Review Article

Promoting early testing and appropriate referral to reduce diagnostic delay for children with suspected inflammatory bowel disease, a narrative review

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Background and Objective: When a child with chronic gastrointestinal (GI) symptoms presents to a primary care physician or general paediatrician, the clinician is challenged with differentiating between functional or organic disease. When there is a high suspicion of inflammatory bowel disease (IBD), rapid referral to a paediatric gastroenterologist for assessment and treatment will help protect against the sequelae of a delayed diagnosis for a child. However, this must be balanced against the need for ensuring appropriate referrals and avoiding invasive diagnostic testing for those with non-organic aetiology. The objective of this narrative review was to present evidence on specific presenting symptoms, testing, and risk factors of paediatric IBD that may aid the identification of children requiring timely referral for specialist care, thereby reducing the chance of a delayed diagnosis.

Methods: Literature databases (Medline, Embase) were searched using terms specific to the population studied, and topic specific terms relating to each section of the review. Year limits were set for 2010–2022. Included papers were limited to original research, with meta-analyses considered where of benefit.

Key Content and Findings: Children often present with non-specific GI symptoms that may be associated with a delayed diagnosis for those with subsequent IBD. Symptoms such as rectal bleeding or weight loss may indicate the need for rapid referral. However, non-specific symptoms necessitate testing strategies to differentiate between those with possible IBD and non-organic conditions. Definitive laboratory testing for IBD is not yet available. This review outlines those metrics that should be considered and monitored, then utilised to make a comprehensive referral to tertiary care for specialist paediatric gastroenterology review. Summaries are provided relating to presenting symptoms, extra-intestinal manifestations (EIMs), and alarm symptoms in order to highlight those reported most frequently. The diagnostic accuracy and importance of interpreting faecal calprotectin (FC) levels, in conjunction with additional measures, are also outlined.

Conclusions: Diagnostic testing to effectively identify children with IBD without the need for endoscopy is not yet available. Primary care physicians and general paediatricians must, therefore, rely on interpreting a combination of symptoms, laboratory parameters, and risk factors to assess the need for specialist referral and diagnosis.

Keywords: Inflammatory bowel disease (IBD); diagnostic; referral; laboratory parameters; risk factors

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Introduction

Chronic gastrointestinal (GI) symptoms among children are a frequent cause of presentation to primary care, and for subsequent referral for tertiary assessment (1). Chronic GI symptoms are characterised as developing over time, as opposed to rapid onset, and lasting more than four consecutive weeks. Chronic GI symptoms in children may be due to organic disease, specific bacterial infection, or functional GI disorders (FGID). There is a high degree of cross-over symptoms between them, such as the triad of abdominal pain, diarrhoea, and weight loss.

The challenge facing primary care physicians and general paediatricians is to differentiate between FGID and organic disease while avoiding invasive diagnostic testing, and ensuring appropriate referral for specialist paediatric gastroenterology review (2). It is often relatively simple to exclude specific conditions that frequently present with common GI symptoms using minimal testing, such as coeliac disease (3), *Helicobacter pylori* infection (4), and infectious diarrhoea (5). However, no one specific test is available for FGIDs such as irritable bowel syndrome (IBS), and functional abdominal pain (FAP), nor yet for the immune-mediated condition inflammatory bowel disease (IBD). The clinical presentation of these specific FGID's and IBD can be remarkably similar, although it is estimated that while FAP and diarrhoea accounts for up to 5% of all paediatric primary care visits, 90% will not have an organic cause for their symptoms (2,6-9). The global prevalence of FGID and IBD in the paediatric population are reported in difference ways so are not directly comparable. For children up to the age of four years aggregated data show that approximately 22% of children will experience at least one FGID (10), and 21.8–23% of those aged four to eighteen years (10,11). The worldwide prevalence of IBD varies by region and clinical sub-type, but for IBD overall has been reported to range from 21.7 to 75 per 100,000 person years (12,13). The annual global incidence of IBD, representing new diagnoses, has been reported at approximately 23 per 100,000 per year (13,14). The incidence and prevalence of paediatric IBD is increasing across all global regions (12-14).

In primary care, or general paediatric secondary care, the incidence of IBD is low so the likelihood of missing a child with IBD will be smaller than the likelihood of referring a child with FGID for unnecessary specialist assessments (15). For those children who may have IBD, prompt testing, referral, and diagnosis will avoid the sequelae of delayed diagnosis and maximise the benefit to their longitudinal disease outcomes. With the incidence and prevalence of paediatric IBD rising worldwide, the burden of the disease to individuals, as well as health-care systems, is of great significance and finding ways to improve early diagnosis and treatment is of paramount importance.

This review aims to highlight how symptoms of paediatric IBD may differentiate from FGIDs, and what is known of the prodromal IBD period and the implications of delayed diagnosis. The research questions addressed include: what clinical testing strategies may be utilised to refine clinical suspicion of IBD and facilitate prompt referral to specialist care for diagnostic testing; which risk factors are known to be associated with paediatric IBD and delayed diagnosis; which clinical information should be included in a referral to a paediatric gastroenterologist that will enable a timely assessment and diagnosis. This review will highlight the importance of identifying, and providing detailed referral information, to reduce delays to an IBD diagnosis. We present this article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-35/rc).

Methods

Literature databases (Medline, Embase) were searched between 1st November 2022 and 31st December 2022. The search terms used consistently included the population studied, with topic specific additional terms added for each section (*Table 1*). Searches were limited to between 2010 and 2022, unless additional data were required for the review that were not considered time sensitive in which case the search was expanded to the years 2000 to 2022. The year parameters were implemented in order to retrieve the most up-to-date data and practices available as the diagnosis and management of chronic conditions can be dynamic and information becomes less relevant over time. Both authors (Vernon-Roberts and Day) reviewed the included literature. Of the citations included in the review 99/111 (89%) were

Table 1 Search strategy summary for narrative review

Items	Specification
Date of search	1st November 2022 to 31st December 2022
Databases and other sources searched	Medline, Embase
Search terms used consistently	P*ediatric*.tw, Pediatric/, Inflammatory bowel disease/, Inflammatory bowel.tw, Crohn*.tw, Ulcerative colitis.tw
Timeframe	2010 to 2022, expanded to 2000 onwards if additional data sought
Inclusion and exclusion criteria	Original studies were included, with select meta-analyses where beneficial. Non-English language papers included if a translation available
Selection process	Both authors (AVR and ASD) reviewed papers for inclusion, with a consensus reached via discussion for any disputed items

tw, textword.

published between the years 2010 and 2022, and 53 (48%) in the most recent 5 years [2018–2022].

Diagnostic delay in paediatric IBD

The time period prior to getting a confirmed diagnosis of IBD in children is associated with a phased longitudinal progression relating to the time between first IBD symptoms and presenting to a primary care physician, the primary care physician making a referral to a tertiary care centre, and a tertiary care specialist obtaining a definitive diagnosis via endoscopy with histology (16). Variation between these periods is considerable and determined by the individual, age group, disease course, IBD clinical sub-type, and country of residence. When these periods are prolonged, it is termed 'Diagnostic delay' (DD). DD has been reported to average four and a half months for IBD overall, with a median of five months for children with Crohn's disease (CD), and three months for children with ulcerative colitis (UC) (16). DD for children with IBD has been associated with an increased likelihood of complications and comorbidities (17), disease extension for those with UC (18), and a higher rate of strictures or internal fistulae, and linear growth delay for children with CD (19-21). A few studies show that there is no increased risk of surgery for those with prolonged DD, as related to colectomy risk for children with UC (22,23), nor surgical resection or internal/perianal fistula surgery for children with CD (20). There is a considerable prodromal period for many children with IBD. Symptoms may be mild and heterogenous, and many may hide their symptoms due to anxiety or embarrassment, thus prolonging presentation to their primary care clinician or general paediatrician (24). When heterogeneous clinical characteristics are accompanied by normal laboratory parameters a differential diagnosis of FGID may be made before more overt symptoms appear, thereby prolonging the time to diagnosis. Such findings emphasize the importance of identifying factors that may increase a child's risk of a prolonged DD period and highlighting effective testing strategies that may be implemented.

Association between presenting symptoms and DD

Symptoms

The most common symptoms across all clinical sub-types of IBD are considered to be the triad of diarrhoea, abdominal pain, and weight loss (25,26), also a common finding among children with FGID. However, studies have shown that only 25–64% of children with CD may present with this specific combination (25,27,28) and other symptoms play an important role in diagnosis (*Table 2*). Rectal bleeding is more common than diarrhoea among children with UC (17,21,25,26,30), and fatigue a more frequent finding then rectal bleeding among children with CD (25,26,29,30). In addition to this inconsistency of dominant symptoms, many children may have ambiguous presentations involving symptoms external to the GI tract, known as extra-intestinal manifestations (EIMs). EIM may dominate the clinical presentation initially, further contributing to DD (33). The relevance of these symptom classifications has been explored in their relation to DD.

Table 2 Presenting symptoms of children diagnosed with inflammatory bowel disease

Paper	Abdominal pain		Weight loss		Diarrhoea		Rectal bleeding		Fatigue	
	CD	UC	CD	UC	CD	UC	CD	UC	CD	UC
Timmer (26)	74	67	61	39	73	86	36	89	41	27
Sawczenko (25)	72	62	58	31	56	74	22	84	27	12
Ricciuto (21)	87	82	73	64	30	5	40	86	–	–
Arcos-Machancoses (29)	97	84	61	53	65	95	45	90	71	68
Ashton (27)	86	88	56	36	79	92	44	92	–	36
Sulkanen (17)	71	62	48	29	44	60	38	77	–	–
Castro (30)	67	50	50	21	36	16	27	60	18	6
Spray (28)	83	63	88	56	41	15	22	75	–	–
Saadah (31,32)	84	93	75	19	72	86	32	93	–	–
Median	83	67	61	36	56	74	36	86	34	27
Range	67–97	50–93	48–88	19–64	30–79	5–95	22–45	60–93	18–71	6–68

Data presented as percentages of each study population experiencing each symptom. CD, Crohn's disease; UC, ulcerative colitis; –, not reported.

Abdominal pain

Abdominal pain as an isolated symptom is an infrequent finding among children prior to diagnosis of IBD (26). Pain may predict a prolonged DD when in isolation from other GI findings (21) as well as when presenting among other symptoms (17). It could be postulated that abdominal pain, unless severe, may be considered a vague, subjective symptom that can be difficult for parents and physicians to recognize as associated with organic disease and more easily assigned to FGID. The prevalence of functional abdominal pain disorders (FAPDs) specifically is high, with pooled estimates showing approximately 13.5% of children experience FAPD (34). While there are varying estimates for the prevalence of the four FAPD sub-categories of functional dyspepsia, IBS, abdominal migraine, and FAP, IBS is generally experienced most frequently and by up to 8.8% of children (10,34,35).

Bloody diarrhoea

Having a child present with rectal bleeding (also termed bloody diarrhoea) is generally shown to be protective against DD (17,19,25,28). This may be the reason that children diagnosed with UC typically have a shorter DD period than children with CD. While the terms rectal bleeding and bloody diarrhoea are used interchangeably there may be distinct differences depending on the origin of the bleed, with melaena (black tarry stools) indicating blood loss proximal to the ileocecal valve, and haematochezia (bright red blood per rectum) indicative of a colonic bleed (36,37). Both melaena and haematochezia may be present in a diagnosis of IBD as well as a number of other organic and benign disorders (36,37). However, fresh blood is an alarming symptom and may prompt more rapid investigation and a subsequent reduced DD, with rectal bleeding being the main presenting symptom for children with UC (38).

Perianal symptoms

While perianal symptoms, such as abscesses, fistula, or fissures, may be a presenting symptom in 8–45% of children who go on to develop CD, and 1% of those with UC (26,28,31,39), causes may also be benign (40). Approximately 3% of children presenting with perianal symptoms may go on to develop CD specifically, but over 40% may not experience accompanying classic CD symptoms (40). Perianal disease as the sole presenting symptom for children with CD has been shown to be associated with DD (40), as has perianal involvement among other symptoms (25). However, this finding is not universal (19-21,29).

Growth

It is generally considered that a history of weight loss (or slow weight gain), as well as poor linear growth, is a frequent finding among children and adolescents prior to diagnosis with IBD (41). However, studies have shown

Table 3 Presence of EIM at diagnosis observed in nine cohorts of children diagnosed with inflammatory bowel disease (overall participants: 9,656 CD, 1,864 UC)

Paper	Joints		Oral		Skin		Eyes	
	CD	UC	CD	UC	CD	UC	CD	UC
Jang (58)	29	63	29	–	15	3	–	13
Duricova (59)	11	–	5	–	16	–	0	–
Jose (60)	26	–	21	–	–	–	–	–
Timmer (26)	7	13	–	–	2	6	1	1
Spray (28)	13	2	–	–	5	–	2	–
Greuter (61)	49	50	46	42	13	16	13	0
Ricciuto (21)	8	–	27	–	4	–	–	–
Castro (30)	23	7	–	–	–	–	2	1
Rahmani (62)	21	13	15	0	6	0	3	0
Median	21	13	24	21	6	5	2	1
Range	7–49	2–63	5–46	0–42	2–16	0–16	0–13	0–13

Joints: arthritis, arthralgia; oral: stomatitis, ulcers; skin: erythema nodosum, pyoderma gangrenosum; eyes: uveitis. Data presented as percentages of study cohorts presenting with each EIM. EIM, extra-intestinal manifestation; CD, Crohn's disease; UC, ulcerative colitis; –, not reported.

that being underweight at diagnosis is significantly more common for children with CD (20–39%) than UC (6–25%) (42-45). In addition, children with IBD may present as being overweight or obese at diagnosis, with this finding being more likely in those with UC (5–30%) than children with CD (0–10%) (42,44-46). The reported risk of overweight/obesity is 3.5 times higher for UC than CD (46).

Linear growth failure is more frequent among those with CD (16%) than UC (5%) (26). These findings highlight that children with IBD may align with population trends towards being overweight or obese at the time of diagnosis, or present with a normalising body mass index (BMI) due to ongoing weight loss from previously being overweight (42,45,46). Children presenting with high BMI should not be overlooked for their risk of IBD due to this factor.

Poor weight gain or linear growth failure have been reported as protective against DD for children with CD and UC (19,21,24,26,47). However, this finding is not universal with studies also reporting no association between weight loss or growth failure for those with CD or UC (25,26,29,48,49).

EIMs at diagnosis

The presence of EIM in children at the time of IBD diagnosis is a common finding and may be the only clinical presentation of IBD and in fact precede GI symptoms in up to 18% of cases (50-52). The spectrum of what may be considered an EIM is broad. Further, there is overlap between what are considered EIM and those considered as comorbidities of IBD.

Much is published on EIM in paediatric IBD as related to the following systems: musculoskeletal, dermatological, respiratory, hepatobiliary, haematological, cardiovascular, ocular, oral GI, and pulmonary (53-57). The most frequently experienced EIM correspond to musculoskeletal, oral, skin, and eye manifestations, and no distinct presenting patterns seen for each clinical sub-type (*Table 3*). Evidence as to whether the presence of EIM at diagnosis significantly affects DD, either to shorten or prolong it, is mixed. A number of studies have shown that the presence of EIM has no association with the time taken to obtain a diagnosis (19,21,29). Other work has published evidence that EIM at presentation causes significantly shorter DD (26,49). EIM at diagnosis have been shown to be associated with an increased risk for corticosteroids and immunosuppressive therapy in children (59), possibly indicating a more severe underlying disease. Nonetheless, improving awareness of the frequency of EIM may expedite diagnosis and treatment (51).

Testing

A definitive diagnosis of IBD can currently only be obtained once children are under specialist GI care as diagnosis requires an endoscopic assessment along with microscopic analysis of mucosal biopsies. However, serum and stool tests may be utilised to differentiate between organic disease and non-organic conditions such as FGID and increase suspicion of underlying IBD. No one individual serum or stool test has been shown to be sufficiently predictive of IBD in terms of accuracy at identifying either true positive or true negative cases. However, patterns of abnormal test results may assist in making rapid and appropriate referrals for specialist assessment and thus reduce DD.

Serum biomarkers

While single blood tests are of limited utility in the diagnostic work-up of IBD (63), specific tests are sensitive markers of inflammation and likely disease activity (50). When compared with control subjects, children with IBD (UC and CD) were shown to have significantly lower levels of: haemoglobin, haematocrit, mean corpuscular volume, iron, albumin, and zinc, and higher erythrocyte sedimentation rate (ESR) and platelets (63-66). While all of these tests are linked to systemic inflammation or anaemia, children may also present with normal blood tests, with this more commonly seen in children with UC than CD (63,64). Children with IBD presenting with specific laboratory abnormalities, in particular: albumin, C-reactive protein (CRP), ESR, and ferritin, have been shown to have lower DD (19,21,49). It should be noted that up to 9% of children diagnosed with IBD present with normal serum markers (63). Up to 22% may have normal CRP and ESR specifically, and children with UC are more likely to have normal test results than those with CD (63), a finding also seen in adults diagnosed with IBD (67).

Normal inflammatory markers were more common in UC compared with CD (UC, 34%; CD, 15.8%; P=0.0035). UC (14.4% normal) presented with all normal results more frequently than CD (CD, 5.3%; P=0.02). CRP, ESR, and platelets were significantly higher in CD compared with UC. Albumin and hemoglobin were significantly lower.

Faecal calprotectin (FC)

A marker of inflammation frequently measured in those presenting with GI symptoms is FC, a calcium- and zinc-binding protein derived from neutrophilic granulocytes (68). Elevated FC levels are associated with gut inflammation, indicating that neutrophils have migrated to the affected area. While FC levels have been shown to also be abnormal (high) in children with infectious diarrhoea and necrotising enterocolitis (NEC) (69), additional stool tests can be used to exclude infectious diarrhoea (5), and NEC is generally seen in early infancy so unlikely to be a differential diagnosis to IBD. Importantly, FC levels are usually normal for children with FGID (70).

The level of FC considered to be 'abnormal' in the situation of possible IBD is much debated, and the age of the child must also be taken into consideration (24,71-73). For children over the age of four years a level greater than 50 µg/g is the laboratory defined 'abnormal' but using this cut-off in suspected IBD may not be sufficiently accurate to eliminate individuals with other diagnoses and may lead to unnecessary invasive diagnostic procedures (66,74-77). Accuracy may be determined using the metrics of 'sensitivity and specificity' referring to the percentage of true positives and true negatives, respectively, with values closer to 100% being most accurate.

A number of studies have assessed the diagnostic accuracy of FC at different levels but with great variation in their findings (*Table 4*). One meta-analysis provides more specific guidance in reporting that the optimal cut-off value is 212 mg/g, providing a sensitivity of 90% and specificity of 85% (73).While the effect of FC level on DD is infrequently studied, at levels greater than 500 µg/g DD has been shown to be reduced (49), and at levels greater than 100 µg/g were more likely to be referred to GI services, although there was no reduction in DD at this level (66). It has been suggested that the utility of FC testing within the primary care setting may be more for the negative predictive value of excluding IBD at normal levels, as opposed to the positive predictive value of indicating a likely diagnosis of IBD (2).

Alarm symptoms

Specific symptoms have been identified as 'red flag' or 'alarm symptoms' to indicate an increased likelihood of IBD when children first present to primary or secondary care. Given the diversity of symptoms at presentation, and the number of differential diagnoses, these have been suggested as a way to discriminate between children with and without an underlying organic condition such as IBD (9). The use of alarm symptoms may improve risk stratification for those

Table 4 Cut-off values of FC, with associated sensitivity and specificity values, across 17 studies that incorporated 1,718 children being assessed for possible inflammatory bowel disease

Paper	FC level (μg/g)	Sensitivity (% true positives)	Specificity (% true negatives)
Van de Vijver (75)	>50	100	73
Henderson (78)	>50	98	44
Orfei (72)	>50	100	94
Holtman (8)	>50	99	84
Güven (79)	>50	94	33
Heida (80)	>50	99	71
Soubieres (81)	>50	77	72
Walker (66)	>100	100	91
Henderson (78)	>100	97	59
Holtman (8)	>100	87	93
Güven (79)	>150	71	73
Henderson (78)	>200	93	74
Orfei (72)	>250	94	39
Holtman (8)	>250	81	98
Henderson (78)	>300	89	83
Orfei (72)	>600	92	22
Henderson (78)	>800	73	95

FC, faecal calprotectin.

with IBD, with the potential to reduce DD, and prevent unnecessary referrals for those with FGID that may delay implementation of appropriate interventions and decrease well-being (8,82).

Recommended alarm symptom criteria vary greatly across the literature (*Table 5*), although the most common metrics include rectal bleeding, weight loss, family history of IBD, and peri-anal disease. Two papers include a raised FC above 50 μg/g, although the diagnostic utility at this level is debated, as above. When FC testing is added to an alarm symptom algorithm it has been shown to increase the diagnostic accuracy of IBD, whereas inclusion of raised CRP does not (82). The association between the presence of defined alarm symptoms and DD has not been studied, although a recent systematic review (16) reported that there was no difference in DD for those presenting with EIM, but was reduced in a number of papers reporting on children presenting with rectal bleeding (19,25,28), linear growth failure (19,21,26), and family history of IBD (26).

Benefit of combining test results

While serum markers, alarm symptoms, and FC are useful indicators of illness when they are studied individually, in combination their efficacy at identifying children at high or low risk of a diagnosis of IBD improves. While this factor has not been tested for association with DD, it is logical that obtaining a combination of results that indicate a higher suspicion of IBD may enable a more rapid and appropriate referral and diagnosis. Previous work has shown that the combination of raised FC and albumin levels improves identification of true positive and true negative IBD cases (78). The combination of FC, alarm symptoms, and raised ESR also improved this identification, as well as enabling effective classification of groups at low and high risk of IBD (82). When primary care physicians and paediatricians are able to utilise ultrasound imaging the combination of raised FC and serum inflammatory markers alongside sonographic evidence of bowel wall thickening also had very high

Table 5 Alarm symptoms that may be indicative of an inflammatory bowel disease diagnosis, as reported in individual literature

Paper	Diarrhoea	Rectal blood	Family history	Abdominal pain	Weight loss	Growth failure	EIM	Perianal	FC (μg/g)	Lab values[†]
Holtman (8,82)		Y	Y		Y; >1 kg	Y; −1 SD	Eyes, skin, ulcers, clubbing, joints	Y	>50	Hb, CRP, ESR, Plt
Ashton (24)	Y; >14 d	Y	Y	Y; >14 d	CD		Eyes, skin, ulcers, joints	Y		Stool MC+S, Hb, Alb, LFT's, CRP, ESR, Plt
Ansems (2)		Y	Y		Y	Y	Eyes, skin, ulcers, joints	Y		
Güven (79)		Y	Y		Y			Y	>50	CRP, ESR, Alb, Hb
Van de Vijver (75)	Y; >4 w	Y		Y	Y	Y	Skin, joints, eyes	Y		ESR, CRP, Hb
Walker (66)		Y	Y		Y					

[†], reference ranges not presented due to variability in papers. EIM, extra-intestinal manifestations; FC, faecal calprotectin; Y, yes; kg, kilogram; SD, standard deviation; Hb, haemoglobin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Plt, platelets; d, days; CD, Crohn's disease; MC+S, microscopy, culture and sensitivity; Alb, albumin; LFT's, liver function tests; w, weeks.

predictability of true positives and negatives (1).

Risk factors for IBD and prolonged DD

A number of risk factors have been identified that increases a person's likelihood of being diagnosed with IBD (83). While some relate specifically to adults, some are more relevant to the paediatric population. The following risk factors may be considered for a child presenting with suspected IBD and are relevant information to include in referral letters for specialist gastroenterology review.

Family history

Having a family history of IBD (generally as a first degree relative) is consistently shown to be a risk factor for developing IBD (83), as well as sub-types of CD (83-86) and UC (83-85). The number of children diagnosed with IBD who report a family history range from 8.5% to 23.5% (19,49,87), although this may be dependent on how the term is defined between studies. However, an association between family history of IBD and a shortened DD period is rarely reported (19,21,25,29,49,87-89), except in one large cohort study (26).

Demographic factors

While the majority of children are diagnosed with IBD during the ages of eleven and sixteen years, more children are being diagnosed below the age of ten years (90,91). Generally those diagnosed earlier experience a more aggressive disease course (92). Younger children have been reported to be at greater risk of DD (25,26,29,87), although this is not a universal finding (19,88,93). Few studies report gender as being associated with longer DD (93), with most research reporting no association (19,25,26,49,87,88).

Environment

Additional, specific risk factors relating to the environment and a child's early years are associated with developing IBD during childhood. While these have not been shown to increase the DD period, their relevance should be considered at the time of presentation of a child to their primary care or general paediatric clinician and this information included in subsequent specialist gastroenterology referrals.

Diet

The diet a child consumes may increase their risk of developing IBD. Consumption of fewer weekly portions of fruits and vegetables have been shown to have a significant association for developing IBD (94), or UC (83). Additionally, for children with CD, white bread consumption, and high weekly intake of sugary drinks have also been identified (83).

Breast feeding

The effect of breastfeeding is generally associated with a

decreased risk of IBD and UC if for more than three to six months (83,95). Ever being breastfed was protective against IBD, CD and UC with longer exposures decreasing risk further (96). However, some studies show an increased risk for IBD and CD (84,85), or no association (86).

Gastroenteritis and antibiotic exposure

Childhood GI infections are consistently shown to be associated with an increased risk of IBD, CD and UC (83,95). The use of antibiotics during early childhood years is also associated with IBD, UC and CD (95,97-99). Both factors contribute to intestinal dysbiosis, and there is a clear consensus on the involvement of the gut microbiome in the development of IBD (100).

Referrals

Primary care physicians and secondary care paediatricians must balance the need for ensuring appropriate referrals are made to specialist paediatric gastroenterologists, with the need to protect against DD for those children with a high suspicion of IBD requiring rapid assessment, diagnosis, and treatment. Identification of the IBD phenotype, and achieving mucosal healing, are the critical first stages of IBD treatment (101). There is also considered to be a window of opportunity for those with IBD during which early treatment in the time following first symptoms, using drugs such as anti-tumor necrosis factor α agents, increases treatment efficacy and alters disease progression (102). However, until effective early identification and testing strategies for IBD are developed to enable early intervention, this approach is not feasible and would lead to unnecessary and inappropriate treatment for many children.

Some reports show that children referred for suspected IBD by paediatricians had shorter DD than those referred by primary care physicians (15,29,49). Children referred by paediatricians are more likely to have unambiguous symptoms such as weight loss, growth failure, rectal bleeding and extra-intestinal symptoms, as well as higher calculated disease activity, leading to earlier diagnosis of IBD (15,29,49).

For primary care physicians and paediatricians who may see children with non-specific symptoms, such as linear growth delay, a pragmatic approach to monitoring may be implemented. This should involve a combination of detailed symptom recording, laboratory testing (serum inflammatory markers, FC), and physical examination (including perianal region) when first presenting with symptoms (103-105). Regarding FC levels, for example, those with levels between 50 and 250 µg/g may benefit from having assessment of additional parameters tested (e.g., CRP, albumin) with repeat measurement in 2–3 months, along with clinical reassessment, as has been suggested for adults in primary care with IBS (8). Close monitoring and re-testing may identify worsening of relevant parameters, especially in combination, that may then be utilised to enable a detailed referral with a higher suspicion of IBD. For those children with worsening parameters and symptoms, as well as those presenting with alarm symptoms, in order to enable a rapid assessment, the clinician must provide all the necessary information in their referral.

In order to facilitate prioritization of a child with a high suspicion of IBD, thereby enabling a rapid assessment and eligibility for timely endoscopic assessment, it is imperative that the primary care physician or paediatrician provide a thorough referral to paediatric gastroenterologists containing all necessary clinical information (74). This should include test results utilised to exclude other conditions (coeliac disease or infectious diarrhoea). It should also include longitudinal symptom and growth records with documented changes in parameters such as pain, stool metrics, and weight loss. Laboratory testing results and changes of monitored variables such as inflammatory markers, iron levels, and FC should be included. In addition, the results of physical examination, and the presence of known risk factors such as family history should be shared in a referral for assessment by a paediatric gastroenterologist (74). Providing comprehensive referrals such as this have been shown to reduce DD for adults with IBD being referred by primary care physicians (106), and to reduce DD in children referred by secondary care paediatricians (107). A number of countries have established referral pathways between primary and secondary care to facilitate prompt and specific referrals for children suspected of having IBD. Pathways such as these may reduce the chance of DD relating to system factors, as opposed to patient factors. However, these are dependent on the health care infrastructure of each country and may not be generalisable to all centres. A reliable source of evidence-based guidelines and up-to-date publications on IBD diagnosis are national and international scientific societies relating to paediatric gastroenterology, hepatology and nutrition (PGHAN), such as those in North America (NASPGHAN), Europe (ESPGHAN), Australasia (AuSPGHAN) and Asia Pacific (APPSPGHAN), among others (101,108,109).

Conclusions

This review aimed to provide a comprehensive overview of factors related to the presentation, testing, and referral of children with suspected IBD that have been shown to relate to minimizing DD in this population. The fact that prolonged DD is still evident for children with IBD may suggest a need for improved awareness and education among primary care physicians and secondary care paediatricians on early, unusual or atypical presentations, as well as the need for appropriate and comprehensive testing, monitoring, and referrals (16). As IBD remains an uncommon condition in children (even though rates are increasing), primary care physicians or paediatricians may not consider IBD in their differential diagnosis when a child presents with non-specific symptoms (49). While the prediction and prevention of IBD remains conceptual, and definitive preclinical signs and symptoms remain elusive, finding ways of ameliorating the possible damage done to the intestinal mucosa during the early evolution of the condition remains a priority and should be the focus of large-scale studies (102,110,111). By improving awareness, it is hoped that fast and comprehensive referral channels for children are developed that may reduce the number of unnecessary referrals and invasive investigations for those at low risk of IBD, as well as protecting against DD for those in need of rapid and effective treatment. The continuation of research to refine a matrix of symptoms, laboratory tests, and risk factors that increase the accuracy of case identification is imperative. The body of work presented in this narrative review may be utilised to refine clinical practice guidelines for primary care physicians and general paediatricians in order to ensure appropriate and timely referrals are made to paediatric gastroenterologists for those children with a high likelihood of having IBD.

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Footnote

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