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Natural History of Pediatric-onset Inflammatory Bowel Disease:

A Systematic Review

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Abstract

Background/Aims—There has been no systematic review of natural history studies of pediatric-onset inflammatory bowel disease (IBD). We conducted a systematic review focused on understanding the long-term risks of growth failure, disease reclassification and extension, hospitalizations, cancer and death among patients with childhood IBD.

Methods—PubMed searches and subsequent data abstraction were performed by 2 independent investigators. Studies published full in english with a 5-year minimum average follow-up in at least 30 patients with IBD onset before age 18 years.

Results—We evaluated 41 total studies (only 2 population-based studies) with 3505 Crohn's disease (CD) patients, 2071 ulcerative colitis (UC) patients, and 461 indeterminate colitis (IC). Growth failure was reported in CD (10% and 56%) more often than UC 0% to 10%) or non-IBD controls. Improvements in growth occurred after surgical resection in patients with CD. There was an increase in disease reclassification over time from UC and indeterminate colitis diagnosis to CD diagnosis. Patients with CD had higher number of hospitalizations and hospital days per year in comparison with UC patients in most studies. The reported surgery rates in CD ranged between 10% and 72%; the colectomy rates in UC ranged between 0% and 50%. Cancers were reported in 6 CD patients during a total 18,270 patient-years (PY) follow-up, and 8 UC patients in 18,115 PY. Deaths directly related to IBD were 63 during 39,719 PY.

Conclusions—Childhood-onset IBD patients had growth failure reported in patients with CD more often than those with UC, had a reclassification of disease type to CD over time. Higher rates of surgery and hospitalizations were found with CD than with UC. The risk of cancer and death is low in this population.

Keywords

natural history; pediatric IBD; long-term risk; growth failure; disease reclassification; disease extension; hospitalization; cancer; death

Inflammatory bowel disease (IBD) is a group of chronic disorders that consists of ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). There has been an increase in the number of patients with pediatric age IBD, with a recent study from Ontario showing an increase in the incidence in pediatric IBD from 9.54 per 100,000 in 1994 to 11.43 per 100,000 population in 2005.¹

Although the incidence and prevalence of pediatric-onset IBD vary among different countries, the general trend shows an overall increase over the past few decades based on a systematic review of the epidemiology of pediatric IBD by Benchimol et al.² Approximately 20% to 30% of patients with IBD have the onset of symptoms before age 18 years.^{3–6}

Providing prognosis estimates and making treatment decisions in patients with pediatric IBD are greatly aided by the knowledge of clinical course and natural history of the disease at that age. Many studies dealt with these aspects of pediatric IBD; however, these studies examined different populations, outcomes, and provided occasions of conflicting findings. There has been no systematic review of natural history studies of childhood IBD. Therefore, we conducted this systematic review to evaluate several specific aspects of natural history, which includes the risks of growth failure, reclassification of disease type, disease extension and complications, hospitalizations, surgery, cancer and death among patients with childhood IBD.

METHODS

Two investigators conducted the literature searches, study selection, and data entry. Differences were resolved by discussion and consensus. Systematic literature searches in PubMed were conducted between 1966 and August 2010. The following search strings were used: (“pediatric” [MeSH Terms] AND (“inflammatory bowel disease” [All Fields] OR “Crohn’s” [All Fields] OR “ulcerative colitis” [All Fields]) AND (“progression” [All Fields] OR “natural history” [All Fields] OR “long-term follow-up” [All Fields]) AND (“surgery” [All Fields] OR “post-operative recurrence” [All Fields] OR hospitalizations” [All Fields] OR growth” [All Fields]) AND (“humans” [MeSH Terms] AND English [lang])). References from pertinent articles were also reviewed.

The inclusion criteria were (1) studies that were published in full manuscript in English; (2) studies that evaluated patients with IBD 18 years of age and younger for the occurrence of growth failure, reclassification of IBD disease type, IBD disease extension, hospitalizations, surgery, cancer and death; (3) studies that included patients with CD, UC, or IC; and (4) as our interest was in the intermediate and long-term complications, we included only studies with a minimum average follow-up of 5 years. We excluded studies with a sample size of < 30 patients with IBD, average (mean or median) follow-up of < 5 years, or IBD onset after 18 years of age.

Studies were defined as retrospective (data collected in the past or based on historical information), concurrent cross-section-retrospective (data collected at a set time to determine the set of patients available and reviewed data collected in the past), concurrent retrospective-prospective data collected on patients in the past and at the time of study design, then followed afterwards), or prospective studies (data collected after the study were designed).

Data were systematically abstracted from the articles that fulfilled inclusion-exclusion criteria and entered into tables. These data included year(s) in which study data were collected, country of enrollment, number of participants, IBD type, length of follow-up, study type, sampling frame, and IBD information (growth failure, reclassification of disease type, disease extension and complications, hospitalizations, surgery, cancer and death).

RESULTS

A total of 684 articles were retrieved based on the general search strategy (Fig. 1). Review of titles and abstracts revealed 57 articles that examined the natural history of childhood IBD. A detailed manual review of the manuscripts identified 39 studies from the search

strategy that fulfilled the inclusion and exclusion criteria, and 2 additional articles were found by reviewing references of eligible studies.

Of the 41 total studies, 32 were retrospective cohort with 28 concurrent cross-section–retrospective and 4 concurrent retrospective-prospective, and 9 prospective cohort evaluation (Table 1). There were only 2 population-based studies involving mailed questionnaires, 1 with 66% response rate³⁶ and the other with 67% response rate,³⁷ whereas the rest were clinic or hospital-based studies. Fifteen studies were from the United States, 3 from Canada, and the remainder from Europe.

Of these 41 studies, 10 studies evaluated patients with UC only, 13 evaluated CD patients only, the remainder studies included both CD and UC with 8 studies describing in addition. The studies recruited patients from as early 1935 to 1980 to as late as 1996 to 2007. Sample sizes ranged from 32 to 639 patients. The follow-up duration in studies was a mean or median of minimum 5 years with a range of 0 to 45 years. These studies described a total of 3505 CD patients, 2071 UC patients, and 461 IC patients, and 48 patients with IBD otherwise unclassified into the 3 previous categories.

Three studies included the same cohort of patients from the Scottish National Health Service.^{17–19} Each were evaluated for different outcomes but presented as 1 study.

Growth Failure

One population-based study and 20 clinic/hospital-based studies evaluated growth in children with CD and 10 clinic/hospital-based studies in children with UC (Table 2). The majority of studies used height below third percentile the main definition for growth failure, and some studies also included weight below third percentile in the definition. Growth failure at the time of diagnosis of CD ranged between 10% and 56%, whereas at end of follow-up ranged between 10% and 40%. In UC, growth failure at diagnosis ranged 0% to 10%, whereas at follow-up ranged between 0% and 17%. Only 1 study evaluated growth failure in patients with IC and reviewed 3 of the 17 (18%) patients who had growth failure at follow-up. Additional studies that examined non-IBD controls, growth failure were reported in CD more frequently than UC or non-IBD controls.^{18,19,37}

Significant improvements in growth occurred after surgical resection in 4 studies of patients with CD.^{8,9,20,30} El-Baba et al³⁰ reported that 6 of 6 (100%) patients post-surgery showed significant catch-up growth in weight and height compared with presurgery where they were all below third percentile in height and weight for age. The 38 prepubertal patients in Griffith et al's study²⁰ increased from a mean (SD) height percentile of 11.1 (12.6) at the time of resection to an ultimate (n=26) or current (n=12) height percentile of 29.5 (27.5; $P < 0.001$). Castile et al's⁹ study showed that the rate of growth from the time of diagnosis to adult height was significantly greater in the surgical group whose height improved by 6.0 percentiles compared with the nonsurgical group whose height actually decreased by 8.4 percentiles ($P < 0.01$). In the study by Homer et al,⁸ 7 of the 11 prepubertal patients with < 3 percentile for height had early relapse of disease after surgery and showed no catch-up growth. However, the 4 without recurrence had significant improvements in growth.

Reclassification of IBD Type

We identified 5 studies (all clinic visit based) that examined reclassification of IBD types over time (Fig. 2). In general, there was an increase over time in the proportions of patients with CD diagnosis and a decrease in IC diagnosis. In the 5 studies, there was an increase of 2%, 4%, 6%, 10%, and 13% in the diagnosis of CD during follow-up. Three of these 5

studies showed an absolute decrease in UC diagnosis by 7%, 11%, and 11% over time, whereas the other 2 showed a slight 3% increase in UC.

IBD Extension and Complications

We identified 3 clinic/hospital-based studies that evaluated the progression of the disease location in UC. In 2 of these studies, the progression to pancolitis increased overtime, while the prevalence of left sided and isolated proctitis declined (Fig. 3). Similarly, 2 clinic/hospital-based CD studies showed an increase in extension of disease to both small and large intestine from the onset of disease to the study follow-up time (Fig. 4). During a follow-up of 6 to 10 years, 4 clinic/hospital-based studies reported 24% to 43% of patients with CD developing stricture, 14% to 27% developing fistulizing disease, and 25% to 30% developing perianal disease.

Hospitalization

We identified 4 clinic/hospital-based studies in CD^{18,19,27,39} and 3 clinic/hospital-based studies in UC^{16,18,19} that evaluated hospitalizations in these patients. In the earliest studies by Ferguson et al^{18,19} CD patients averaged 6.6 admissions during a reported mean follow-up of 13.4 years (SD 4.8), with a mean of 102.5 (SD 85.6) hospital days. UC patients averaged 6.4 (SD 4.9) admissions during the reported mean follow-up of 14.6 (SD 5.5) years with a mean of 93.4 (SD 70.7) days in the hospital. In the study by Hyams et al,¹⁶ 24% of UC patients were hospitalized during a 27-year maximum follow-up. In Vernier-Massouille et al's³⁹ study, 152 (37%) of CD patients were hospitalized during a 14-year maximum follow-up. Gryboski²⁷ also showed more hospitalization days per year in CD patients (mean 4.8 d) compared with UC patients (mean 1.6 d). Within their CD group, those with colitis had more hospitalization days compared with those with ileocolonic disease, which was still higher than terminal ileal disease alone.

Surgery

We identified 18 clinic/hospital-based studies that reported on the occurrence of surgery in CD (defined as intestinal resections but no abscess drainage or fistula Seton placement) and 18 for UC (defined as colectomy). For CD, the cumulative surgical resection rates ranged between 10% and 72%. In all 18 studies, 743 CD patients underwent colectomy during a combined 32,656 patient-years (PY; 228 per 10,000 PY). For UC, the reported colectomy rates ranged between 0% and 50%. In all 18 studies, 271 UC patients underwent at least 1 surgery during a combined 23,527 PY (115 per 10,000 PY).

Cancer

The occurrence of cancer was reported in only 11 clinic/hospital-based studies (Table 3). In 6 studies of CD, 6 cancers were reported in 6 different patients during a total of 18,270 PY of follow-up (3.3 per 10,000 PY). These cancers included 1 metastatic breast cancer, 3 colon adenocarcinomas, and 2 small bowel adenocarcinomas. In 9 studies of UC, 8 cancers (in 8 different patients) were reported in 18,115 PY (4.4 per 10,000 PY); cases were colonic adenocarcinoma and 1 cholangiocarcinoma in a patient with a concomitant diagnosis of primary sclerosing cholangitis.

Death

Death was reported in 17 clinic/hospital-based studies. Deaths directly related to IBD were relatively low at 63 per 39,719 PY (16 per 10,000 PY; Table 4). The highest rates were found in the earlier studies. For example, the study by Castile et al⁹ conducted during 1950 to 1973 reported 16 CD-related deaths in 5340 PY (0.3 per 100 PY) and Farmer and Michener¹⁰ conducted in 1955 to 1974 reported 13 CD-related deaths during 1044 PY.

follow-up (1.25 per 100 PY). The more recent studies from Gower-Rousseau et al³⁸ and Vernier-Massouille et al³⁹ (1988 to 2002) reported 1 death per 1582 PY (0.06 per 100 PY) in UC patients and no deaths during 6060 PY in CD patients. The reported underlying cause of death included sepsis, colon cancer, surgery-related complications, and intestinal perforation.

Extraintestinal Manifestations (EIMs)

Although EIMs were reported in 2% to 23% of patients, only 2 studies showed follow-up data. Gryboski and Spiro¹⁵ showed an increase of skin lesions from 6% to 13% from presentation to the end of follow-up, and arthritis from 7% to 12%, whereas the presence of arthralgias remained at about 7% at presentation and at follow-up. Vernier-Massouille et al³⁹ showed a doubling of EIMS from diagnosis to the end of follow-up period in almost all examined EIMS (uveitis from 1% to 2%, skin manifestations from 16% to 30%, axial arthropathies from 3% to 5%, and peripheral arthritis from 7% to 25%).

DISCUSSION

We conducted a systematic review of the published literature on the natural history of pediatric-onset IBD. We identified 41 studies that fulfilled strict inclusion criteria including a minimum average follow-up of 5 years for 3505 CD patients, 2071 UC patients, and 461 IC patients and were able to summarize findings regarding growth failure, reclassification of disease type, disease extension and complications, hospitalizations, surgery, cancer and death.

Most studies in this review reported high prevalence of growth failure in IBD patients. Growth failure was reported in CD patients more often than UC or non-IBD controls. Improvements in growth occurred after surgical resection in patients with CD based on 4 studies in this review.^{8,9,20,30} Surgery for refractory disease or obstruction has been linked to enhanced growth in other short-term studies.^{48–50}

None of the long-term follow-up data in this review pertained to the use of enteral therapy or medications and their association with growth. These interventions were examined in studies with short-term follow-up. A prospective interventional study by Belli et al⁵¹ showed that although growth velocity (cm/y) in 8 CD patients receiving intermittent nasogastric tube feeding was not different from that of controls at 1 year of follow-up but by the end of the second year, there was a statistically significant increase in growth velocity in the nasogastric tube-feeding group. A randomized placebo-controlled trial of 55 children with CD randomized to either 6-mercaptopurine or placebo within 8 weeks of initial diagnosis, showed that despite contributing to prolonged remission and steroid sparing effect, children on 6-mercaptopurine had the same linear growth as those on placebo at 18 months.⁵² However, the week 54 data on height velocity *z* score from the REACH trial showed a significant increase from baseline in IBD children receiving infliximab therapy compared with the placebo group.⁵³

Studies in this review indicate the change of IBD diagnosis from UC and IC to CD. In 5 studies that examined reclassification of IBD type over time, there was an increase in the diagnosis of CD during follow-up with a concomitant decrease in IC diagnosis and a decrease in UC in 3 of the 5 studies. Although there may be a true change of IBD type to CD, this finding may represent an improvement in the diagnosis of CD over time as a result of new modalities such as capsule endoscopy or serologic markers. Studies in this review also showed an extension from limited IBD involvement to more extensive disease. Two of the 3 UC studies showed that progression to pancolitis increased over time, and similarly in

CD, an increase in extension of the disease to small and large intestine from the onset of disease to study follow-up occurred.

Pediatric-onset IBD was associated with hospitalization rates that ranged between 9 and 27 per 1000 PY follow-up. In the early studies by Ferguson et al^{18,19} that examined hospitalizations, UC and CD patients had similar admissions rates and mean days in the hospital. However, subsequent studies showed that on an average CD patients had higher number of annual hospitalizations for disease-related complications than those with UC.^{16,27,35,39} In 1 study, patients with Crohn's colitis had the highest hospitalization days followed by those with ileocolonic disease and terminal ileal disease alone.²⁷ Cumulative surgical resection rates for pediatric CD ranged between 10% and 72% in this review. The increasing use of immunomodulators and antitumor necrosis factors may reduce the surgery rates over time. However, short-term data from Afzal et al⁵⁴ showed that despite achieving clinical remission in 70% of CD children with infliximab, 58% still required surgery within the next 12 months.

Cancer was rare in pediatric-onset IBD with most cases either small or large bowel adenocarcinomas suggesting that underlying disease activity contributed to the cancer. The studies however, may not have captured many patients who had disease for 8 to 10 years or longer. No lymphomas were reported; the latter being a specific concern in pediatric patients who can be exposed to immunomodulating drugs for a longer period of time than adults. Data on medications were generally not available in the studies.

Deaths directly related to IBD were infrequent in 17 studies that reported on this outcome and were generally less reported in more recent studies. The earlier 10 studies conducted in the 1930s to 1960s reported 0.002 to 1.25 deaths per 100 PY follow-up, whereas the later 7 studies conducted during the 1970s to 2000s reported 0 to 0.54 deaths per 100 PY. Although there were differences in the study populations and study designs, this decline in mortality could represent improvement in perioperative care, surveillance for cancer, and use of medications in the severe cases of IBD.

Comparison of the natural history of IBD between children and adults is not possible from this review. A Scottish study by Van Limbergen et al⁵⁵ that did not meet our inclusion criteria because of a follow-up time of < 5 years compared natural history of adult-onset IBD to pediatric-onset IBD. In UC, extensive colitis was found in almost twice as many children (82%) as adults (48%), and the median time to operation in children was significantly shorter than in adults. In CD, childhood-onset IBD was characterized by more extensive CD than adult-onset IBD (43.2% vs. 3.2% $P < 0.0001$). However, among the childhood-onset CD patients, 17.1% required surgery compared with 52.8% of adult-onset CD patients ($P < 0.0001$). These findings suggest that pediatric-onset IBD may have different pathogenic mechanisms from adult-onset IBD with distinct phenotypic characteristics.⁵⁶ Lastly, very-early-onset IBD is far more likely than that of IBD presenting in older children and teenagers to have pathogenic mechanisms that are distinct from those observed in adult-onset disease. For example, IBD diagnosed within 1 year of life is associated with the presence of specific mutations affecting the interleukin-10 receptor.⁵⁷

The limitations of this review include the inability to account for regional differences in evaluation and treatment of these patients. Data from multiple studies were not sufficiently detailed for the application of the Montreal classification or the Paris pediatric modification of IBD.⁵⁸ Because the review encompassed multiple studies spanning several decades, it was difficult to examine changes in management over time. However, studies that started as early as 1930s provide us a true "natural history" before the advent of newer medications. Most studies were retrospective and hospital or clinic based. Easier access to and use of

improved diagnostic testing such as fiber-optic endoscopy, video capsule endoscopy, magnetic resonance enterography, and serologic testing could account for observed variations over time as well.

We found few studies that evaluated medication use thus making it difficult to determine its effect on disease behavior and complications. Only 5 studies in this review reported the use of antitumor necrosis factors in some patients, but none of these studies reported on the association between these medications and any of the outcomes of interest. We also found only 2 studies that met our criteria and discussed results of serologic testing. Carvalho et al⁴⁴ reported negative testing for anti-saccharomyces cerevisiae antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) in all 9 IC patients. Mamula et al²⁹ also tested pANCA and ASCA in 15 children; none tested positive for ASCA, whereas pANCA antibodies were not significantly different among UC, CD, or IC.

The results of our systematic review showed that growth failure is prevalent among pediatric patients with IBD and is more frequent in CD more so than UC, and more patients were reclassified as CD from UC or IC. It also revealed possible progression of disease location to pancolitis over time with UC and to both small and large bowel disease in CD. Hospitalizations, number of hospital days, and surgery rates were higher in CD compared with UC. There were few cancers and deaths reported in the population and number of hospital days was higher in CD. Further studies are needed to evaluate the long-term role of medications, serologic testing, and genetic information in this group of patients.

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FIGURE 1.

Natural history of pediatric IBD. Literature search results for studies published in full papers in english between 1935 and 2007.

FIGURE 2.
Change in type of IBD diagnosis from onset to long-term follow-up: results of 4 studies.

FIGURE 3.
Change in location of ulcerative colitis from onset to long-term follow-up: results of 3 studies.

FIGURE 4.
Change in location of Crohn's disease at long-term follow-up: findings of 2 studies.

TABLE 1

Basic Characteristics of 41 Studies that Were Published Between 1977 and 2010 and Fulfilled Inclusion and Exclusion Criteria for the Systematic Review. Studies are Presented in Descending Order of Study Date

References	Date of Study	Country	No. Patients	IBD Type	Duration of Follow-up (y) [†]	Study Design	Data Collection
Puntis et al ⁷	1935–1980	USA	67	CD	Mean 15 (range, 1.5–47)	P	Clinic visits
Homer et al ⁸	1948–1974	USA	37	CD	Average 12 [‡]	R	Record review
Castile et al ⁹	1950–1973	USA	177	CD	Mean 8.8 (SD 6)	R	Record review
Farmer and Michener ¹⁰	1955–1974	USA	513	CD	Mean 7.7	P	Record review, phone interview
Absgren et al ¹¹	1961–1990	Sweden	32	UC	Mean 18 (range, 0–30)	RP	Record review, practitioner interview, clinical visits
Lindberg et al ¹²	1961–2005	Sweden	46	UC	Mean 22.3 (range, 0–44)	R	Record review
Jakobsen et al ¹³	1962–1987	Denmark	119	Both	Average 12 [‡]	R	Record review
Langholz et al ¹⁴	1962–1987	Denmark	103	Both	Average 12 [‡]	R	Record review
Gryboski and Spiro ¹⁵	1966–1976	USA	86	CD	Mean 6	P	Clinic visits
Hyams et al ¹⁶	1967–1994	USA	171	UC	Mean 5.1 (SD 4)	R	Record review
Barton and Ferguson ¹⁷	1968–1983	Scotland	105	Both	Mean 7.05 (range, 0.8–18.7)	R	Record review
Ferguson and Sedgwick ¹⁸	1968–1983	Scotland	105	Both	Mean 14	R	Record review, clinic visits/phone interview
Ferguson and Sedgwick ¹⁹	1968–1983	Scotland	105	Both	Mean 14	P	Record review, clinic visits/phone interview
Griffiths et al ²⁰	1970–1987	Canada	275	CD	Mean 5.3	R	Record review
Markowitz et al ²¹	1970–1989	USA	48	Both	Mean 10	P	Clinic visits
Postuma and Moroz ²²	1974–1983	Canada	33	CD	Mean 10	R	Record review
Pigneur et al ²³	1974–2007	France	206	CD	Median 14.7 (range, 10.8–45.2)	RP	Clinic visit, phone/mail contact
Falcone et al ²⁴	1975–1990	USA	73	UC	Mean 5.4 (range, 0.4–13.8)	R	Record review
Besnard et al ²⁵	1975–1994	France	119	CD	Mean 5 (range, 0.3–9)	R	Record review, phone interview
Bland et al ²⁶	1976–1995	Scotland	105	Both	Average 10 [‡]	R	Record review
Gryboski ²⁷	1977–1990	USA	78	Both	Mean 6.5 (SD 3)	R	Record review
Gryboski ²⁸	1977–1990	USA	38	UC	Mean 6.7 (SD 2.3)	R	Record review
Mamula et al ²⁹	1977–2000	USA	82	Both	Median 7.5	R	Record review
El-Baba et al ³⁰	1979–1992	USA	32	Both	Mean 8.4	R	Record review
Dumo et al ³¹	1980–1995	Canada	73	UC	Mean 5.8 (SD 3.3)	R	Record review, questionnaires

References	Date of Study	Country	No. Patients	IBD Type	Duration of Follow-up (y) [†]	Study Design	Data Collection
Roma et al ³²	1981–2007	Greece	411	Both	Median 5 (range, 1–16)	R	Record review
Alexander et al ³³	1982–1999	USA	144	Both	Mean 7.2 (range, 2–15)	R	Record review, phone interview
Sedgwick et al ³⁴	1983–1987	Scotland	37	UC	Mean 7.4 (range, 0.3–18.5)	R	Record review
Lindberg et al ³⁵	1984–1995	Sweden	639	Both	Average 6 [†]	P	Protocol reporting of patients and data
Pakarinen et al ^{36*}	1985–2005	Finland	52	UC	Mean 10	R	Mailed questionnaires 66% response rate
Turunen et al ^{37*}	1987–2003	Finland	368	Both	Average 10 [†]	R	Questionnaire with control pts 67% response rate
Gower-Rousseau et al ³⁸	1988–2002	France	113	UC	Median 6.4 (range, 3.8–10.3)	R	Record review
Vernier-Massouille et al ³⁹	1988–2002	France	404	CD	Median 7	P	Phone interview of gastroenterologist+clinic visit
Vasseur et al ⁴⁰	1988–2004	France	261	CD	Mean 6 (range, 4.3–10.3)	R	Record review
Størdal et al ⁴¹	1990–1998	Norway	33	Both	Mean 5	P	Clinic visits
Hildebrand et al ⁴²	1990–2001	Sweden	152	Both	Average 6 [†]	P	Clinic visits
Pozler et al ⁴³	1990–2001	Czech Republic	470	Both	Average 5 [†]	RP	Record review and confirmation of data
Carvalho et al ⁴⁴	1996–2001	USA	250	Both	Mean 7	RP	Record review, clinic follow-up
Markel et al ⁴⁵	1996–2007	USA	51	UC	Average 5 [†]	R	Record review
Mesker et al ⁴⁶	1998–2007	The Netherlands	43	CD	Mean 5	R	Record review
Tietjen et al ⁴⁷	NA 2008 published	Germany	40	CD	Mean 5.6 (range, 0.67–16.7)	R	Record review

* Population-based studies.

[†] Used if study did not clarify specifically mean/median.

CD indicates Crohn's disease; IBD, inflammatory bowel disease; NA, not applicable; P, prospective; PY, patient-years; R, cross-sectional retrospective; RP, retrospective prospective; UC, ulcerative colitis; US, United States.

TABLE 2
Growth Failure in Patients With Pediatric-onset Crohn's Disease and Ulcerative Colitis at Diagnosis and End of Follow-up

References	Definition of Growth	Failure CD Growth	Failure at Dx	CD Growth Failure at FU	UC Growth Failure at Dx	UC Growth Failure at FU
Puntis et al ⁷	Ht and Wt < 3rd%ile	31%		15%	N/A	N/A
Homer et al ⁸	No linear growth > 1 y or Ht < 2SD below mean	38% (preoperative)		32% (postoperative)	N/A	N/A
Castile et al ⁹	Ht %	Mean Ht < nl population * Mean Ht of surgical CD=nonsurgical CD		Surgical CD (6%) Nonsurgical CD (8.4%)	N/A	N/A
Langholz et al ¹⁴	Ht and Wt < 5th%ile	13%		26%	4%	0%
Gryboski and Spiro ¹⁵	Ht < 3rd%ile	33%		21%	N/A	N/A
Barton and Ferguson ¹⁷	Ht and Wt<3rd %ile	Ht: 28% Wt: 56%		Ht: 22% Wt: 40%		Ht: 17% Wt: 0%
Ferguson and Sedgwick ¹⁹	Self-assessment (# reporting delay comparing to peers)	N/A		48%	N/A	25%
Markowitz et al ²¹	2 of 3: Ht/age curves, BP method*, RWT method	N/A		37%	N/A	10%
Bland et al ²⁶	Ht z score < 0 (Ht < 50%)	2%		NA "majority"	2%	>50%
Gryboski ²⁷	<1SD in Ht % bone age retardation > 2 SD	45%		10%	N/A	N/A
Gryboski ²⁸	< 1SD in Ht % Bone age retardation > 2SD	N/A		N/A	5%	0%
Mamula et al ²⁹	Ht < 5th %ile	N/A		29%	N/A	3%
Vasseur et al ⁴⁰	Ht z score	9.5%		6.9%	N/A	N/A
Pozler et al ⁴³	Ht z score r1.5	N/A		15%	N/A	7%
Mesker et al ⁴⁶	Ht z score – 1.64 (5th %ile)	9.5%		16.3%	N/A	N/A
Tietjen et al ⁴⁷	Ht < 3rd %ile	N/A		75%	N/A	N/A

RWT method: midparental height (mother's height + father's height)/2 in addition to BP method information.

* BP method: skeletal age, chronological age, and height.

%ile indicates percentile; BP, Bayley-Pinneau; CD, Crohn's disease; Dx, diagnosis; FU, follow up; N/A, not applicable; nl, normal; Ht, height; RWT, Roche-Wainer-Thissen; UC, ulcerative colitis; Wt, weight.

TABLE 3

Cancer in Studies of Pediatric-onset IBD

References	Study Date	No. Patients	No. Reported Cancer	Type
Ahsgren et al ¹¹	1961–1990	32 UC	0	
Falcone et al ²⁴	1975–1990	73 UC	0	
Gower-Rousseau et al ³⁸	1988–2002	113 UC	1	Stage I rectal adenocarcinoma: male age 14
Gryboski ²⁷	1977–1990	38 UC 40 CD	1	Metastatic breast carcinoma: colonic CD, 6 y after diagnosis
Gryboski ²⁸	1977–1990	38 UC	0	
Hyams et al ¹⁶	1967–1994	171 UC	2	Metastatic colon adenocarcinoma: age 27 male, UC, 25 y after diagnosis Duke C colon adenocarcinoma
Jakobsen et al ¹³	1962–1987	77 UC 42 CD	2	Colon adenocarcinoma (age 21 male, UC, 10 y after diagnosis) Colon adenocarcinoma (age 15 male, UC, 3 y after diagnosis)
Langholz et al ¹⁴	1962–1987	80 UC 23 CD	1	Sigmoid adenocarcinoma: UC
Mamula et al ²⁹	1977–2000	36 UC 27 CD 19 IC	2	Cecal Duke B adenocarcinoma age 32, UC, 26 y after diagnosis Cholangiocarcinoma: UC, 25 y after diagnosis and PSC 9 y after diagnosis
Pigneur et al ²³	1974–2007	206 CD	5	Colon adenocarcinoma (3) Small bowel adenocarcinoma (2): mean age 36.2±10.9 y
Vernier-Massouille et al ³⁹	1988–2002	404 CD	0	

CD indicates Crohn's disease; IBD, inflammatory bowel disease; IC, indeterminate colitis; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

TABLE 4

IBD-related Deaths Reported in 17 Studies of Pediatric-onset IBD

References	Study Date	UC	CD	Total	Death Rate (per 100 PY)	IBD-related Cause of Death
Puntis et al ⁷	1935–1980	NA	7	7	0.002	Diffuse small bowel disease (6), perforation (3) (2 colon, 1 small bowel)
Castile et al ⁹	1950–1973	NA	16	16	0.3	Malnutrition (7), GI perforation (2), bowel obstruction (2), bleeding (2), peritonitis (2), pulmonary embolus (1)
Farmer and Michener ¹⁰	1955–1974	NA	13	13	1.25	Sepsis (12), postoperative (1)
Absgren et al ¹¹	1961–1990	1	NA	1	0.1	Fulminant colitis; death after surgery
Lindberg et al ¹²	1961–2005	2	NA	2	0.2	Cholangiocarcinoma (1) (UC and PSC; 7 y), Fulminant UC (1)
Jakobsen et al ¹³	1962–1987	4	NA	4	0.25	Not mentioned
Langholz et al ¹⁴	1962–1987	2	0	2	0.07	Cerebral hemorrhage after colectomy (1), colon cancer in UC (1)
Hyams et al ¹⁶	1967–1994	1	NA	1	0.0002	Not mentioned
Barton and Ferguson ¹⁷ Ferguson and Sedgwick ¹⁸	1968–1983	1	6	6	0.36	UC; obstruction, perforation, bacteremia; CD: bowel obstruction + bacteremia (1), peritonitis + bacteremia (2), depression + malnutrition (1), abscess + bacteremia (1)
Pigneur et al ²³	1974–2007	NA	2	2	0.03	Short bowel syndrome (1), postoperative septic complications (1)
Bland et al ²⁶	1976–1995	1	NA	1	0.05	Not mentioned
Gryboski ²⁷	1977–1990	NA	0	0	0	—
El-Baba et al ³⁰	1979–1992	NA	NA	0	0	—
Sedgwick et al ³⁴	1983–1987	1	NA	1	0.54	Small bowel obstruction, perforation, sepsis
Gower-Rousseau et al ³⁸	1988–2002	1	NA	1	0.06	Hepatic failure in PSC
Vernier-Massouille et al ³⁹	1988–2002	NA	0	0	0	—

CD indicates Crohn's disease; GI, gastrointestinal; IBD, inflammatory bowel disease; NA, not applicable; PSC, primary sclerosing cholangitis; PY, patient-years; UC, ulcerative colitis.