**Title:** Diagnostic Delay in Paediatric Inflammatory Bowel Disease: A Systematic Review

**Short title:** Delay in diagnosis of paediatric IBD

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**Abstract**

Delays in diagnosing paediatric Inflammatory Bowel Disease (IBD) are common, but the extent of this delay remains unclear due to variations in reported time-periods between studies. The objectives of this systematic review were to examine the extent of diagnostic delay in paediatric IBD and examine any association between specific characteristics and length of diagnostic delay. We identified studies from several medical bibliographical databases (EMBASE, Medline and CINAHL) from their inception to April 2021. Studies examining paediatric cohorts (<18 years old) defined as having a diagnosis of Crohn’s Disease (CD), Ulcerative Colitis (UC), or by the more general definition of IBD, and reporting a median time-period between the onset of symptoms and a final diagnosis (diagnostic delay) were included. Two reviewers selected each study, extracted data and assessed their quality using the Newcastle-Ottawa scale. Narrative synthesis was then used to examine the extent of overall diagnostic delay and delay associated with specific sample characteristics. Of the 10,119 studies initially identified, 24were included in the review. The overall median diagnostic delay range was 2-10.4 months for IBD, 2.0-18.0 months for UC and 4.0-24.0 months for CD. However, for approximately two thirds of UC (68.8%) and CD (66.7%) studies, delay ranged from 2.0-3.0 and 4.0-6.3 months respectively. A longer delay was significantly associated with several sample characteristics; however, these were too infrequently examined to draw robust conclusion on their role. Children continue to wait several months for a final diagnosis of IBD, and those with CD experience longer delay than those with UC. The role of specific characteristics on delay needs further exploration.

**Keywords:** Diagnostic Delay, Inflammatory Bowel Disease, Crohn’s Disease, Ulcerative Colitis, Paediatric

**Introduction**

The worldwide incidence of Inflammatory bowel disease (IBD) is increasing, particularly in the paediatric population [1]. Although the aetiology of IBD remains incompletely understood [2, 3], the most common presenting symptoms are chronic diarrhoea, rectal bleeding, weight loss and abdominal pain, although an individual’s presentation can be pleomorphic [2, 4, 5]. Such symptoms are often insidious, non-specific, and common to other paediatric digestive disorders, and as such, IBD may not be readily included in the differential diagnosis [6]. Furthermore, children may present with non-classical signs of IBD, such as mild abdominal discomfort, lethargy, tiredness, delayed puberty, and growth failure, although the latter is more common in CD than UC [2, 7]. Extraintestinal manifestations (EIM) are also common, and these can affect multiple systems including the skin, eyes, and the musculoskeletal system [6, 8-10], which can further confound the diagnosis. As such, diagnostic delay (the time-period between the onset of symptom(s) and the patient receiving a diagnosis) is not uncommon in paediatric populations.

Diagnostic delay may also occur for a multitude of other reasons, including but not limited to, the patient (delay in healthcare seeking), the healthcare professional (lack of appreciation of the diagnosis and system factors) and institutional factors (delays in review and investigation in secondary care), all of which have been reported in other rheumatological conditions, such as rheumatoid arthritis and giant cell arteritis [11, 12]. Reported diagnostic delay varies from one population to another and a better understanding of delay in children and adolescents is important, as a delay in treatment is associated with deleterious health outcomes [8, 9, 13].

The aim of this systematic review was to provide insight into the extent of diagnostic delay of IBD, CD and UC in children and adolescents under the age of 18, and to examine whether any specific sample characteristics are associated with such delay.

**Methods**

A systematic review of the literature and a narrative synthesis of the extracted data was undertaken. A search of medical bibliographical databases (EMBASE, MEDLINE, and CINAHL) from their inception to April 2021 identified studies containing data on the median time-periods between the onset of IBD, CD or UC symptoms and a final respective diagnosis. Narrative synthesis was then used to examine the overall extent of diagnostic delay and report any specific sample characteristics related to the delay experienced. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the completion of this systematic review and the protocol was logged with PROSPERO (Registration number: CRD42018108886).

*Search criteria*

This review included studies with 1) a paediatric sample (<18 years old) with IBD, CD and/or UC, and 2) a reported time-period of diagnostic delay. Articles with combined paediatric and adult data were not included. Articles were included regardless of the language they were written in if they meet the aforementioned inclusion criteria. If any studies had used data from an overlapping time-period within the same dataset, then the study with the largest sample was included in the review. This review excluded studies: 1) with an adult sample (>18 years old), 2) without data for diagnostic delay, 3) which reported average data as a mean, rather than median and 4) those that used case-series or case-report design.

 The total number of paediatric studies were initially identified by a single reviewer (shared by EC & JAP), who removed duplicate titles and then excluded studies based on title review. At least two reviewers (SM, AA & CAH) then independently screened the studies for inclusion based on abstract content. Disagreements were resolved by consultation with the principal investigator (JAP). Once an agreement on which studies to include was reached, those studies were then reviewed in full. The reference list of each included study was checked for additional studies of relevance by the principal investigator (JAP). Three reviewers (SM, AA & JAP) assessed the quality of the final studies using a modified version of the Newcastle-Ottawa quality assessment scale.

*Data extraction*

The data were extracted from relevant studies by at least two reviewers (shared amongst EC, LB, SM & AA), with final analysis conducted by CAH and JAP. The primary outcome of interest was the average time-period between the onset of symptoms relating to a final CD, UC or a general IBD diagnosis. Where data were reported in two formats of central tendency, mean or median, median data was utilised for the purposes of this review. Diagnostic delay data is typically positively skewed, with the majority of delay data being found towards the shorter end of the range of delay and a minimal number of patients experiencing extremely long periods of delay. Therefore, the appropriate statistical approach is to use median values, as the use of mean data will potentially result in an over-estimation of average diagnostic delay, while median values offer a more accurate representation of the average sample data [14]. We reported the primary outcome by months of delay, therefore, where delay was reported as the median number of weeks or years it was converted to months (Months = Years \* 12; or Months = Weeks/4.345).

Results of the studies included in the review were compiled into a narrative synthesis. In addition to the primary outcome of diagnostic delay, other extracted data included: the lead author’s name; year of publication; study design and country of study; the period of time during which patients were sampled from medical records; the age range of patients, patients’ sex; size of the sample; the key symptoms and method of IBD diagnosis and the authors’ definition of delay. Relevant sections of non-English language studies were translated into English and the required data extracted.

**Results**

*Search results*

A total of 10,119 studies were initially identified. Following the exclusion of 6746 studies based upon title review and removal of duplicates, 3373 underwent abstract review. Of the 429 subsequent studies that were reviewed in full, 39 had reported data on average diagnostic delay, 24 met the inclusion criteria of reporting median diagnostic delay and were included in the review (**Figure 1**), the remaining 15 [15-29] reported mean data were excluded (**Supplementary Table 1**).

*Study characteristics*

Of the 24 included studies, 12 were retrospective cohort studies, seven were prospective cohort studies, three combined both methods and two were cross-sectional studies. The majority of studies were from the European continent (n=16), including 5 from the UK [30-34], 3 from Spain [35-37], 2 each from France [38, 39], Germany [8, 40] and Switzerland [10, 41], and 1 each from Croatia [42] and Italy [43]. The remaining studies were undertaken in North America (n=4) [13, 44-46], the Middle East (n=2) [6, 47] and Asia (n=2) [2, 48]. Most studies were conducted solely in secondary care settings (n=17), with the remainder across primary & secondary care (n=4), tertiary care (n=1) or using registry data (n=2). Several studies used established diagnostic criteria; for example, the Porto criteria [49] was used for CD and UC (n=5), Gower-Rousseau criteria [50] for CD (n=1) and European Crohn’s & Colitis criteria (n=1). However, the majority of these studies used a combination of clinical, histological and radiological findings for diagnosis (n=14) or did not report a diagnostic method (n=3). There was a total of 4451 participants providing data for IBD, 5196 for CD and 2365 for UC (**Table 1**).

*Extent of diagnostic delay*

The median delay from the onset of IBD symptoms to diagnosis was reported in ten studies. The median delay from symptom onset to IBD diagnosis ranged from 2 months (range 0.2-24) in Croatia [42] to 10.38 months (range 0.5-24.1) in the UK [32]. However, the majority (80.0%) ranged from 2-5 months. Diagnostic delay in CD was the most frequently examined of these disease definitions, with the median delay from onset of symptoms to diagnosis reported in 18 studies. These time-periods ranged from 4 months (Interquartile range (IQR) 2-8)) in Germany [40] to 24 months in Saudi Arabia [6]. However, for the majority of studies (66.7%) the median delay in paediatric patients receiving a diagnosis of CD ranged from 4.0 to 6.3 months. For UC, the median delay from the onset of UC symptoms to diagnosis was reported in 16 studies. The shortest median delay from symptom onset to diagnosis was from 2 months (range 0.5-1) in the UK [30] to the longest delay of 18 months (IQR 3-29) in India [48]. For the majority of studies (68.8%), the median delay in paediatric patients receiving a diagnosis of UC ranged from 2 to 3 months (**Table 2**). Where studies had reported data for both CD & UC samples (n=14), the delay reported for CD was consistently higher than that reported for UC (**Supplementary Table 2**).

*Characteristics associated with diagnostic delay*

The role of 15 different characteristics related to diagnostic delay were identified across nine separate articles [8, 32-35, 40, 41, 45, 47]. These were categorised into five main areas including: sociodemographic, signs and symptoms, disease location, healthcare related, and surgical intervention. Of the 15 identified characteristics, 18 statistical comparisons had been made, eight were found to be significantly associated with diagnostic delay and 10 were not.

Of those studies which found a significant association between specified characteristics and diagnostic delay, Timmer *et al.* [8] found that a younger age of presentation (<5 years old) and presence of growth failure were significantly associated with increased diagnostic delay for IBD, while a family history of IBD was associated with significantly reduced diagnostic delay. Timmer also reported a significant difference in delay depending on disease location in the bowel and depending on who was the diagnosing physician. Spray *et al.* [32] reported that a lack of diarrhoea as a presenting symptom resulted in a significantly higher diagnostic delay for CD compared to those presenting with diarrhoea (15.2 vs 6.4 months; *p*=0.005). Gerasimidis *et al.* [34] showed that for CD, there was significantly lower diagnostic delay for those with severe anaemia compared to those with either mild (3 *vs.* 6 months) or no anaemia (3 *vs.* 8 months). Sawczenko *et al.* [33] demonstrated that oral disease in CD was associated with significantly higher delays versus other disease activity (8 vs 6 months; *p*=0.04) (**Table 3**).

*Quality Assessment*

Using independent blind assessment, 20 studies scored the highest score for the true representativeness of their selected samples and the remaining four were somewhat representative of the general population. All included studies scored the highest available score for ascertainment of exposure, using secure medical records to determine diagnosis. Eighteen studies ascertained the outcome of delay through record linkage, with the remaining 6 via self-report.

**Discussion**

Our systematic review examining the extent of diagnostic delay in paediatric cases of IBD found that, on average, the majority of children with Crohn’s Disease will receive their final diagnosis within 6 months of their first symptoms, and patients with Ulcerative Colitis generally receiving a prompter diagnosis within 3 months. However, there remain instances of diagnoses taking many more months, even years, to be made. Though several disease, healthcare and patient-related characteristics have been shown to be associated with such delays in diagnosis, this information is too limited to draw firm conclusions on those children vulnerable to experiencing delay.

Due to heterogeneity of included studies, we are unable to make direct inferences as to whether the issue of diagnostic delay has improved over time. However, Timmer et al [8] did examine the extent of delay over several time periods in Germany (Up to 1995, 1996-1999, 2000-2003, 2004-2007, 2008-2009) and, although they urge caution with their results, time to diagnosis did improve across these time-period. Furthermore, the issue of particularly protracted periods to receive a diagnosis (medians between 1-2 years) which we identified in recent studies, were isolated to just three outliers from India [2, 48] & Saudi Arabia [6], with contrasting healthcare systems to the majority of studies we identified from European and North American countries.

When comparing CD and UC, diagnostic delay was longer for CD across our review overall and within individual studies which had made such comparisons directly within the same sample. This increased diagnostic delay for patients with CD could be due to CD symptoms being more insidious and less alarming to both patients and healthcare professionals, and less specific than those for UC. CD can also occur anywhere along the gastrointestinal tract, while UC commences in the rectum and extends proximally within the colon for a variable extent [51, 52]. Therefore, identification of UC in the colon makes it easier to identify as it is more readily visualised at endoscopy. Classically, UC presents with rectal bleeding which may prompt referral and investigation by the physician [4, 5]. EIMs may also appear before, or even divert attention from the gastrointestinal symptoms of IBD [10]. Isene *et al.* [53] showed that patients with CD are twice as likely to develop EIMs than those with UC, this may result in misdiagnosis prior to a correct IBD diagnosis. Jose *et al.* [54] found that 6% of a paediatric IBD patient sample developed at least one EIM before diagnosis and furthermore, Ardizzone *et al.* [55] found that the presence of one EIM increases the susceptibility to develop other manifestations.

Misdiagnosis could also occur due to similar presentations and thus leading to misinterpretation of symptoms or confusing the current symptoms with a co-existing illness [21]. In this regard, Card *et al.* [56] found that 10% of IBD cases are misdiagnosed as irritable bowel syndrome (IBS) and that there has been a rise in IBS cases where physicians attribute the symptoms to IBD. Physicians could also be attempting to solve the presenting problem, rather than the underlying disease. For example, iron-deficiency anaemia could be labelled as the diagnosis, rather than further investigating the cause of the anaemia [21]. Also, abdominal pain, a symptom of both UC and CD, is sometimes classified as “functional”, and not warranting any further investigations [57]. Finally, in some regions, such as Japan, medical facilities do not provide easy access to colonoscopy for paediatric patients which may also contribute to the delay [28].

Features of IBD and patient characteristics, such as age at presentation, presence and severity of symptoms, and disease behaviour have been shown to significantly influence the diagnostic delay experienced by paediatric patients. However, research into the role of such characteristics on delay remains limited and has not been repeated, meaning that more research is required to determine whether specific characteristics have a part to play in reducing diagnostic delay.

It should be noted that diagnosis of IBD requires a combination of haematological, endoscopic, histological and imaging-based investigations[58]. According to the National Institute for Health and Clinical Excellence (NICE) guidelines, IBD should be suspected if patients demonstrate the following gastrointestinal symptoms for at least 6 weeks (less in more severe cases): 1) abdominal pain or discomfort, 2) bloating and 3) changes in bowel habits [58]. In a primary care setting, after clinical assessment, non-invasive markers such as faecal calprotectin should be performed, which has reasonable sensitivity and specificity [58, 59]. If IBD is not excluded, then prompt referral to a paediatric gastroenterologist must follow to confirm the diagnosis [28, 59]. NICE guidelines recommend that patients with suspected IBD should be seen by a specialist within 4 weeks of referral by a GP [58]. Early diagnosis is important to reduce potential complications. For example, Zaharie et al. found that delayed diagnosis of IBD is correlated with bowel stenoses, intestinal fistulas and the need of surgery [60]. Growth failure, another serious complication of IBD, is also associated with diagnostic delay and occur in 10-40% of CD patients. [6, 8, 61-63].

The strengths of this study lie in the review’s unique collation of delay data, providing a more robust benchmark of the diagnostic delay experienced by children due to sole use of median, rather than mean data. Furthermore, it employed a rigorous search process, with independent reviewers individually extracting data and assessing the quality of the studies. In addition, non-English language studies were included in our search criteria and every effort made to translate these. Finally, our quality appraisal revealed that the majority of studies included were of the highest possible quality in terms of representativeness, with the majority selecting samples from the general population or national repositories, and ascertainment of exposure and outcomes as data was extracted from medical records. However, limitations of this work include the marked heterogeneity of the methodologies used by the studies included in our review. The wide range of diagnostic delay values reported could be explained by disparities in factors relating to sample size, different countries, or socioeconomic factors of samples. The use of median data meant that pooling of study data through meta-analysis was not possible; however, despite our review identifying a range of diagnostic delay values for each condition, we found that the majority of these did fall within a relatively narrow window of just a few months, and therefore provide a new range for future diagnostic delay data to be compared against.

In conclusion, children and adolescents continue to wait for several months for a final diagnosis of IBD, and those with CD can experience several more months of delay than those with UC. Considering the increasing incidence of paediatric-onset IBD, coupled with the possible long-term complications associated with IBD, early detection and diagnosis are vital in the quest for optimisation of favourable outcomes in affected patients. Therefore, healthcare professionals, particularly general practitioners need to be able to recognise the early signs of IBD in children and have clear pathways to facilitate a prompt referral to a paediatric gastroenterologist. Finally, further research is needed to explore whether certain sample characteristics are associated with length of diagnostic delay in IBD and methods to minimise such delay.

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**Conflict of Interest**

The authors declare no conflict of interest.

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**Author contributions**

AA: Article review, data extraction, writing of manuscript

EC: Creation of search strategy, database search, writing of manuscript

SM: Article review, data extraction, writing of manuscript

CH: Narrative synthesis, writing of manuscript

LB: Article review, data extraction

BS: Initial study design, article review, writing of manuscript

ADF: Initial study design, creation of search strategy, clinical input, article review, writing of manuscript

JAP: Initial study design, creation of search strategy, article review, data extraction, narrative synthesis, writing of manuscript

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