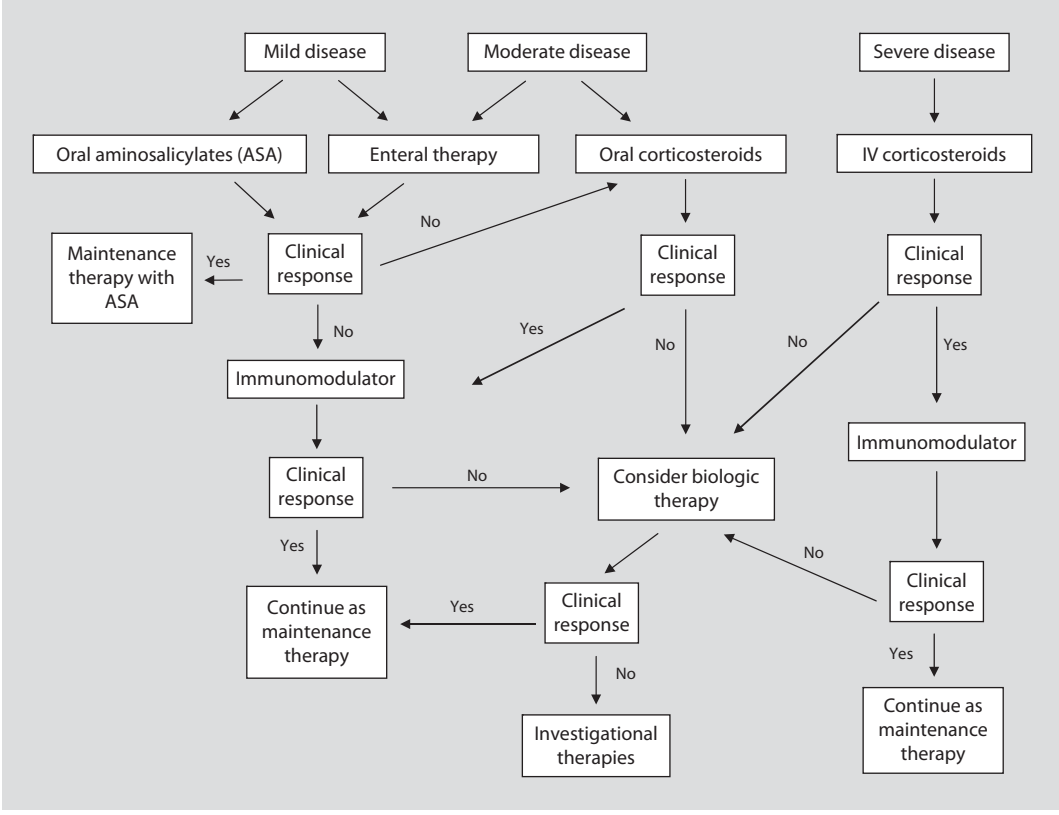

Fig. 2. Algorithm for the management of Crohn's disease.

intermittent nausea or vomiting, or significant anemia can typically be brought into clinical remission with oral corticosteroid therapy [23, 33]. Dosing typically begins in the range of 1–2 mg/kg/day, and is continued for 2 weeks, followed by a slow taper over an 8- to 12-week period.

Biologic therapy utilizing anti-tumor necrosis factor antibodies such as infliximab, or possibly adalimumab (Humira®, Abbot Laboratories, London, UK) have proven efficacy in patients unresponsive to corticosteroids, or in those who have developed corticosteroid dependence. In the REACH (a Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF Monoclonal Antibody REMICADE in Pediatric Subjects with Moderate to Severe Crohn's Disease) trial, 112 children and adolescents with active CD received open-label induction therapy with 5 mg/kg infliximab at weeks 0, 2 and 6. Ninety-nine patients (88%) responded at week 10 and were randomized to receive maintenance therapy with 5 mg/kg infliximab administered every 8 or 12 weeks through week 46, and then followed through week 54. At week 54, 64 and 56% of patients receiving infliximab every 8 weeks were in clinical response and clinical remission, respectively, compared with 33 and 24% of patients randomized to receive infliximab every 12 weeks ($p = 0.002$ and $p < 0.001$,

respectively) [34]. These data prompted the FDA to approve infliximab use for the treatment of CD in children. Adverse events associated with infliximab include a 5% risk of infusion reactions, infectious complications such as the reactivation of latent tuberculosis, hepatitis, lupus-like syndrome, and a possible risk of malignancy [35, 36]. Recently, an association between infliximab use and the development of hepatosplenic T cell lymphoma has been reported [37].

Severe-to-Fulminant CD

Patients with persistent symptoms, despite adequate treatment with oral steroids or infliximab, or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized [23]. Imaging such as computerized tomography of the abdomen and pelvis to evaluate for abscess should be obtained and surgical consultation is warranted. Once an abscess has been excluded, parenteral methylprednisolone 1–2 mg/kg/day in two divided doses should be administered. In the hospitalized patient who has not responded to intravenous corticosteroids, CSA and tacrolimus may be used to induce remission [38, 39]. As in UC, these agents should not be used long term and are typically utilized as 'bridge' to immunomodulator maintenance therapy. Biologic therapy is an alternative to those patients not responding to corticosteroid therapy.

Maintenance Therapy

Corticosteroid therapy has been generally ineffective in maintaining remission in the majority of patients with CD. In efforts to avoid long-term adverse effects associated with corticosteroid use, various maintenance strategies have been studied. For patients with relatively mild disease, aminosalicylate therapy may be utilized. However, a recent meta-analysis suggests limited efficacy over placebo [40]. In contrast, the immunomodulators 6-MP and azathioprine are a highly effective means of maintaining disease remission [1]. Due to the prolonged onset of action, these agents are typically started along with corticosteroid induction therapy. Because of the previously mentioned risks of immunomodulator use, a careful risk-benefit analysis in the context of shared decision-making should be used prior to initiation of therapy.

Methotrexate appears to be another effective corticosteroid sparing option for maintaining remission in patients with CD. Subcutaneous injections of 15 or 15 mg/m^2/week in older children have been effective in patients for whom immunomodulators were either not tolerated or ineffective [41]. Oral dosing, although available, may not be as efficacious as subcutaneous injections [42, 43]. Adverse effects associated with methotrexate include nausea, anorexia, fatigue, diarrhea, hepatitis, bone marrow toxicity, and pulmonary disease. Daily folate supplementation can reduce the incidence and severity of these adverse effects [44]. The onset of action of this agent is only 3–4 weeks, making methotrexate a possible induction agent as well.

Finally, infliximab has demonstrated efficacy as both an induction and maintenance therapy as described above. This biologic has been approved for use on a long-term basis to prolong remission in pediatric and adult patients who have responded to initial therapy.

Other Considerations in Crohn's Disease Therapy

Upper Gastrointestinal CD

The geographic location of upper GI tract CD can make it an especially difficult disease subgroup to treat. Patients presenting with peptic symptoms can benefit from sucralfate and acid blockade to promote gastric healing and minimize mucosal disease. Pentasa, a time-released mesalamine preparation, may be released in the small bowel in sufficient quantity to be useful with mid to distal small intestinal involvement [45]. However, patients with evidence of gastric or proximal duodenal involvement are likely to require systemic therapy with immunomodulators or infliximab.

Perianal CD

Perianal drainage and abscesses are the result of infected fistulous tracts from the rectum to the perineum. Antibiotics have long been mainstays in the management of pediatric and adult patients with CD involving the rectum and perianal region. Metronidazole (10–20 mg/kg/day) and ciprofloxacin (500 mg twice daily) have both been studied in adults for this indication [46, 47]. Infliximab appears to be the most effective agent for the management of patients with persistent or refractory fistulizing or perianal CD [48].

Fistulizing CD

Transmural disease extending beyond the intestine to involve adjacent skin, other small or large bowel loops, or other abdominal organs is often resistant to corticosteroid and oral aminosalicylate therapy. Immunomodulators are effective in helping to close fistulae in pediatric and adult patients, though the onset of action is often delayed. Infliximab, as described above, had good efficacy in patients with this indication [48, 49].

Prevention of Postoperative Recurrence

The question of how to best manage patients that have undergone surgery to address medically refractory Crohn's is a matter of active debate in the pediatric and adult literature. Corticosteroids and sulfasalazine are ineffective for the prevention of relapse in postoperative patients [50, 51], and mesalamine preparations appear to confer only a modest reduction in the risk of postoperative recurrence [52]. Hanauer et al. [53] recently published their blinded and placebo-controlled study evaluating 131 patients randomized to receive 6-MP (50 mg/day), mesalamine (3 g/day), or placebo. Clinical

recurrence rates at 24 months were 50, 58 and 77%, respectively. Endoscopic recurrence rates were 43, 63 and 64%. Another recent open-label study which randomized 142 patients to treatment with either azathioprine (2 mg/kg/day) or mesalamine (3 g/day) failed to demonstrate a difference in surgical recurrence at 24 months between the two treatment groups [54]. Additional prospective studies are necessary to define the optimal agent(s) and doses to minimize postoperative recurrences in pediatric and adult populations with stricturing CD.

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Surgical Therapy

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Abstract

Operative management often plays a critical role in the optimal treatment of inflammatory bowel disease in children. Delay in total proctocolectomy in older children and adolescents with severe ulcerative colitis sometimes leads to significant growth delay and nutritional deficiency. This paper discusses the risks and benefits of both surgery and medical management which must be taken into account when deciding on the most appropriate therapy for Crohn's disease and ulcerative colitis in pediatric patients.

Indications for Surgery

Many advances have been made over the last several decades in the medical management of inflammatory bowel disease. However, surgery continues to play an important role in the successful treatment of both ulcerative colitis (UC) and Crohn's disease (CD).

Ulcerative Colitis

As mentioned in previous chapters, therapies for UC include 5-aminosalicylate-based anti-inflammatory agents, immunosuppressive medications such as azothioprine, 6-mercaptopurine, cyclosporine, and corticosteroids. However, many children remain refractory to these medications and require frequent hospitalizations as well as long-term use of steroids. The result in children with chronic UC may be delayed growth (weight and height), delayed puberty, Cushingoid features, hypertension, cataracts and glaucoma, and osteopenia.

While medical therapy may put UC in remission for variable periods of time, UC cannot truly be cured without removal of the colon and rectum. Given the long-term problems associated with immunosuppression and steroid therapy in children, surgery should be considered in any child with UC before permanent disability develops. Indications for surgery include persistent symptoms despite maximal medical

therapy, growth retardation, and an inability to participate in school, sports, or social activities secondary to disease. An additional reason to proceed with surgery in children is to prevent compromise of stature by removing the colon prior to closure of the growth plates. Emergency surgery is indicated for a small subset of patients with acute, fulminant disease characterized by extensive rectal bleeding, toxic megacolon, or systemic sepsis. Lastly, as the risk of cancer in patients with UC increases at a rate of 1% per year after 10 years of disease, prophylactic colectomy should be considered in patients with long-standing disease [1].

Crohn's Disease

Medical management of CD utilizes many of the same drugs used to treat UC – corticosteroids, 5-aminosalicylates, 6-mercaptopurine, azothioprine, methotrexate, and cyclosporine. In addition, both metronidazole and ciprofloxacin have a supportive role in disease flares. Most recently, infliximab (Remicade) has shown significant success in CD. This is a chimeric monoclonal antibody against tumor necrosis factor-α that has proven effectiveness in CD refractory to standard immunosuppressive therapy in both children and adults. Lastly, nutritional therapy plays an important role in CD in reversing growth retardation and nutritional deficiencies.

In contrast to UC, surgery in CD cannot cure the disease. Therefore, the indications for operative intervention are limited to failure of medical therapy and complications of the disease. The most common complications requiring surgery are bowel obstruction, perforation, perianal abscess and fistula, intra-abdominal abscess, small bowel fistula, and rarely megacolon. A retrospective review of patients with CD at the Children's Hospital in Boston revealed that 46% eventually required surgical resection [2]. The majority of these operations were performed for failure of medical therapy or growth retardation (47%), intra-abdominal abscess or perforation (16%), or obstruction (16%). In this study group of 204 patients, the probability of needing surgery was 28.8% by 3 years after diagnosis and increased to 47.2% by 5 years from diagnosis. As mentioned above for UC, a localized resection in CD can allow for a rapid withdrawal of medications and subsequent catch-up growth in adolescent patients near the closure of their osseous growth plates. Less common indications for surgical intervention include fistula formation and hemorrhage.

Surgical Options

Ulcerative Colitis

The cornerstone of surgical therapy in UC is removal of the entire colon and rectum. The simplest manner in which to accomplish this is a standard proctocolectomy with

end ileostomy. However, a permanent ostomy may be unacceptable to many children and adolescents and their families. Currently, total colectomy with rectal mucosectomy and ileoanal pouch procedure (IPAA) and colectomy with subtotal mucosectomy and stapled ileorectal anastomosis are the two most common operations performed for UC. Alternatively, a straight ileoanal endorectal pull-through without an ileal reservoir may be performed. In most cases, a temporary diverting ileostomy is added to protect the distal anastomosis. Advantages to performing an endorectal dissection include minimal disruption of the extra-rectal space with a subsequent decreased risk of injury to the sphincter muscle and surrounding deep pelvic nerves. This approach also maintains continence by preservation of the anorectal angle, levator muscle complex, anal sphincters, rectal ampulla, and anorectal sensation.

In children with acute life-threatening disease, initial emergency surgery consists of colectomy and end-ileostomy. This may later be followed by an ileoanal pull-through with or without a pouch to restore intestinal continuity. This second operation is usually performed with a diverting ostomy, which would be closed in a third and final procedure.

Recently, there have been two new trends in operative management of UC. One is the use of a double-stapled technique in restorative proctocolectomy in UC [3]. Rather than performing a hand-sewn ileoanal anastomosis, the distal 1.5 cm of rectal mucosa is preserved and utilized for a double-stapled, end-to-end anastomosis using the circular stapler. The data suggest that this is a safe technique and comparable to the hand-sewn approach. The second trend is toward the use of laparoscopic or lap-assisted subtotal colectomy. Although operative times may be longer, perioperative clinical outcomes are similar to open subtotal colectomy and cosmesis is improved [4, 5].

Crohn's Disease

The surgical procedures performed for CD are dictated by the site of involvement and the particular complication. In the 50–60% of children with CD limited to the terminal ileum, ileo-cecal resection with primary anastomosis is indicated for local perforation with abscess, persistent fistula, or obstructive symptoms secondary to refractory inflammation. Although localized perforation and abscess formation may initially be managed with intravenous antibiotics and bowel reset, ileocecal resection is often required for complete resolution of terminal ileal disease. In our institution, the laparoscopic-assisted ileocectomy is favored over the open approach for this procedure. Both retrospective and prospective, randomized trials in adults suggest advantages of shorter hospital stay, faster return of bowel function, and decreased complications in laparoscopically treated patients compared to their open surgery counterparts [6, 7]. These benefits appear to extend to the pediatric population [8]. Further, if the disease process is confined to the ileocecal region, then the long-term recurrence free interval is substantially increased compared to those with associated

colonic disease [9, 10]. The resection margin of the involved small intestine should extend proximally to only just beyond the area of gross disease, as resection to microscopically clear margins offers no protection against recurrent disease [11].

Many children with CD suffer both acute bowel obstruction secondary to active inflammation, and chronic obstruction secondary to stricture formation. While acute disease can be managed with anti-inflammatory medications and immunotherapy, many will develop chronic bowel obstruction secondary to multiple strictures with associated abdominal pain, anorexia, and growth failure. In the past, these strictures were managed with multiple intestinal resections, which often led to development of short-bowel syndrome. The current standard of care limits bowel resection to patients with perforation, fistula formation, areas of severe bowel wall thickening, and long-segment areas of disease. In other situations, strictureplasty is a safe and effective surgical alternative and has become the operation of choice [12]. Strictures of up to 10 cm in length may be treated with a Heineke-Mikulicz strictureplasty, while involved segments up to 30 cm may be treated with a Finney side-to-side anastomosis. Strictureplasty is recommended for all strictures in which the inner diameter is 2 cm or less but may also be beneficial when the lumen is less compromised. This procedure preserves intestinal length and provides relief of obstructive symptoms as well as discontinuation of steroids in up to 85% of patients.

Management of children with colorectal CD again depends on the extent of the disease and the secondary complications. Crohn's colitis often manifests as abdominal pain and diarrhea with subsequent weight loss. Surgery is required to alleviate symptoms refractory to medical management and is most often accomplished by total colectomy with ileorectal anastomosis. Partial colectomy is no longer recommended as it has been shown to have a recurrence rate of up to 60% at 5 years [13, 14]. In Crohn's colitis with rectal sparing, total colectomy with ileorectal anastomosis is an excellent choice as long as the rectum has normal sphincter function and distensibility, there is no perianal disease, and the terminal ileum is not involved. Fibrosis in the area of the rectal canal is a known complication of Crohn's colitis, and may require the child to undergo a permanent diverting ostomy. If perianal disease is present but the rectum appears normal, total colectomy with ileostomy and Hartmann's pouch can be performed as a first-stage procedure, allowing for a later ileorectal anastomosis after the perianal disease has healed. Total proctocolectomy with permanent ileostomy is reserved for patients with severe, refractory rectal or perianal CD, failed ileorectal anastomosis, or carcinoma. Total proctocolectomy with ileoanal pouch anastomosis is currently not recommended in patients with CD as over half of these patients will require their pouch to be excised or defunctionalized [15].

Severe perianal disease, which occurs in 5–10% of children with adolescent CD, can be quite challenging to treat. While many patients will respond to medical therapy, surgery is often required for drainage and debridement of perianal abscesses. Small, superficial lesions respond well to incision and packing. However, large abscesses involving the deeper ischiorectal space often require fluoroscopically guided

placement of bulky drains. These drains are left in place for several weeks to create controlled sinus tracts which can then be treated with silver nitrate or fibrin glue [16]. Recent reports have documented some success in using local injection of infliximab into perianal fistulae but this strategy remains experimental [17].

Fistula in ano is another common complication of perianal CD that often requires surgical intervention. Fistulae below the sphincters can be treated with fistulotomy and fistulectomy, while suprasphincteric fistulae are best treated with either a Seton suture or debridement of the tract followed by instillation of silver nitrate or fibrin glue [16]. There is much controversy and little in the way of randomized, controlled trials to support the use of fibrin glue in complex perianal fistulae, but most authors conclude that the low risk and potential for success make it an acceptable first-line treatment in this setting [18, 19]. Recent reports have demonstrated that the use of Surgisis plugs (bioabsorbable xenograft made of lyophilized porcine intestinal mucosa) is successful in closing deep anorectal fistulae in 80% of Crohn's patients [20]. Anal fissures in patients with CD are best managed with medical therapy as fissurectomy is complicated by poor wound healing, loss of sphincteric control, and a high rate of recurrence. Severe fissures may be managed medically with dietary restriction and TPN or surgically by proximal diversion with an end colostomy. Lateral internal sphincterotomy should be reserved for the rare patient with a classic posterior midline fissure and documented anal sphincter hypertonia on manometry.

Less severe perianal CD may be manifested by anal strictures and skin tags. The skin tags may become swollen and inflamed in the setting of diarrhea, but are best managed with sitz baths and control of the inciting diarrhea. Excision of skin tags is not recommended due to poor wound healing. Strictures are generally asymptomatic but on occasion lead to urgency and tenesmus. Short symptomatic strictures may be gently dilated either in the operating room or at home using Hagar dilators. Long strictures or those that do not respond to dilation are usually associated with more aggressive disease that often leads to diversion or proctocolectomy.

Details of Surgical Procedures

Ulcerative Colitis

The hallmark of the restorative proctocolectomy is removal of the entire abdominal colon and a portion of the rectum. This may be accomplished via a midline incision or a transverse suprapubic skin incision with division of the underlying fascia in a vertical fashion. Laparoscopic mobilization of the colon is commonly employed to limit the size of the open incision. This is performed by introducing a 5-mm umbilical port and 30° 5-mm camera, followed by placement of four working ports. Three operative ports are placed in the lower abdomen, while one is placed in the epigastric region. Blunt graspers are used to provide traction as the lateral attachments of the ascending

and descending colon are taken down with hook cautery or the harmonic scalpel. Initial mobilization of the lateral attachments can be facilitated by angling or 'airplaning' the table to elevate the side of dissection. A variety of instruments, including the harmonic scalpel, Ligasure, and Gyrus, can be utilized to take down the gastrocolic ligament and enter the lesser space. Following mobilization of the entire colon, the colonic vessels can then be either divided laparoscopically or taken between clamps in the standard fashion through the limited lower abdominal incision. The rectum is usually divided 4–5 cm above the dentate line, which will leave an adequate muscular cuff for the pull-through.

The endorectal dissection with mucosectomy may be approached from either the abdomen or the perineum. In the perineal approach, the mucosa of the distal rectum is divided circumferentially at the level of the dentate line. Dilute epinephrine or saline may be injected between the muscularis and mucosa to facilitate dissection, and all rectal mucosa is dissected free from the muscular wall and removed. A complete mucosectomy is appropriate only for a hand-sewn anastomosis, which is performed between anoderm and rectal muscularis and the ileal pouch at the level of the dentate line.

Endorectal dissection from the pelvis is begun by dividing the muscular layers of the rectum to the level of the submucosa circumferentially starting approximately at the peritoneal reflection and carried down to within a centimeter above the dentate line. Gentle dissection is often aided by use of a moistened cotton-tip applicator or saline-soaked gauze on the fingertip. Two approaches may be taken for the anastomosis. For a hand-sewn anastomosis, the dissection is carried down to 1 cm above the dentate line. The mucosal/submucosal tube is everted onto the perineum, divided, and a hand-sewn anastomosis is performed. Alternatively, a stapled anastomosis may be used. For this, the mucosal tube is everted and stapled transversely with a TA stapler. In cases where the endorectal dissection begins from above, the mucosectomy extends to 1.0–1.5 cm above the dentate line. In overweight patients with a deep gluteal cleft, a reticulating endo-GIA stapling device is often necessary to perform an adequate mucosal excision. Prior to eversion and stapling, the rectum should be calibrated with sizers and an appropriate sized EEA stapler chosen.

Creation of the ileal pouch depends on which configuration is used. The J-pouch is the most commonly selected and is simply constructed. Following mobilization of the ileal mesentery, the distal 8–12 cm of ileum is doubled back on itself, placing the antimesenteric borders adjacent to each other. The bowel is opened at one corner of the stapled distal ileum and at an adjacent position on the proximal ileum. A stapler is fired once or twice to create an anastomosis. More recently, there has been a trend toward creation of a shorter pouch. In this case, a small incision can be performed at the apex of the loop and a GIA stapler placed with one side in each limb of the loop and a single firing of the stapler. Completion of the loop will often require a second firing of the stapler. This step eliminates the need for opening the ileal staple line. The anastomotic staple line should be buttressed at points of tension with additional absorbable Lembert sutures. The S-pouch is created in a manner very similar to the

J-pouch, except for the presence of two overlapping limbs, each of which is 10 cm long. A short 2 cm spout at the distal end is used for the ileoanal anastomosis. The S-pouch is used by some surgeons but has fallen out of favor by most groups because of a high incidence of complications.

In the hand-sewn ileoanal anastomosis, the open apex of the pouch is guided through the muscular cuff and sewn directly to the anoderm and rectal muscularis at the dentate line using interrupted absorbable sutures. In the straight pull-through, the ileoanal anastomosis is performed 1 cm above the dentate line. In either case, the pulled through ileum is then often additionally tacked to the rectal cuff in all four quadrants to secure the ileum in place.

The double-stapled ileoanal technique places the anvil of the EEA stapler in the open apex of the J-pouch. This is secured in place with a running monofilament purse string suture. The circular stapler is then inserted transanally and the trocar advanced through the transverse staple line of the mucosa. The temporary trocar is removed and the instrument mated, then fired according to standard EEA protocol. The stapler is removed and examined to ensure that two intact rings of tissue are present.

Following completion of the anastomosis, it is our policy to perform a temporary diverting loop ileostomy in the right lower quadrant. This is created approximately 25 cm proximal to the superior end of the ileal reservoir over a red rubber catheter, which is removed approximately 10 days postoperatively. In cases where there is excess tension placed on the mesentery by a loop configuration, an end ileostomy is constructed. In this situation, the distal ileum is stapled closed, then anchored to the inner abdominal wall adjacent to the stoma to aid in later ileostomy closure. Figure 1a represents the completed appearance for a straight pullthrough, and figure 1b represents the appearance of a J-pouch pullthrough.

In cases where patients are nutritionally sound and on minimal steroids, creation of the anastomosis without an ostomy may be considered. An additional group of patients where forgoing the ostomy may be advisable may be the obese patient where stomal complications are very high, and may far outweigh any risk of an anastomotic leak.

Crohn's Disease

Ileo-Cecal Resection

Laparoscopic-assisted ileo-cecal resection is a safe and effective approach to terminal ileal CD. The operation begins with placement of a 5-mm port in the umbilicus and a 30° angled 5-mm laparoscope. Screening laparoscopy is used to guide placement of two additional ports. A combination of blunt dissection and electrocautery is used to mobilize the cecum and right colon off the lateral sidewall and take down the hepatic flexure. Care must be taken to avoid entering the retroperitoneal fascial plane that contains the ureter and gonadal vessels. In cases where fistulae or abscesses are encountered, the normal bowel should be mobilized first. Separation of normal and

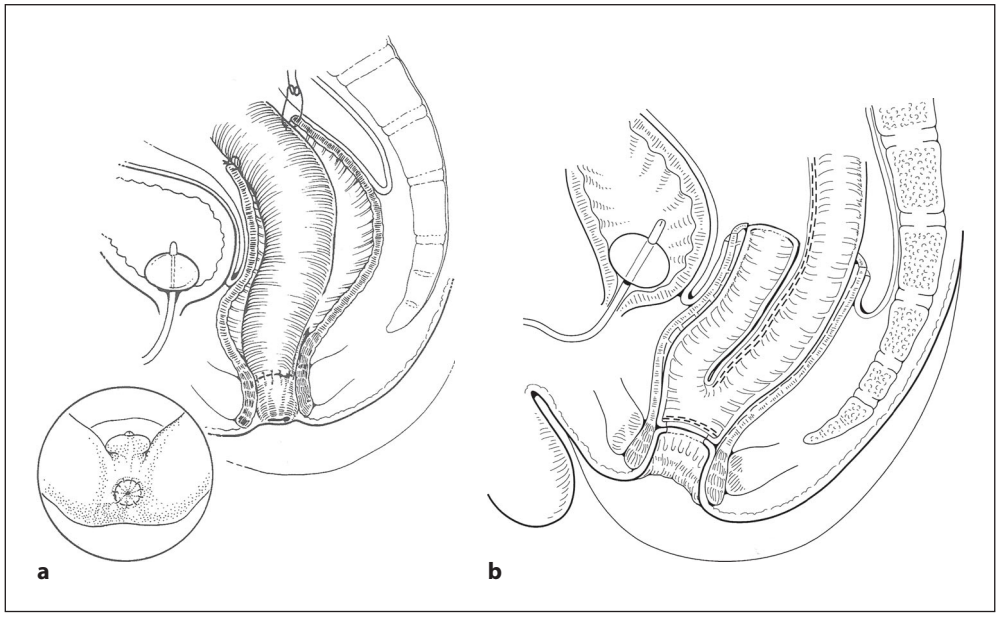

Fig. 1. Ileo-anal pullthrough for UC. **a** Completed appearance for a straight pull-through. **b** Appearance of a J-pouch pull-through.

diseased loops of bowel should always remain close to the wall of the healthy bowel. Fistulae may be divided with a laparoscopic stapler or divided sharply and closed with interrupted intracorporeal sutures. The entire small bowel is then run laparoscopically to identify any additional areas of disease, as concurrent disease in other areas of the intestine may alter the originally planned procedure. Following mobilization of the right colon and cecum, a small, transverse right lower quadrant incision is performed. Care is taken not to make this incision too low, as it is generally easier to bring the colon out through a mid-abdominal incision. The terminal ileum and cecum are delivered into the wound and resected. Either a stapled or a hand-sewn ileocolonic anastomosis is then performed. Any additional diseased areas of small bowel may be examined manually through this small incision and operated upon if needed.

Strictureplasty

Prior to performing either resection or strictureplasty for Crohn's small bowel strictures, the entire bowel should be examined from the Ligament of Treitz to the rectum. Strictureplasty of short segment disease is accomplished by performing a full-thickness longitudinal incision along the anti-mesenteric border of the strictured bowel and extending this 2–3 cm into normal bowel on both ends of the stricture. Stay sutures are placed along the antimesenteric border approximately 1 cm above and 1 cm below the midportion of the stricture prior to performing the enterotomy. A Foley catheter with the balloon inflated to an internal diameter of 2.0–2.5 cm can be

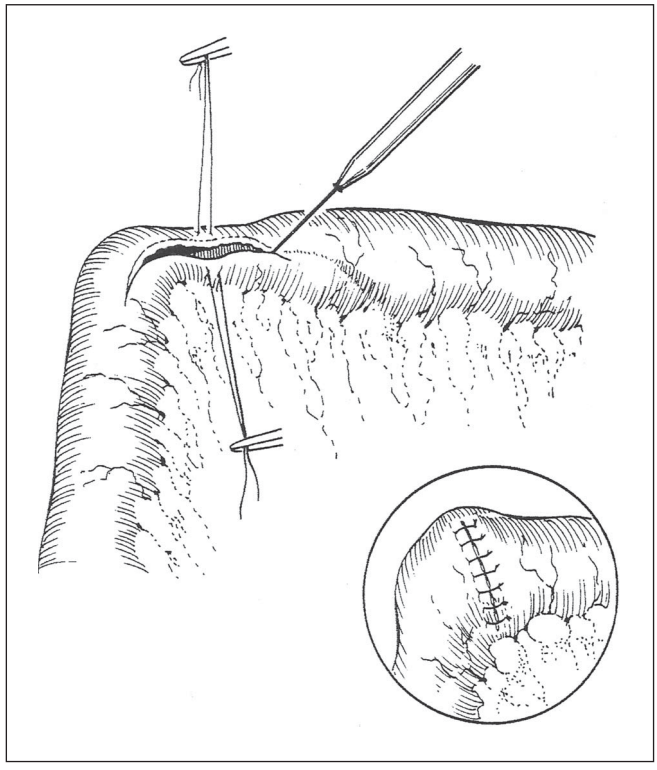

Fig. 2. Strictureplasty. The bowel is closed transversely using interrupted seromuscular absorbable sutures.

placed into the lumen and passed both proximally and distally to identify strictures not detected on external examination. The bowel is then closed transversely using interrupted seromuscular absorbable sutures (fig. 2).

Longer strictures of up to 30 cm may be treated by a Finney side-to-side anastomosis. In this case, the entire stricture is opened along the antimesenteric border of the affected loop to include 2–3 cm of normal bowel on each side. The open segment of bowel is then folded in half upon itself at the midpoint of the incision. Stay sutures are again placed in both corners and the posterior two edges are approximated with a running full-thickness single layer absorbable suture. The anterior wall is then closed with interrupted seromuscular sutures. Alternatively, a stapled Finney strictureplasty may be performed by introducing a linear cutting stapler through a small enterotomy at the apex of the folded stricture. The arms of the stapler are placed in the proximal and distal loops of bowel and the stapler fired, creating a side-to-side anastomosis. The enterotomy may be closed by a noncutting TA stapler, or reapproximated with interrupted seromuscular sutures.

Total Abdominal Colectomy

Total abdominal colectomy with ileorectal anastomosis in patients with Crohn's colitis who have sparing of the rectal segment may be undertaken in either an open or

laparoscopic-assisted manner. The entire colon is mobilized to the level of the peritoneal reflection and its blood supply divided near the wall of the colon. The terminal ileum is divided just proximal to the ileocecal junction, and the colon divided at the rectosigmoid junction, at the level of the sacral promontory. The anastomosis between the rectum and terminal ileum may be sewn by hand or completed using a circular stapler. In the latter, the anvil of the EEA is placed in the distal ileum and secured with a monofilament pursestring. The EEA stapler is then placed transanally to the level of the rectal staple line. The trocar is advanced through the rectal staple line and removed, allowing the instrument to be mated with the ileal anvil. The stapler is then fired according to standard EEA protocol, then removed and examined to ensure that two intact rings of full-thickness bowel wall are present. The anastomosis may be tested by insufflation with a rigid sigmoidoscope while placing the anastomosis under saline irrigation in the pelvis.

Perianal Disease

The most common procedure for complications of perianal CD is incision and drainage of abscesses. This is performed with a scalpel under local or general anesthesia. Following incision over the area of fluctuance, the abscess cavity is interrogated with a hemostat or finger to break up any loculations. The area is then generously irrigated with sterile saline and packed loosely with gauze packing, which is removed in 24–48 h. Larger abscesses that communicate with the ischiorectal space are identified by either pre-operative computed tomography scans or instillation of contrast under live fluoroscopy in the operating room. Irrigation of these cavities should be followed by placement of large drains that will be left in place for 1–2 months to create controlled fistulae. Post-operative care in theses cases involves both antibiotic therapy and frequent daily baths to cleanse the area. After the abscess has resolved, as documented by radiographic injection studies, the drains are removed and the tracts managed with either silver nitrate or injection of fibrin glue.

Infrasphincteric fistulae in ano are most often treated by fistulotomy with debridement of the tract or fistulectomy. Digital rectal exam is first performed to palpate the tract along the wall of the anal canal. Identification of the internal opening often requires use of a lacrimal probe; this can be facilitated by the injection of saline or hydrogen peroxide into the external opening while observing the anal canal at the level of the dentate line. Once the tract is successfully intubated, it is opened along the probe to expose the inner layer of granulation tissue. The inside of the tract may be debrided or the entire lining of the tract excised (fistulectomy). This is followed by frequent daily baths and medical management of the intestinal component of the disease.

Suprasphincteric fistulae in ano are best treated conservatively so as to avoid interference with anal continence. One approach is placement of a seton through the tract after curetting the fistula. A seton is a piece of heavy, nonabsorbable material, such as a silk suture, vessel loop, or Penrose drain, that is passed from the opening on the perianal skin along the fistula, through the internal opening in the anal canal, and

out through the anus. The two ends are tied together in a loop to form the seton. The skin and subcutaneous tissue between the two fistulous openings is divided but the sphincter muscle is left intact. A loose 'draining' seton acts as a wick to promote drainage of infected material and improve perianal sepsis. The tissue gradually heals around the seton, leaving a very small tract. This may later be converted to a 'cutting' seton, which is tightened slowly over several weeks. During this time, the seton gradually cuts through the sphincter muscles, allowing them to heal and thus limiting the risk of incontinence. Alternatively, the tract created by the initial seton may be carefully debrided, then injected with fibrin or an anal fistula plug. If the Surgisis plug is used, the patient should undergo a mechanical bowel prep the day before surgery, followed by oral metronidazole that evening. In the operating room, the tract is irrigated with hydrogen peroxide and the primary opening identified. As described by O'Connor et al. [20], the Surgisis plug is pulled tip-first into the internal opening until resistance is met. The excess plug is then trimmed at both openings and the plug buried into the internal opening using a large, absorbable suture. Patients are placed on a clear liquid diet for 48 hours and instructed to use sitz baths as needed. Topical metronidazole gel is applied topically.

Lastly, high trans-sphincteric fistulae may be managed by closing the internal opening via a mucosal advancement flap if the rectum is not diseased. A transanal approach is used to elevate and mobilize a 4- to 5-cm rhomboid-shaped flap containing mucosa, submucosa, and a small amount of internal sphincter muscle. This flap is then mobilized inferiorly and sutured in place to cover the internal opening with the advancement flap. Patients who fail these conservative management techniques will require proximal diversion with an end colostomy.

Occasionally, patients with extensive perianal sepsis secondary to multiple ischiorectal abscesses and rectocutaneous fistulae may have such extensive destruction of the rectal sphincter and perianal tissue that a two-stage procedure is required. Initial operation includes a total abdominal colectomy with end-ileostomy in combination with drainage of all abscesses and opening of the fistulous tracts. Once the infection is better controlled, a proctectomy is completed from the perineal approach with excision of residual fistulae and repair of any associated vaginal defects in women.

Early Complications of Surgical Therapy

Ulcerative Colitis

The complication rate following the IAPP may reach as high as 65% but the mortality is less than 1%. The incidence of complications following surgical therapy of UC increases proportionately with both the duration of disease and the length and intensity of medical treatment [21]. Fonkalsrud et al. [22] reviewed the results of the ileoanal pouch procedure in 168 children (79% of which had UC) at a single pediatric hospital in Los Angeles. Early complications included pouchitis (16%), ileoanal stricture

(14%), and adhesions (7%). Another review of pediatric patients with UC reported the complications seen in 47 children who underwent surgery between 1985 and 2005 in Finland [23]. These patients included 37 patients with J-pouches and 10 patients with straight ileoanal anastamoses. Koivusalo et al. [23] found an overall complication rate of 55%. Early complications included anastomotic stenosis (9%), pelvic abscess/sepsis (9%), wound complications (15%), and early obstruction (23%).

Anastomotic strictures should be addressed in the early postoperative period by serial Hegar dilation at least twice a week for several months to prevent a long-term narrowing, which predisposes to pouch distention and stasis.

Technical problems at the time of operation may lead to fistulae of the pouch to the perianal skin or vagina in 4–9% of patients [23]. These will often require operative intervention, including a protective ostomy as well as a revision of the pull-through. Pelvic abscess or sepsis, presumably secondary to anastomotic leak, is present in up to 10% of patients. Other documented complications include wound infection (5–15%), small bowel obstruction (23–27%), incisional hernia (3–8%), severe incontinence (2–6%), and pouch hemorrhage (1–5%). Additional complications are seen secondary to the protective, temporary ileostomy. Up to 20% of these ostomies have been associated with an obstruction either secondary to a enteric food bolus, or adhesive obstruction [24].

Alexander et al. [25] reviewed the fate of 151 pediatric patients after ileal pouch anal anastomoses. In this retrospective study of patients under 21 who underwent colectomy with ileal pouch anal anastomosis, both short and long-term outcomes were assessed. The surgical techniques varied widely and included both mucosectomy and extramuscular dissection of the distal rectum and several varieties of pouch formation, including hand-sewn and stapled J, S, and S-W pouches. Early complications included ileoanal separation (5%), pelvic infection/abscess (9%), small bowel obstruction, and anal stricture. Late complications were delayed ileoanal separation (5%), pelvic infection/abscess, (25%), bowel obstruction (12%), and anal stricture (18%). Poor outcomes were associated with longer duration of symptoms, perineal disease, late complications, pouch fistulae, and CD. Interestingly, the finding of indeterminate colitis did not influence the long-term outcome of the pouch in this study.

Crohn's Disease

Ileo-Cecal Resection

Early complications of ileo-cecal resection for isolated terminal ileal disease depend on the technique employed. Laparoscopic ileocectomy has been associated with early post-operative bowel obstruction in 8% of patients. The risk for this complication is much higher in patients undergoing reoperation for ileocecal CD. The wound infection rate in open ileocectomy is documented at 6–10%, but this number appears less in patients undergoing the laparoscopic-assisted procedure. Other reported

complications include urinary tract infection and postoperative hemorrhage, which presumably arises from the anastomosis.

Strictureplasty

Strictureplasty has been associated with moderate morbidity of 18–22% in long-term studies [12, 26]. The risk factors associated with post-operative complications include preoperative weight loss, the need for parenteral nutrition prior to operation, and older age. Perioperative complications include wound infection, leak from strictureplasty sites, fistulae, and intra-abdominal abscess in 10%, with recurrent stenosis and gastrointestinal hemorrhage seen in only 5% of patients.

Colectomy

Early complications from total colectomy and ileorectal anastomosis are seen in approximately 15% of patients. The most common problems are anastomotic leak (3%), sepsis (4%), and bowel obstruction (2%) [27]. Other problems include wound infection and anastamotic stricture. Of additional concern is the risk of long-term problems in male patients with retrograde ejaculation and impotence. Fortunately, the overall incidence of these more serious problems is strikingly uncommon using current surgical techniques [28, 29].

Perianal Disease

Short-term complications of operative intervention for perianal CD are mostly due to persistence or recurrence. Initial healing for perianal fistulae in CD occurs in approximately 80% of patients in most studies, but many have recurrence after initial healing [30]. Recent studies using Surgisis anal fistula plugs have demonstrated equivalent fistula closure rates in patients with CD in a median of 10 months of follow-up [20]. However, patients with multiple fistulae had lower rates of closure than those with single fistula tracts.

In adults, 2-year recurrence rates for initial abscesses can be up to 50%, while recurrences following a second abscess are higher at 62% [31]. Most of these repeat infections are seen in association with transsphincteric and ischiorectal fistulae. In contrast, abscesses secondary to superficial anal fistulae have a very low recurrence rate. Fecal incontinence following management of transsphincteric fistulae has been documented at less than 1%, although incontinence of liquid stool or flatus may be slightly higher [32].

Long-Term Outcomes of Surgical Therapy

Ulcerative Colitis

Pouchitis is a problematic long-term complication of the ileoanal pouch procedure for UC. The incidence is as high as 50% in patients followed for more than 10 years.

Pouchitis is characterized by a constellation of symptoms including low-grade fever, lower abdominal pain, diarrhea, bloody stools, and malaise or fatigue. It is most common in the first few years following IAPP, and episodes are more frequent and severe in children [33]. It is hypothesized that stasis of fecal matter within the ileal reservoir leads to bacterial overgrowth and subsequent mucosal inflammation. As pouchitis is rarely seen in patients who undergo IAPP for familial polyposis, the underlying UC is thought to play an important role in development of pouchitis. Furthermore, patients with positive pANCA (perinuclear anti-neutrophil cytoplasmic antibody) serology and preoperative 'backwash ileitis' are at increased risk for pouchitis. Treatment of pouchitis with antibiotics (ciprofloxacin and metronidazole), steroid enemas, and dilation of any ileoanal strictures is usually successful. Studies suggest the addition of probiotics such as lactobacillus after the resolution of pouchitis may reduce the incidence of subsequent episodes of pouchitis [34]. Recurrent pouchitis should prompt endoscopy with biopsy of the pouch to rule out CD.

Long-term follow-up in children who underwent IAPP with J-pouches reveals that the average number of bowel movements per day is 6.1 at 3 months. This number decreases to 4.2 stools a day at 6 months. The rate of twice-weekly nocturnal stooling or soiling was 17% 3 months after surgery but had decreased to only 6% by 6 months [35]. Earlier publications from this author report that 33% of children undergoing an ileoanal pouch procedure require reoperation, including revisions of large pouches [22]. In patients who undergo a straight pull-through without a pouch, stool frequency also undergoes a progressive decline to 7.7 bowel movements per 24 h at 3 years [24]. A recent meta-analysis of studies comparing outcomes of straight versus pouch ileoanal anastamoses concluded that while the pouch procedures appear to be slightly more favorable in terms of reconstruction survival and functional outcome, the paucity of good published papers limits the significance of these results [36]. After reviewing five studies meeting inclusion criteria, the authors found the rates of perineal sepsis and the need for salvage operation to be higher in the straight pull-through group. However, the rate of stricture was significantly higher in the pouch group. Another consideration of this paper is that the pouches were constructed in a variety of manners (58% lateral, 34% J-pouch, and 8% S pouch) and constituted the majority of patients in the studies (71.9%) [36].

Up to 45% of patients eventually require re-operation for complications following ileoanal pull-through, and up to 9% experience pouch failure requiring ileostomy with or without pouch excision [25]. Fazio et al. [37] at the Cleveland Clinic reported that repeat ileal pouch-anal anastomosis is a safe and effective procedure to salvage the pelvic pouch in patients who suffer major chronic pelvic sepsis. In their study of 35 patients undergoing reoperation for septic indications, there were no deaths or intraoperative ureteral injuries. Complications after repeat surgery included ventral hernia, need for transfusion, anal fissure, mucosal prolapse, and erectile dysfunction. At greater than six months of follow-up, 86% of their patients had functioning

pouches. The incidence of adhesive obstruction after any surgery for UC is reported to be 20–25%, although lower rates have been reported.

Children with UC have an increased risk of colorectal cancer than the average population. A long-term, retrospective study from the Cleveland Clinic found that colorectal cancer developed in 2% of adolescents with UC. In procedures where any rectal mucosa is left behind, routine surveillance should be established within 8–10 years after initial diagnosis of the disease [38]. While dysplastic transformation within the ileal pouch mucosa is rare after long-term follow-up, carcinoma of the pouch has been reported. Both adenocarcinoma and squamous cell carcinoma occurring in the anorectal epithelium below the ileorectal anastomosis have been reported. Patients at highest risk are those with either dysplasia or carcinoma in the resected colon or those with long-standing disease [39].

Colectomy and ileoanal anastomosis can also lead to problems with fertility in women. A meta-analysis addressed the risk of infertility in women with UC undergoing colonic resection and ileoanal anastomoses and found that the risk of infertility was increased threefold. Infertility increased from approximately 15% in UC patients before proctocolectomy with J pouch to approximately 50% after the surgery. One included study performed hysterosalpingograms demonstrating 52% fallopian tube occlusion and 48% adherence to the pelvic floor, suggesting a role of post-operative adhesions in producing infertility. These data are limited by inconsistent definitions of infertility, lack of details of the surgical procedures in many included studies, and lack of information on disease duration prior to surgery. Hopefully, future studies of the young girls who have undergone surgery for UC will provide data applicable to the pediatric and adolescent patient population.

Crohn's Disease

Ileocolectomy

Ileocolectomy, whether laparoscopic or open, is associated with a 5-year recurrence rate of just over 25% in adults [6]. In a study out of the Children's Hospital of Philadelphia, the risk for recurrence in pediatric CD has been documented at 17% at 1 year, 38% at 3 years, and 60% at 5 years [9]. Recurrence was defined as a Pediatric CD Activity Index (PCDAI) greater than 30 in combination with either response to escalation in medical therapy or confirmation with radiographic, histologic, or endoscopic evaluation. Patients with colonic CD had a higher rate of recurrence and a shorter time to recurrence than ileocecal disease (1.2 vs. 4.4 and 3.0 years, respectively). The highest risk of recurrence was in patients with a high PCDAI at time of operation and pre-operative use of 6-mercaptopurine.

Creation of a permanent stoma is the only surgical procedure that appears to decrease disease recurrence, and is required in nearly 25% of patients with juvenile onset Crohn's by 10 years following onset of symptoms [40]. However, adult studies suggest that

pharmacologic therapy can decrease the rate of recurrence after resection. Data suggests that administration of Pentasa (4 g/day) to patients after resection of localized ileal disease can decrease the clinical relapse rate at 18 months [41]. Other studies suggest that oral metronidazole (20 mg/kg/day for 3 months) can delay symptomatic and endoscopic recurrence at 1 year after resection with ileocolonic anastamosis [42].

Strictureplasty

Strictureplasty has been shown in multiple studies to be both safe and effective in treating obstructing small bowel CD. This procedure has been shown to increase weight gain and growth in almost 75% of young patients with CD [43]. In several studies, strictureplasty is associated with recurrence rates of 34–52%, which are comparable to the results seen with open intestinal resection [22, 26]. The most significant risk factor for early reoperation was young age at first operation. In the aforementioned literature, reoperative rates appear comparable following initial and repeat strictureplasty [26]. On the other hand, reports out of the University of Chicago suggest that fewer recurrences occurred at strictureplasty lines when compared to sites of resection (45 vs. 70%) [44]. It is unclear whether this data can be extrapolated to the pediatric population.

Prior to the widespread use and acceptance of strictureplasty, CD led to the development of short bowel syndrome and TPN dependence due to multiple intestinal resections. Investigations into mechanisms of intestinal failure in Crohn's have shown 83% of patients developed intestinal failure secondary to intestinal resection, while only 17% were due to extensive primary disease [45]. Several patients developed short bowel syndrome after uncomplicated serial intestinal resections over a median period of 17 years. In contrast, a much larger percentage of Crohn's patients with short bowel syndrome developed intestinal failure secondary to multiple, unplanned laparotomies for intra-abdominal sepsis.

Colectomy

In patients with Crohn's colitis, proctocolectomy is associated with the lowest recurrence rate of 15% at 5 years and 20% at 10 years [12]. This rate is nearly doubled in patients undergoing total abdominal colectomy, which has recurrence rates of 40% at 5 years and 50% at 10 years. However, patients with total colectomy and ileorectal anastomosis demonstrated complete continence throughout the day and night with an average of four bowel movements a day [27]. In a study of 131 patients, 36 patients who underwent total abdominal colectomy with ileorectal anastomosis eventually required either fecal diversion or proctocolectomy due to excessive stooling, bleeding, or persistent steroid dependence [46].

Perianal Disease

Surgical treatment of perianal disease in Crohn's remains only somewhat successful. Failure of healing after local procedures often leads to a proximal ostomy. Data from

the pediatric surgery literature suggests 20–30% of patients who undergo intestinal resection or diversion see resolution of their perianal symptoms [47]. Studies predating the use of infliximab demonstrate that proctectomy is eventually required for extensive fistular disease, fecal incontinence, and anal stenosis in 38% of patients. Patients with multiple perianal fistulae and abscesses and active rectal disease are at highest risk for requiring a proctectomy [32]. While salvage proctectomy or proctocolectomy is effective, these patients still have a 10% risk of further operation at 5 years, which increases to 30% at 10 years [48].

Conclusions

Operative management often plays a critical role in the optimal treatment of inflammatory bowel disease in children. Delay in total proctocolectomy in older children and adolescents with severe UC can lead to significant growth delay and nutritional deficiency. The risks and benefits of both surgery and medical management must be taken into account when deciding on the most appropriate therapy for CD and UC in pediatric patients.

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Transition to Adult Care

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Abstract

Young adults with inflammatory bowel disease need to be transitioned to the adult medical system with as much continuity of care as possible. Transition from pediatric to adult medical care continues to present significant barriers. Transitioning inflammatory bowel disease patients involves a careful process involving concrete steps that help patients prepare for new responsibilities. The aim of this review is to propose a clinical and developmental timeline for both patients and their medical team, in order to promote a successful transition.

The passage from adolescence to adulthood can be a period of tremendous turmoil, both physically and mentally, even in the healthiest of children. It is a particularly challenging process for young adults with inflammatory bowel disease (IBD). Children with IBD have unique issues compared with adults who suffer from this disease. Transitioning from pediatric to adult medical care is a major milestone in the life of a young person with IBD, yet it is often poorly done. In this chapter, we review the issues surrounding the transitioning of medical care to adult providers and provide practical recommendations for the transition process.

Barriers to Transition

There are considerable differences between pediatric and adult medical services, and recognizing this distinction is essential for a successful transition. Pediatric care tends to be multidisciplinary, family focused, and requires parental direction and consent. Adult care is often provided by a single doctor, is patient focused, includes a greater emphasis on procedures and diagnostic testing, and expects the patient to be autonomous and independent [1].

Obstacles to transition appear to be universal among chronic medical conditions with a childhood onset. Our pediatric colleagues who care for patients with congenital

cardiac disease, juvenile diabetes, cystic fibrosis, sickle cell disease and organ transplantation have long recognized the issues surrounding transition of care [2–7]. Hauser et al.'s [8] study of patients with sickle cell disease concluded that adolescents are worried about leaving a familiar setting with physicians they trusted. Patterson et al. [9] conducted focus groups of adolescents with special health care needs in the Adolescent Health Transition Project. Their study identified that these young adults trusted their pediatric caregivers, were 'burned out' on healthcare, and felt their parents had trouble letting go.

In McCurdy et al.'s [10] study of transplant recipients, recently transitioned patients specifically requested more detailed information about the consequences of risky behaviors. They wanted more information about alcohol and drug use, smoking, and safe sex practices but did not want to initiate these discussions. Subjects in this study also expressed that it was not made clear prior to transition the extent that they were going to assume responsibility of their own care once in the adult setting. The authors concluded that the adult healthcare team needs to be aware that this shift in responsibility is new for these patients and that some direction may be required until they become more independent.

There are several obstacles to transition that must be recognized and incorporated into the process of transitioning young adults with IBD [11]. They may be reluctant to give up the familiar atmosphere that is part of their pediatric setting. They have had a long and close relationship with the pediatric team since disease onset. They often do not want to have to educate their new adult caregiver about their medical condition.

Parents of children with IBD may have a similarly close relationship with the pediatric team. They may be overprotective, seeing their child as more fragile than average. Since they have often been intimately involved in the care of their child, they may feel ignored when adult caregivers involve them only with the permission of the patient (Clinical Case 1).

The pediatric caregivers may also complicate the transition due to their strong ties to the patients and families. The provider may avoid the topic, thus causing anxiety about the process and surprise about a seemingly sudden transfer. They may unintentionally infantilize the patient by not recognizing the development of the patient. Without understanding the difference in medical culture, they may mistrust the adult team in meeting the psychosocial challenges of pediatric patients with IBD. Moreover, these feelings can unintentionally be communicated to the patients and their families, compounding their resistance to transition. The pediatric provider's attitude and age appropriate care have significant impact on the patient's experience of transition.

Finally, adult medical providers can also contribute to transition problems. Difficulties in scheduling may cause a delay in re-establishing medical care after discharge from the pediatric setting. This becomes all the more problematic when an urgent problem is the event instigating the attempt to establish care. With limited

understanding of the developmental aspects of late adolescence, adult providers may expect patients to behave like other adult patients. They may feel that patients with childhood-onset IBD are immature and that their families are too involved. Conversely, they may not recognize the family or young adult's proven expertise. They may not recognize the untapped anger or grief experienced by the patient who feels abandoned. Consequently, adult medical providers may be prone to personalizing their new patient's behaviors and attitudes. Another important barrier to successful transition is the general lack of communication between pediatric and adult providers.

The Transition Process

Essential to the success of transition is the recognition that it is a process, not a single point in time. It is not synonymous with transfer of care and thus is far more than the mere act of providing contact information for an adult provider. Transition should be a planned program that includes providing developmentally and age appropriate uninterrupted health care. It involves the promotion of skills in communication, decision making, and self advocacy. It also ensures the accumulation of relevant knowledge about the patient's own history, disease, medications and resources. The actual act of transfer to an adult provider is just the culminating step of this carefully planned process.

Perhaps the most crucial element in the transition process is anticipation. This allows for practice and problem solving. To anticipate the course of the transition process, practitioners must approach this within a developmental framework. The process should be initiated well before the act of transferring care and should encompass services and supports that provide the young adult with the skills necessary to empower them to navigate the world of adult health care [12].

The transition process should begin as soon as the patient is capable of abstract thinking and future orientation. The child should be approached from their developmental stage, roughly defined by age. We propose the following timeline, but it is important to note that the clinical transition course must be tailored to the developmental abilities of the individual patient.

Ages 11–13

By this age, the child should be able to articulate that they have IBD. The patient should be able to name his or her medications, including dosages and side effects. These children should start to identify strategies to take their medications. They should be able to use a thermometer. The child should be able to express the impact of IBD on his or her daily functioning at school, socially, and at home.

At this age, the medical team should introduce the idea of future independent visits. Parents should remain in the waiting room for a portion of the visit. Anticipatory guidance on the impact of fitness, sexuality, and substance use on their illness should be given.

Ages 14–16

Patients in this age group should be able to identify their primary caregivers, both family members and professionals. They should be able to name the procedures and tests that evaluate their disease, as well as understand their purpose. They should be able to articulate their medical history. They should be able to identify names of IBD social support groups and community organizations. Patients should be able to articulate the medical risk of nonadherence, and they should understand the impact of illicit drugs and alcohol on their illness.

The medical team should direct all questions and explanations to the patient, not the parent. It should be explained to the parent that the physician will ask the patient for input first, and then solicit feedback from the parent. This is a good opportunity for the physician to address the family's apprehensions about the patient taking on a primary role during the office visit. The physician should ask the patient during which portions of the visit he or she would like his or her parents out of the room. As with all adolescent patients, the physician must clarify with the patient what must legally be shared with his or her parents.

At this point, the physician should initiate discussion about the eventual transfer of care and why this is important. Post-high school plans should be discussed, and intermediate goals set to help achieve these plans. The patient should be instructed how to schedule appointments, fill prescriptions, access medical records, and to keep medication and medical team contact information.

Ages 17–19

At this age, patients should be able to gather information about IBD. Patients should demonstrate the ability to access and coordinate medical needs. They should be able to book their own appointments, fill prescriptions, and contact the medical team directly with medical issues. They should be able to name their insurance carrier and plans for the next 2 years of coverage. They should carry their insurance information in their wallet.

The medical team should initiate conversation about potential barriers to transfer of care, including financial issues, attitudes, access, and family resistance. The physician should identify potential adult providers for the patient to begin exploring. The patient should be encouraged to start meeting potential providers. The patient and family should be reminded that at age 18 the patient has the right to make his or her

Table 1. Suggested details to be included in the medical summary letter

Date of diagnosis
Location and severity of disease
Endoscopic findings – include dates
Pathology
Radiology – fluoroscopy, CT scans, MRIs
Surgeries (and complications)
Medical therapies used – doses, duration
Adverse reactions to medications
Reasons for discontinuing a medication (e.g. refractory disease, elevated transaminases)

own healthcare decisions. The medical team should begin to discuss differences in the cultures of pediatric and adult medicine.

Ages 20–23

By this age, the patient should have had telephone conversations with potential adult providers. The pediatric gastroenterologist should provide the patient with a detailed medical summary to give to the adult provider (table 1). The patient may have a final visit with his or her pediatric provider to discuss their experience with the adult provider. The pediatric gastroenterologist and family can then troubleshoot remaining concerns.

It is important to note that transition is most likely to be successful if the actual transfer of care occurs at a time of relative medical and social stability (Clinical Case 2). This may occur at different ages for various patients. For those who attend college, the transfer may be after graduation and after a job is secured or graduate education has begun. For those who choose not to attend college, the transfer of care should occur when housing and employment arrangements are stabilized.

Other Recommendations

The National Association for Crohn's and Colitis (NACC) in the United Kingdom, along with the Crohn's in Childhood Research Appeal (CICRA), have spearheaded tremendous effort to raise awareness about transitioning young adults with IBD to adult care [13]. They recommend that each patient have an individualized formal transition plan that can be assessed yearly for progress. In addition, they suggest that a transition co-ordinator be allocated to each patient to assist with the oversight of the transition process. This person could be a physician, nurse, or social worker, and would serve as a primary contact for patients and families.

Table 2. Appropriate roles of pediatric and adult providers in the transition from pediatric to adult care

Pediatric provider	Adult provider
Establish and maintain contact with an adult provider team to facilitate trust and communication	Establish and maintain contact with pediatric provider team to facilitate trust and communication
Educate the adult provider team about key developmental issues related to chronic disease in children and IBD	Learn about key developmental issues related to chronic disease in children and IBD
Initiate patient and family discussions about transitioning care well in advance of planned time of transfer	Accept referred patient in a timely fashion
Refer patient in time of disease quiescence, if possible	Anticipate questions about substance use and sexuality; elicit this information if it is not volunteered
Provide detailed summary of medical and developmental issues	Educate the patient regarding the adult model of care, and negotiate the nature of the initial doctor-patient-family relationship in a developmentally appropriate (rather than age-specific) manner Recognize and address the potential psychosocial impacts of chronic disease in childhood

Another excellent recommendation by NACC and CICRA is to attempt buddying or mentoring arrangements. Linking young adults in the process of transition with those who have already successfully navigated the system can be extremely beneficial for patients. For more useful recommendations, we refer you to their website: www.ibdtransition.org.uk.

Conclusion

Transition is a long, complex process that requires careful planning. The process should begin early and should be done in a consistent and open manner. All participants, including providers, patients, and families, should be aware of the process and understand the underlying rationale and eventual goal. This will help the patient and family with this difficult life change, without feeling abandoned. Anticipation is the key to a successful transition. When done effectively, transition can be an extremely empowering experience for patients.

Clinical Case 1

Kyle is a 23-year-old who has suffered from ulcerative colitis since the age of 7. He recently transferred care to Dr. Gutierrez, an adult gastroenterologist, upon graduation from college. Kyle's mother frequently leaves telephone messages for Dr. Gutierrez describing Kyle's symptoms and her concerns about his health. She requests that Dr. Gutierrez call her son back, but not mention to him that she called. Kyle's mother is frustrated that her son does not seek medical attention when his symptoms recur. Kyle minimizes his symptoms and is annoyed that his mother is so overprotective. Dr. Gutierrez is frustrated because Kyle's mother seems to exaggerate his symptoms, and it requires twice as long to make two telephone calls.

Clinical Case 2

Julie is a 20-year-old with Crohn's ileocolitis. She attends college locally and has been clinically in remission for several years. During a particularly stressful exam period, Julie experienced severe right lower quadrant tenderness with fevers and rigors. She presented to the Children's Hospital emergency room where an evaluation revealed an intra-abdominal abscess. Unfortunately, the policy at Children's Hospital prevents patients over the age of 19 from being admitted to their facility. Therefore, Julie was transferred to an adult medical facility for treatment. The adult medical team found it extremely difficult to acquire Julie's medical records in such an urgent setting. Julie was quite ill and was unable to reliably relay important medical information to the team.

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