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Long-term outcomes of pediatric inflammatory bowel disease

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ABSTRACT

The incidence and prevalence of childhood-onset inflammatory bowel diseases (IBD), including subtypes Crohn's disease and ulcerative colitis, have risen dramatically in recent years, and have emerged globally as important pediatric chronic diseases. Therefore, health care providers are more frequently encountering very young children with IBD, a chronic and incurable condition requiring life-long therapy. These children are living long lives with IBD and therefore knowledge of long-term outcomes is increasingly important to better counsel families and determine the best course of treatment. This review summarizes the current knowledge and literature surrounding long-term outcomes of pediatric IBD, with emphasis on the following areas: need for surgery due to complicated disease behavior, risk of disease remission and recurrence, mental health and psychosocial well-being, educational outcomes, linear growth impairment, cancer risk, and mortality. In addition, we review recent research about predicting negative long-term outcomes in children with IBD.

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Introduction

While the incidence of inflammatory bowel disease (IBD) has stabilized in developed nations,[1] rates of Crohn's disease (CD) and ulcerative colitis (UC) continue to climb in children and adolescents.[2] This is particularly evident in children with very early onset (VEO) IBD,[3,4] defined as disease onset before the age of 10 years by the Paris Modification of the Montreal Classification.[5] The rising incidence in young children, combined with improved treatments and a lack of disease-attributable mortality, will result in a long life ahead for these children. Therefore, it has become more important to emphasize the long-term disease course, complication rates, treatment-associated risks and benefits, and quality of life in those diagnosed with IBD in childhood. Only with the knowledge of long-term outcomes of childhood-onset IBD can health care providers adequately counsel patients and their families on the future, thereby educating them on their chronic disease, guiding treatment decisions, and improving adherence to therapy. This article reviews the literature on long-term outcomes of childhood-onset IBD from the perspective of medical and surgical treatments, complications of the disease (including cancer and mortality), and psychosocial well-being.

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Complicated disease behavior and need for surgery

Complicated disease behavior and long-term risk of intestinal resection in Crohn's disease

Most children with CD present with an inflammatory (i.e., non-penetrating and non-stricturing) disease behavior.[6–8] However, progression to a stricturing and/or fistulizing behavior is common. Between 24% and 43% of children progress to a stricturing phenotype and 14–44% develop fistulae or abscesses (i.e., penetrating disease complications).[6–9] Children with medically refractory or complicated CD require surgery. Children may also require surgery for the treatment of perianal fistulae or abscesses. A systematic review and meta-analysis of population-based studies indicated that the 1-, 5-, and 10-year risk of intestinal resection in pediatric-onset CD is 7.9%, 25.5%, and 35.6%, respectively.[10] In all, 11% of hospital admissions for pediatric CD result in intestinal resection.[11]

The rates of intestinal resection in patients with CD, diagnosed at any age, has decreased since the 1960s.[10] However, trends in surgery in pediatric CD patients are less clear. A population-based study of temporal trends conducted in Ontario, Canada found that rates of surgery had decreased over time among children diagnosed with CD after 10 years of age, but not among children diagnosed at a younger age.[12] However, children diagnosed before

10 years of age were less likely to undergo surgical resection compared to those with diagnosis above the age of 10.[4] Similarly, in the United States, the rate of intestinal resection among children hospitalized for CD had declined between 1997 and 2009, whereas the overall incidence of admission for CD-related intestinal resection increased by 2% per year,[11] likely due to the increasing incidence and prevalence of CD in children.

Estimates of perianal disease in pediatric patients with CD are highly variable. Some studies suggest between 20% and 30% of patients will develop perianal disease[8,9,13] while others estimate the rate of perianal disease to be almost 60% within 10 years of diagnosis.[7,14] Comparison of rates across studies is challenging due to differences in how perianal disease is defined. For example, some studies limit their description of perianal disease to complex perianal disease (i.e., multiple perianal fistulae or abscesses), while others include mild perianal disease (i.e., skin tags and fissures).

Nearly three-quarters of children with perianal CD will require drainage of a perianal abscess; 12% will require fistulotomy and 32% will require seton placement.[15] In cases of refractory perianal disease, patients may require defunctioning ileostomy or proctocolectomy when ileostomy provides inadequate control of perianal disease. This was reportedly performed in 23% of children with perianal disease at one pediatric tertiary-care center.[15]

Long-term risk of colectomy in UC

The risk of colectomy in children diagnosed with UC after 1, 5, and 10 years are 6.7%, 17.4%, and 21.6%, respectively.[10] Approximately 13% of hospitalizations for children with UC result in colectomy.[11] The need for colectomy has decreased over the past half-century.[10] However, the need for colectomy in pediatric patients with UC has remained stable since the mid-1990s.[11,12]

Remission and recurrence

Discussion on remission and recurrence rates of pediatric IBD is difficult, in part due to a lack of long-term studies, as well as differing definitions of disease recurrence in the literature. Recurrence can be defined as onset of symptoms, elevation of disease activity indices, elevated inflammatory markers, abnormal radiological studies, and/or macroscopic or microscopic inflammation detected by colonoscopy. In addition, older reports of recurrence rates may not apply to patients treated in the biological era.

Nevertheless, some research exists on the natural history of pediatric IBD—that is, risk of remission and recurrence in the absence of modern therapies. Population-based studies from the latter half of the 20th century reported high rates of corticosteroid utilization and refractoriness to medical therapy requiring surgery in children with CD.[16] In a group of 62 British children with UC followed from diagnosis in the 1950s, twelve (20%) required surgery in the years following diagnosis, five (8%) died, six (10%) were steroid-dependent, and twenty (32%) had symptoms despite steroids.[17] These findings compared favorably to a Swedish cohort from 1955 which reported 13.8% mortality, 32.2% remission rate (no symptoms), and 54% rate of ongoing symptoms.[18]

More recent research demonstrated similar rates of steroid-dependence in CD (12.3–36.8%)[16] and UC (10–50%).[19] However, the introduction of biologic therapies has allowed for options to maintain remission in these difficult patients. In clinical trials, 88% and 58.9% of children responded to infliximab and were in remission, respectively, by week 10 of therapy; after one year, 55.8% were in remisison.[20] In a real-world cohort study from Scotland, 88% of children had responded and 47% were in remission by week 10, and 40% were in remission after 1 year of therapy.[21] Similarly, in a clinical trial of children receiving adalimumab, 45% were in remission after 1 year of therapy.[22] These studies defined remission and response based on disease activity indices, without endoscopic confirmation. However, these results indicate the rapidly changing prognosis of pediatric IBD in the 21st century.

Hansen et al.[23] reported a high risk of clinical recurrence in pediatric patients with CD following intestinal resection (50%, 73%, and 77% clinical relapse rate at 1, 5, and 10 years, respectively). Half of all patients relapsed within 121 months of surgery, and the risk of disease recurrence was similar regardless of the type of surgery. Prophylactic azathioprine did not impact the time to recurrence.[23] While adult studies have demonstrated reduced rates of post-operative recurrence with the use of prophylactic anti-TNF biologic therapy,[24] data are still lacking on this strategy in children following surgery.

Mental health and psychosocial well-being

Our understanding of the long-term impact of pediatric-onset IBD on mental health and psychosocial well-being is limited by the quality of studies published in this area. The vast majority of studies evaluating the mental health of these children and adolescents are (1) cross-sectional, (2) conducted in small numbers of patients recruited from tertiary-care centers, (3) lack a control group, (4) have a limited duration of follow-up, and (5) the directionality of the association may be unclear.[25] Further, there is a high degree of heterogeneity across studies both in terms of the rates of depression and/or anxiety, as well as the relative frequency of these disorders compared to non-IBD controls.

Teenagers with IBD reported anxiety to be related to (1) side effects of IBD therapies, (2) altered body image, and (3) a feeling of a lack of control of their lives.[26] More severe or active disease, elevated inflammatory markers, current steroid use, and the need for an ostomy are associated with increased risk of clinically significant depressive symptoms, while use of anti-TNF therapies protect against the presence of these symptoms.[27,28] In light of these findings, a study comparing the risk of depression and anxiety following the diagnosis of pediatric IBD observed a higher incidence of both depression [incidence rate ratio (IRR) = 2.21, 95% confidence interval (CI): 1.78–2.73] and anxiety (IRR = 3.16, 95% CI: 2.40–4.16).[29] Within 5 years of IBD diagnosis, 2.83% of CD patients were being persistently treated for depression and 2.71% received persistent treatment for anxiety. This compares to 1.05% and 0.36% of controls without CD being persistently treated for depression and anxiety, respectively. The number of children and adolescents with anxiety or depression were much lower in this study than estimates reported a prior systematic review reporting that rates of clinically significant symptoms of depression and anxiety range from 25% to 73% in children and adolescents with IBD,[25] perhaps owing to different definitions of these conditions.

Depression is associated with perceived abdominal pain in patients with CD and UC.[30] Although perceived stress is associated with symptoms in patients with IBD, there is no association between perceived stress and intestinal inflammation (as measured by fecal calprotectin).[31]

Furthering our understanding of the psychosocial sequalae of pediatric-onset IBD is particularly important in light of evidence suggesting that symptoms of anxiety and depression may decrease adherence to treatment.[32,33] Non-adherence may, in turn, result in a worse disease course.

Educational outcomes

Diagnosis with a chronic illness during childhood or adolescence can have significant implications on the educational

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