Pediatric Crohn’s disease: epidemiology and emerging treatment options

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Abstract: There has been a dramatic increase in the incidence of Crohn’s disease over the last two to three decades worldwide, which has affected both the developed world and increasingly also the developing world. Crohn’s disease is a disease of youth and can have a profound effect on the growing child, both in terms of growth and skeletal health as well psychosocial maturation. Environmental risk factors appear to be crucially important, but it is not clear at present whether improved hygiene, especially in childhood, influences immunological conditioning, or whether there is a direct impact on the gut from a disturbed gut microbiota. Genetic variation appears to relate to how the host interacts with its microbiota, determining susceptibility rather than causation. The outcome is a sustained immune response, clinically presenting as a relapsing/remitting disease process. There is no current cure for Crohn’s disease; treatments are designed to reduce symptoms and control inflammation, initially by inducing a remission, then trying to maintain it. Historical therapies have included 5-aminosalicylic acid-based drugs, corticosteroids, and immunomodulators. Two approaches which are gaining increasing interest are the use of exclusive enteral nutrition and biologicals. Enteral nutrition is a remarkably effective approach, though there is a limited understanding of its mechanism and difficulties in acceptance among the medical community. Biologicals are a class of drugs which specifically target molecules and pathways central to the inflammatory process; they are also very effective, but patients can develop a secondary loss of response as a result of antibodies to the biological agent. Infection and the development of secondary malignancies have provided concerns with these very potent agents and with combination therapies, but inadequately controlled disease appears to pose a bigger threat for many patients than the side effects of medications. A wide range of alternative therapies are also being explored, such as the manipulation of gut flora and pathways which might influence immune responsiveness. The marked recent increase in Crohn’s disease, especially in children, has prompted a large research effort which to date has led to a better knowledge of the biology of the disease and more effective treatments. These therapies need to be used judiciously to optimize benefit and minimize side effects.

Keywords: inflammatory bowel disease, ulcerative colitis, tumor necrosis factor, biologicals, microbiota, enteral nutrition

Introduction

Crohn’s disease and ulcerative colitis are chronic inflammatory conditions affecting the gastrointestinal tract which are associated with substantial morbidity. Up until two to three decades ago they were relatively rare in children, but in recent years they have become increasingly more common. This change in incidence has been associated with substantial improvements in therapeutic options, although a cure is not yet available for either condition. The lifelong relapsing–remitting nature of these conditions has
the potential for impacting growth, development, and quality of life. This review will focus particularly on Crohn’s disease, with discussion of its changing epidemiology, emerging treatment options, and its impact in children.

Epidemiology

Crohn’s disease was first described as a clinical entity by Burrril B Crohn and colleagues in the USA in 1932 and has traditionally been regarded as a disease of the Western world. A rising incidence in both adults and children has been observed in recent years, with some studies suggesting a ten-fold to 20-fold increase in children over three decades. Crohn’s disease currently affects about 700,000 people in the USA and about a million people in Europe. The annual all-age incidence rate from Australia is now of the order of 17 per 100,000 per year. However, it is now also being increasingly recognized in the more affluent areas of Asia, Eastern Europe, and South America. The situation in the developing world is not clear, as population-based data on the incidence and prevalence is generally lacking. This may in part explain the apparently disproportionately high incidence further from the equator in more developed countries, which are likely to have better population data. Not surprisingly, there is evidence that access to medical services may influence the reported incidence of inflammatory bowel disease (IBD). One study from the Punjab in North India was only able to be carried out by utilizing a house-to-house search with gastrointestinal endoscopy carried out on suspected cases.

Nevertheless, there is some evidence that environmental risk factors are important, especially those present during childhood. Crohn’s disease occurs more commonly in urban versus rural regions. Improved hygiene, especially in childhood, is thought to be an important risk factor. Migration from areas of low incidence to high incidence countries increases risk to that present in the population of the adoptive country, but age is of pivotal importance. This increased risk is only present for those who migrate during childhood, not as adults. Early life events, the environment, or immunological conditioning appear to be crucial determinants in the later development of IBD, emphasizing both the importance of childhood studies and the primacy of environment over genetic susceptibility.

Crohn’s disease is likely to occur equally among the sexes, as reported sex differences are largely inconsistent. Although Crohn’s disease can present at almost any age, it is most likely to present between the second and fourth decades of life.

Fifteen percent to 25% of patients with Crohn’s disease present in childhood. The incidence of Crohn’s disease during childhood has been reported to range between 2.2 to 6.8 per 100,000 children aged 0–16 years, but there are marked variations between different parts of the world. There has been a dramatic increase in pediatric Crohn’s disease in Australia over the last three to four decades (Figure 1), with the current standardized incidence rate being greater than 2.0 per 100,000 children aged 16 years or younger. While the peak age of new diagnosis for Crohn’s disease overall is between the second and fourth decades, the average age in pediatric practice is about 11 years (Figure 2). A study from Scotland reported a doubling of the incidence of pediatric Crohn’s disease over the 15-year period to 1995, with an overall averaged standardized incidence rate of 2.5 cases per 100,000 population for the period. Marked increases in pediatric diagnoses have also been confirmed in other parts of Europe, such as Sweden, Czechoslovakia, and the UK, while elsewhere, such as Canada and the USA, they appear to have plateaued after previously documented increases.

What is clear is that the trend is for an increase in most parts of the world, and now particularly in areas that were previously of very low incidence. Twenty years ago, IBD was almost unknown in the People’s Republic of China. Recently, a multicenter, retrospective audit of over a decade of experience with childhood IBD from 2000–2010 in Shanghai has shown a steadily increasing trend in children aged 0–14 years. The peak prevalence was in children aged 10–14 years. Ng et al compared regions within the Asia Pacific of newly increased incidence with others of established high incidence, such as Australia, for affected adults. While the incidence of IBD was still less in Asia than that of Australia, the numbers involved were still substantial. Southeast Asia had an incidence rate varying from 0.15–1.0 per 100,000 individuals. The People’s Republic of China had the highest

Figure 1 Historical trends in numbers of children diagnosed with UC and CD in Victoria, Australia.

Notes: Data trends presented in 5-year epochs. Data taken from Phavichitr et al16 and Schildkraut et al.17

Abbreviations: CD, Crohn’s disease; UC, ulcerative colitis.
Epidemiology and etiology

Any discussion of the epidemiology of Crohn’s disease requires a summary of current theories of causation. The exact etiology of Crohn’s disease remains unknown. It appears to represent a sustained immune response, clinically presenting as a relapsing/remitting disease process. It is currently believed that Crohn’s disease occurs as part of an interplay between environmental and immunological factors in a genetically susceptible host. Epidemiological studies which have shown a rapid increase in incidence and studies that have shown strong environmental influences point to the environment as being key. These changes have come too quickly to represent any change in the gene pool.14 Nevertheless, genetic studies have provided intriguing information. One of the most interesting conclusions is that genetic susceptibility for Crohn’s disease is defined by variations in how the host interacts with its microbiota.15 These have been recognized as alterations in epithelial barrier function, and at the level of innate and adaptive immunity to the microbiota.13 It appears to be the host’s relationship to its own microbial environment that is the key trigger for Crohn’s disease in particular.

The first gene implicated in susceptibility to Crohn’s disease was the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene, also called caspase recruitment domain-containing protein 15 or inflammatory bowel disease protein 1.18 It is located on chromosome 16, recognizes bacterial muramyl dipeptide, and regulates immune response to bacteria.19,20 Loss of function variants of the NOD2 gene have been associated with increased susceptibility to Crohn’s disease, especially small bowel disease.18,21–23 Other loci involved with increased susceptibility to Crohn’s disease include IBD5,3,6 on chromosomes 5, 6, and 19, respectively.20,24

Another genetically defined process which can contribute to susceptibility to Crohn’s disease is that of autophagy. Autophagy is a process that mediates degradation of intracellular proteins via vesicle-mediated delivery to lysosomes. Defects in autophagy could potentially alter the immune responsiveness to intracellular pathogens. Autophagy is believed to be mediated through at least three component genes – ATG16L1, IRGM, and NOD2.25 ATG16L1 is essential for autophagy, and the coding mutation T300A is associated with an increased risk of Crohn’s disease.26

The search for a microbial trigger for Crohn’s disease has been carried out along two pathways – either a specific transmissible agent, or a dysbiosis involving the gastrointestinal microbial milieu. Dysbiosis refers to the breakdown of balance between commensal bacteria and harmful bacteria in the gut.25 The gut microbiota is relatively difficult to characterize, and the functional implications of differing populations and their interactions are not really understood.26 Recent advances in metagenomics have certainly strongly supported the presence of a dysbiosis in patients with Crohn’s disease.27 One of the most interesting observations, however, is that Crohn’s disease is associated with markedly reduced bacterial diversity.27 Whether this is a cause or effect of inflammation is unknown.

Although most interest has focused on bacterial populations, some attention has been provided to other members of the gut microbiota, such as viruses.28 There is little evidence at present to support them as specific transmissible agents,28 but an area that is starting to be explored is that of bacterial viruses, or bacteriophages.29 The introduction of next-generation sequencing has transformed our ability to define bacteriophages, which represent the most genetically diverse components in the biosphere.30 Bacteriophages themselves are extremely numerous, and are reported to be the most abundant replicating entities on the planet.31 They are likely to impact gut function via their impact on bacterial metabolism, interactions, pathogenicity, and diversity.31

The other major thrust of research has been into a specific transmissible agent. Although a number have been proposed,
one which has received the most enduring interest and also been the most controversial has been *Mycobacterium avium* subspecies *paratuberculosis*.\(^3\) This has been identified in up to half of newly diagnosed children.\(^3\) The infection is widely disseminated in cattle populations and is the cause of bovine bowel disease, which has many similarities to Crohn’s disease in humans; there is also evidence that it has been increasing in cattle herds.\(^3\) The controversial aspect is whether or not it might be of etiological importance in human disease.\(^4\) The economic implications were this to be confirmed would be very substantial, but strong circumstantial evidence continues to emerge.\(^5,6\)

The hygienic hypothesis has been an attempt to synthesize this complex interplay between genetically defined immunological susceptibility factors and the microbiome.\(^10\) This postulates that multiple childhood exposures to enteral pathogens and immunological stimuli protect an individual from developing Crohn’s disease later in life, while individuals raised in a more sanitary environment are more likely to develop Crohn’s disease.

### Current and emerging treatment options

In the absence of a deeper understanding of the pathogenesis of Crohn’s disease, treatments are for the most part directed at influencing inflammation. A cure is not possible, and therapeutic interventions are designed to relieve symptoms, improve the quality of life, and avert long-term complications. Historically, medications have been employed either to induce or to maintain a remission. Step-up therapy has been the traditional approach, using, for instance, aminosalicylates, then topical steroids, then systemic steroids, and going to immunosuppression or potent new biological agents if necessary.\(^37\) Clinical symptoms have by and large driven each step. Unfortunately, the natural history of Crohn’s disease is marked by recurrent acute flares and progressive bowel wall damage.\(^37\) This has led to the concept of top-down treatment with prevention of structural damage by achieving mucosal healing, necessitating more aggressive treatment with earlier use of immunosuppressants and biologicals together with closer surveillance of mucosal inflammation, whether by endoscopy or by indirect fecal markers of gut inflammation.

It is widely believed that this top-down approach helps to modify the natural course of the disease.\(^38\) Studies have also shown that early introduction of immunomodulators has a steroid-sparing effect and improved maintenance of remission.\(^39\) Top-down therapy has been associated with reduced rates of surgery and hospitalizations, but the concern has been for the increased risk of infections associated with immunosuppressants together with the cost of agents such as biologicals. Under-treatment and over-treatment are both to be avoided, and there is increasing interest in tailoring therapy to the individual’s needs – personalized medicine.\(^40,41\) One aspiration is that defining genetic susceptibility patterns may help guide treatments on an individual basis.\(^41\)

### 5-ASA-based preparations

Preparations of 5-aminosalicylic acid (5-ASA) are frequently the first-line management in patients with mild Crohn’s disease, particularly when it involves the colon. Sulfasalazine is a combination of 5-ASA and sulfapyridine which acts as a carrier to the colon.\(^51\) In the colon, the sulfasalazine is broken down into 5-ASA and sulfapyridine by azoreductase enzymatic activity from colonic bacteria.\(^43\) 5-ASA is the active moiety. Randomized controlled trials have shown sulfasalazine to be better than placebo in inducing remission in active colonic Crohn’s disease.\(^44,46\) However, it does not have a steroid-sparing effect. The European Crohn’s and Colitis Organization consensus guidelines recommend use of sulfasalazine in patients with mildly active colonic Crohn’s disease.\(^46,47\) It may also be appropriate in patients with associated arthropathy.\(^47\) Effective adult doses range from 4–6 gm per day (40–75 mg/kg/day in children).\(^48\) The sulfapyridine component of sulfasalazine has been implicated in many of its side effects, including allergic reactions,\(^49,50\) and efforts have been directed toward producing an effective 5-ASA-based drug which lacks sulfapyridine and is formulated in such a manner as to maximize delivery to the inflamed tissue – either colon or terminal ileum.

Delivery systems include enemas or suppositories, which provide the drug to the rectum and left colon; coating with protective materials that release the drug in a pH-dependent manner to achieve controlled (Pentasa, Ferring Pharmaceuticals, Pymble, NSW, Australia) or delayed (Asacol, Warner Chilcott, Rockaway, NJ, USA) delivery, and diazo-bonding the drug to a second 5-ASA molecule (olsalazine) or to an inert carrier (balsalazine). Release profiles of the oral drugs vary depending on the coating preparation. Mesalamine delayed release (Asacol) has a Eudragit–S coating which releases at a pH of 7 or above, hence delivering the drug to the terminal ileum and distally.\(^51\) Salofalk (Orphan Australia, Dandenong, VIC, Australia), and Mesasal (Aspen Pharmaceauticals, St Leonards, NSW, Australia) have a Eudragit L coating which releases at a pH of 6 or above and also delivers the drug to the terminal ileum. Controlled-release mesalamine capsules (Pentasa) have
ethylcellulose-coated microgranules, releasing approximately half the dose in the duodenum, jejunum, and ileum, with the other half in the colon. Diazobonded preparations have release profiles closely resembling that of sulfasalazine.52–54

However, there is conflicting evidence for mesalamine in inducing remission, and the role of the 5-ASA-derived drugs in Crohn’s disease is still being established. One study has shown efficacy.55 A minimum daily dose of 4 gm in adults was associated with a 43% remission rate in adults, compared to 18% for placebo. Moreover, there was some suggestion that it conferred additional benefit in patients with ileal disease, a benefit over sulfasalazine. However, subsequent trials have failed to show clinically significant benefit for Pentasa 4 gm a day in inducing remission in patients with mild to moderate Crohn’s disease,56 or any clinically significant value in the prevention of relapse.57

5-ASA drugs remain frequently used in Crohn’s disease. Side effects of sulfasalazine include fever, rash, hemolytic anemia, hepatitis, pancreatitis, headache, nausea, malaise, and anorexia.49,50 Newer ASA preparations are generally considered safer than sulfasalazine, but nevertheless are associated with adverse effects. Mesalamine has been reported to cause diarrhea, nephrotoxicity at an average rate of 0.26% per patient year and pancreatitis seven times more frequently than sulfasalazine.49,58,59 It can also rarely but dramatically affect the lungs, most likely through an allergic reaction, causing eosinophilic pneumonia, bronchiolitis obliterans, pleural effusion, or pulmonary fibrosis.42,50,59,60

Mesalamine has been reported to be safe and effective in children and adolescents in the limited data that is available.61 However, it has not been shown to be effective in maintaining remission in a double-blind, multicenter, randomized, placebo-controlled trial.62

A Cochrane meta-analysis on the efficacy of aminosalicylates concluded that sulfasalazine has modest efficacy compared to placebo but is inferior to steroids in the treatment of mild to moderate Crohn’s disease.63 High-dose mesalamine was reported to be inferior to budesonide and not more effective than placebo for inducing remission.53

Corticosteroids
Corticosteroids, usually prednisolone and its equivalents, are frequently used as first-line agents to induce remission in moderate to severe Crohn’s disease.38,64 Systemic corticosteroids achieve response rates of up to 90% for active disease in most distributions.44 Typically, steroids are administered as a pulse and tapered over weeks to months, depending on clinical response. There is no evidence that any one tapering regimen is better than another.64 Recurrent symptoms on tapering or shortly after cessation are termed steroid dependency; this is fairly common, occurring in about a third of patients.64 Steroid resistance, which can develop over time in about 40% of patients, can result from a range of molecular mechanisms.64,65

The concern with the use of systemic corticosteroids lies in the increased risks for infection, growth, and skeletal health,66,67 although their impact on bone health may not be as much as was once thought.68,69 Steroid-naive newly diagnosed patients have lower bone density than healthy controls,70 and so it would appear that uncontrolled IBD itself is likely to have the most important impact on bone health in current treatment regimens. Toxicity relates to dose and duration. Mood swings, acne, and Cushingoid facies can be very difficult for the adolescent patient in particular.

Budesonide is a corticosteroid with extensive first-pass metabolism (85%) and low systemic bioavailability. Targeted delivery to the ileum and the right colon is achieved through specific pH and time-dependent formulation. Clinical efficacy is nearly the same as prednisolone in adults,71 which is also the case for children with Crohn’s disease.72 The potential advantage of budesonide with particular relevance to pediatric practice is that it is associated with significantly fewer side effects and less adrenal suppression than prednisolone.73 However, neither drug decreases the risk of relapse during maintenance therapy,44,74 and so should not form part of long-term therapy.

Exclusive enteral nutrition
Exclusive enteral nutrition (EEN) refers to the exclusive use of either an elemental or polymeric liquid formula for 6–8 weeks to induce remission in Crohn’s disease.75 Normal diet is slowly reintroduced after the 8-week period.76 Despite its low risk and relatively high efficacy, it is relatively underused except in pediatric practice in some countries, and in Japan in both adults and children.77 Multiple studies have shown EEN to be a safe and effective agent for inducing remission in active Crohn’s disease without the side effects of corticosteroids.75,78–80 There is evidence, for instance, that EEN may provide for better skeletal health outcomes compared to steroid-induced remission.81 Mucosal healing rates are substantially better than for corticosteroids,75,81,82 although there is controversy as to whether clinical response rates are equivalent, worse, or better than with steroids.75,77,83

Enteral feeds appear to be effective in maintaining remission, either alone or alternating with normal feeds, as partial EEN or combined with conventional pharmacotherapy.75,84
Notwithstanding the advantages of EEN, its uptake has been extremely limited with wide variability worldwide in its use as a first-line therapy, ranging from 62% among European pediatric gastroenterologists to only 4% of North American gastroenterologists.\textsuperscript{75,85} Likely reasons include lack of experience among treating physicians, perceptions of poor acceptability, lack of dietetic support, and difficulty in organizing feeds comparing to prescribing conventional pharmacotherapy.\textsuperscript{75} The feeds are of limited palatability, monotonous, and may require an enteral tube, and patients crave the sensation of eating.\textsuperscript{76,86}

**Immunomodulators**

Immunomodulators are another group of drugs used in the management of moderate to severe Crohn’s disease both for induction and in maintenance therapy.\textsuperscript{87} They were initially used in the treatment of steroid-dependent or -resistant Crohn’s disease, but now are increasingly used as a primary adjunctive therapy in more severe disease, especially in children.\textsuperscript{88} The thiopurines azathioprine and 6-mercaptopurine are the most widely used, with increasing use of methotrexate. Azathioprine is converted nonenzymatically into 6-mercaptopurine.\textsuperscript{89}

Neither azathioprine nor 6-mercaptopurine are very effective as single agents for induction, but when added to corticosteroids at first commencement of therapy were associated with lower cumulative corticosteroid dose and prolonged remission in a double-blind, placebo-controlled study in children.\textsuperscript{89} There is relatively little evidence regarding methotrexate as a similar adjunctive agent in inducing a remission, but prevailing guidelines suggest that it is probably as effective as thiopurines in this situation.\textsuperscript{90}

Both azathioprine and 6-mercaptopurine effectively maintain remission. Studies have shown that there is a clear benefit of continuing azathioprine or 6-mercaptopurine for at least 18 months to maintain remission.\textsuperscript{90} Methotrexate is also effective for maintenance therapy and tends to be used in patients resistant to or intolerant to thiopurines.\textsuperscript{91} There is limited data on the safety and efficacy in children, but available studies suggest that methotrexate is a safe and effective alternative to thiopurines in maintaining remission.\textsuperscript{92,93} Methotrexate is usually given by a parenteral route, either subcutaneous or intramuscular, to patients with Crohn’s disease, but there is some evidence that the bioavailability of orally administered methotrexate may be only slightly less than parenteral and a small dose adjustment may enable the drug to be given orally with similar clinical efficacy.\textsuperscript{94} Methotrexate has been implicated in hypersensitivity pneumonitis (0.3%), nausea, and rash. The risk of hepatic fibrosis is thought to be low in patients with IBD treated with methotrexate.

The metabolism of thiopurines is moderately complex but of importance clinically. The therapeutically active metabolite is 6-thioguanine. A rare mutation resulting in impaired activity of the enzyme thiopurine methyl transferase (TPMT) may lead to raised 6-thioguanine levels with consequent toxicity, including myelosuppression. TPMT activity or the genotype should be measured before commencing full-dose therapy with azathioprine or 6-mercaptopurine.\textsuperscript{95} Thiopurines may still be used, but the dose should be reduced to 9%-28%. This cohort of patients often experiences clinical response despite the relatively lower doses of the drug.\textsuperscript{95} Variation in the metabolism of thiopurines separately also warrants measurements of metabolites, which can be used to optimize dosing.\textsuperscript{95} Under- and overdosing can be identified, as well as nonadherence and shunting, which may be amenable to manipulation by dose adjustment and coadministration of allopurinol.\textsuperscript{96}

**Biologics**

Although the primary cause of Crohn’s disease remains poorly understood, it is recognized to represent a process of unopposed inflammation in the gut. A number of endogenously produced biologically active molecules mediate this inflammation. Biologics represent a class of drugs which specifically target molecules and pathways central to the inflammatory process. Infliximab, the first of these to become available, is a monoclonal antibody directed against tumor necrosis factor-alpha (TNF-\(\alpha\)), a major proinflammatory cytokine in both Crohn’s disease and ulcerative colitis. TNF-\(\alpha\) is released from macrophages, monocytes, and T-cell lymphocytes (most likely CD4+ cells) in response to various stimuli, including bacterial endotoxins, viral antigens, and radiation. It is also believed to be pivotal in granuloma formation.\textsuperscript{97}

Infliximab has dramatically transformed the treatment paradigm in IBD.\textsuperscript{98} It has been used both to induce remission and as a maintenance agent. There is long-standing experience with it in both adults and children. Adalimumab and certolizumab are also monoclonal antibodies directed against TNF-\(\alpha\), but there is less experience with these agents in children and access to both varies from country to country. Other agents directed against a range of molecular targets are undergoing development and evaluation.

Trial data has established the efficacy of infliximab, adalimumab, and certolizumab in inducing response in adult patients with moderate to severe luminal disease.\textsuperscript{99,101} Similar or better results have been established for infliximab
and adalimumab in children.\textsuperscript{102,103} Short-term response rates vary from 50\%–80\%, with endoscopic healing in a substantial proportion. The ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) trial established that a single infusion of 5 mg/kg infliximab produced a clinical response in 58\% of adult patients with moderate to severe Crohn's disease.\textsuperscript{104} Infliximab is also effective in healing fistulizing disease, and for extraintestinal complications of Crohn's disease such as pyoderma gangrenosum.\textsuperscript{105}

The biologics are also effective maintenance agents. Regular scheduled treatments with either infliximab (every 8 weeks) or adalimumab (every 2 weeks) are effective in maintaining remission in both luminal Crohn's disease and fistulæ. The ACCENT trial in adults found that 42\% of adult patients receiving regular scheduled infliximab every 8 weeks were still in remission 7 months later.\textsuperscript{104} Experience with duration of efficacy in children has been better, with maintenance of remission varying from 56\%–93\% after 54 weeks.\textsuperscript{102,106} Long-term duration of response in children has been reported to vary from 67\%–72\% at 3 years.

Maintenance of clinical response with long-term biological therapy in children is accompanied by normal growth, progression through puberty, and optimized skeletal health, as well as the resolution of symptoms that can have a profound impact on quality of life and psychosexual well-being and development.\textsuperscript{107–110} Loss of response to the biological can represent a disaster for any patient, but particularly for a growing and maturing child or adolescent. It is believed that the most likely cause of secondary loss of response is the development of antibodies to the biologic agent. Concomitant therapy with an immunosuppressant appears likely to reduce the chances of antibody development.\textsuperscript{111–113} but this practice has been complicated by the recognition of the potential increased risk of development of malignancy, especially hepatosplenic T-cell lymphoma (HSTCL). HSTCL is a rare and usually fatal lymphoma reported in association with past use of thiopurines, either alone or in combination with infliximab or adalimumab.\textsuperscript{114–116} It has occurred primarily in young males. Explaining and balancing the relative risks of an extremely rare but fatal complication with that of a much more likely serious morbidity can be extremely challenging, and invariably management will be individualized depending on many factors.\textsuperscript{117,118}

Although biologics are generally well tolerated, they do have to be administered parenterally – in the case of infliximab, by infusions every 8 weeks, and for adalimumab, by subcutaneous injection every 2 weeks. Potential adverse effects usually relate to infusion reactions, opportunistic infections, dermatological conditions, or malignancy.\textsuperscript{98,116}

Immediate hypersensitivity reaction to infliximab infusion presenting as hypotension, headache, and pruritus has been reported in 15\% patients in various studies.\textsuperscript{119,120} Female gender and short duration of immunomodulator use have been reported to be risk factors for a reaction.\textsuperscript{116,121,122} However, desensitization by gradual incremental re-exposure to infliximab has been shown to be effective.\textsuperscript{116,122,123} Approximately 6\% of patients are reported to have delayed hypersensitivity reactions presenting as polyarthralgia or fever.\textsuperscript{124} Delayed hypersensitivity reactions are believed to be more common in adults with a significant interval between doses, but the same has not been reported in children.\textsuperscript{119,124}

Treatment with infliximab is often associated with an increase in titer of antinuclear antibodies but the development of antidualle-stranded DNA is uncommon.\textsuperscript{125} Lupus is a well-recognized, albeit rare, development, but it usually responds well to modification of biologic therapy.\textsuperscript{126} There have also been case reports of psoriasis induced by infliximab therapy, with up to 10\% of pediatric patients developing new-onset psoriasis.\textsuperscript{127} There is a suspected link between polymorphisms in the IL-23R gene and the development of psoriasis in this situation.\textsuperscript{127}

Severe infections are also known to occur more frequently in patients on anti-TNF-\(\alpha\) agents,\textsuperscript{128} but the risks contributed by concurrent presence of moderate to severe Crohn's disease, use of narcotic analgesics, and steroid therapy are proportionately greater. There is also no evidence from the Crohn's Therapy Resource, Evaluation and Assessment Tool registry of an increased risk of mortality with infliximab therapy.\textsuperscript{128} In the REACH (A Randomized, multicenter, open-label study to Evaluate the safety and efficacy of Anti-TNF-\(\alpha\) Chimeric monoclonal antibody in pediatric subjects with moderate to severe Crohn's disease) study, nearly 8\% of children developed a serious infection.\textsuperscript{102} The greatest risks are for opportunistic infections or reactivation of latent infections.\textsuperscript{116,129} It is extremely important to screen the patient for possible evidence of latent chronic infections such as tuberculosis and hepatitis B or C before embarking on anti-TNF-\(\alpha\) therapy, but even more important to appropriately manage any infections that develop in the immunosuppressed patient using established guidelines.\textsuperscript{130}

**Other therapeutic options**

Despite the advances in pharmacotherapy in the last few decades, no current drug is either ideal or curative. Other therapeutic options that have been pursued with variable success...
include antibiotics, probiotics, nutritional supplementation, drugs for symptomatic relief (such as antidiarrheals), and of course surgery. In the absence of success with mainstream medical approaches, many patients pursue alternative medical therapies.

**Emerging trends**

We have come a long way in our understanding of Crohn’s disease since it was first described in 1932. The last decade has been a period of rapid discoveries, especially in the field of metagenomics. It has been common knowledge that the human gut harbors a large number of commensal microorganisms. However, their role in causing or preventing illnesses has only been a matter of speculation until recently. There is now increasing evidence that imbalance in the gut microbiota, dysbiosis, could be implicated in the pathogenesis of Crohn’s disease. Further research is now targeted to try and find the exact mechanism of causation of Crohn’s disease. Recent research has also shown that bacteriophages may also be implicated in the pathogenesis of Crohn’s disease. Expanding our knowledge of the role of microbiota will allow better and more personalized management of Crohn’s disease.

Advances in microbiological and immunological analytical techniques have allowed us to target specific proteins at a molecular level. Drugs are being trialled that target specific inflammatory molecules. ABT 874 (J695), a human immunoglobulin (IgG1) monoclonal antibody to interleukin12/23, was found to induce clinical remission in patients with active Crohn’s disease.131 Since then, ustekinumab, another humanized monoclonal antibody against the p40 subunit of interleukins 12/23, has been found to have clinical efficacy in adults with active Crohn’s disease.132 There are no reports on its use in pediatric population. Similarly, CCX282-B (a chemokine receptor 9 antagonist), MLN 0002 (an anti-α4 β7 antibody), ruMab β-7 (an anti-β7 antibody), CP-690, 550 (an agonist to janus kinase 3), AIN476 (an anti-IL-7 antibody), and basiliximab (Simulect®, Novartis Pharmaceuticals, Basel, Basel-Stadt, Switzerland; an anti-IL-2 receptor [CD25]) antibody are all undergoing trials as potential therapies in Crohn’s disease.133 Further longitudinal studies are required to establish their safety over prolonged use. Further research is now directed towards finding more effective and safer modalities of treatment and possibly a cure.

Extracorporeal photopheresis (ECP) has been on the horizon for almost a decade and has been successfully used for treatment of various T-cell-mediated conditions, including advanced T-cell lymphoma, systemic sclerosis, graft-versus-host disease, and prevention and treatment of solid organ transplant rejection.134 It was first trialled in Crohn’s disease in 2001; recently, there has been a renewed interest in its use in steroid-dependent Crohn’s disease. It involves exposure of autologous peripheral blood mononuclear cells to 8-methoxypsoralen and long wavelength ultraviolet-A light followed by reinfusion into the patient. Animal studies suggest that the photopheresed cells induce an antigen-specific immune response directed to pathogenic T-cells while sparing general immunocompetence.134 ECP was shown to have a steroid-sparing effect in adults with steroid-dependent Crohn’s disease in a prospective, single-center study in 2001.135 A multicenter prospective trial has shown that ECP permitted discontinuation or reduction in steroid doses in steroid-dependent adult Crohn’s disease patients.134 There is limited pediatric data on the safety and efficacy of ECP. Recently, a case of a 12-year-old patient with severe, unremitting Crohn’s disease was reported who responded favorably to ECP.136 However, prospective long-term studies are needed in children to conclusively demonstrate its efficacy and safety.

**Growth and bone health**

Impaired growth is a major concern for families and children affected by Crohn’s disease. It has both physical and psychosocial implications. Children are not infrequently growth-impaired at diagnosis, but improvements in therapies have allowed a better long-term outcome, with most children going on to achieve an adult height within the normal range.137-139 About 20% of children will still fail to achieve normal growth expectations; late diagnosis and jejunal disease are predictive of long-term growth impairment.139

With optimization of growth in mind, there are three important aims to follow in management: 1) control disease activity, 2) optimize nutrition, and 3) minimize the use of corticosteroids (but not at the expense of poor disease control).137,140,141 Disease activity has the strongest influence on growth failure, with smaller nutritional and iatrogenic components.137 This inhibition appears to be mediated through inflammatory cytokines,142 with a knock-on impact on pubertal development. Several different growth impairment phenotypes have been identified, including growth hormone and insulin-like growth factor-1 (IGF1) deficiency states.143 Therapeutic targets can be difficult to identify. Interleukin-6 and TNF-α have been implicated in the suppression of the growth hormone axis by inhibiting hepatocyte IGF1 production.144,145 Interleukin-1 and TNF-α both inhibit activity at the growth plate in long bones in vitro.146

Given the importance of TNF-α in growth retardation, the specifically targeted action of anti-TNF-α agents may have...
a disproportionately beneficial impact on growth compared to standard therapies.\textsuperscript{116} The REACH study found a mean improvement in \textit{z}-score for height of 0.5 ($P<0.001$) after 54 week therapy with infliximab.\textsuperscript{102} The limitation of this finding was the failure to control for pubertal status.\textsuperscript{147} Subsequent studies have provided more compelling evidence of infliximab’s efficacy in growth. Walters et al\textsuperscript{148} established the importance of appropriately early timing of treatment; height and height velocities were most improved when (infliximab) therapy was initiated before or during early puberty (Tanner I–III). The heterogeneity of growth impairment was supported by a study of 28 children who were retrospectively assessed over an 18-month period, during which time all received induction therapy with infliximab, with some also receiving maintenance therapy.\textsuperscript{149} Patients who responded to infliximab (75%) had a mean improvement in height velocity of 4.4 cm/year compared to nonresponders whose height velocity remained static. Although many progressed into puberty during the study, children who remained prepubertal also had improvements in growth. The implication was that growth improved independent of any permissive effect infliximab had on pubertal progression. There is also evidence that increasing infliximab dosing frequency may further improve growth.\textsuperscript{150}

Skeletal health can also be impaired in Crohn’s disease.\textsuperscript{66} Treatment with infliximab can result in dramatic improvements in biomarkers of bone formation,\textsuperscript{151} as might be expected given the known inhibitory effects of TNF-α on osteoblast differentiation, osteoblast collagen secretion, and induction of osteoblast apoptosis.\textsuperscript{152,153} A similar beneficial effect on growth has also been established for adalimumab.\textsuperscript{109}

### Psychosocial implications

Crohn’s disease is a lifelong disease with no cure and a substantial psychosocial burden. Studies have reported a higher lifetime risk of depressive disorders in patients with IBD compared to cystic fibrosis patients.\textsuperscript{154,155} A few other studies have shown a higher incidence of depression and anxiety-related disorders in patients with IBD compared to healthy children but similar to children with other chronic illnesses.\textsuperscript{155–157} Studies of the effect of steroids on mood disorders have shown that patients on steroids had significantly more problems with verbal memory, working memory, and depression compared to patients not on steroids.\textsuperscript{155}

Crohn’s disease in particular also has a significant impact on social functioning in patients, especially those diagnosed in adolescence.\textsuperscript{155,158} Children with IBD have been shown to have fewer close friends and participate in fewer organized leisure activities as compared to healthy peers.\textsuperscript{155,159} Families of children with IBD also experience significant psychosocial problems. It has been shown that 51% of mothers of children with Crohn’s disease had a lifetime history of depression and 10% had a current diagnosis of depression.\textsuperscript{160} These rates have been shown to be similar to those in families of cystic fibrosis patients.\textsuperscript{155,160}

Studies have also shown that IBD adversely affects self-esteem. These patients also had poorer coping skills in stressful situations and were more likely to adopt avoidant coping styles.\textsuperscript{155,157,161}

### Conclusion

Crohn’s disease is at present a lifelong, incurable condition with a substantial and ongoing impact on health, normal development, and psychosocial functioning. Despite significant improvements in our understanding and management of Crohn’s disease, many unanswered questions remain. Most of these center around its pathogenesis, with tantalizing clues that may yet yield a cure. We are still unable to explain the increasing incidence and its spread to Asian and African nations. The relative importance and roles of environment, genetics, and dysbiosis are unknown. Can we prevent Crohn’s disease by modifying our lifestyle or dietary habits? This remains to be answered.

Therapeutic interventions are at present limited to medications that inhibit the persistent inflammation without a real understanding of the trigger. The nature of symptoms and the disease process has a profound impact on the growing child and adolescent, but in general, better therapeutic control of the disease provides a much better outcome than unfettered inflammation.

### Disclosure

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### References


