AN EPIDEMIOLOGICAL STUDY OF PEDIATRIC-ONSET CROHN'S DISEASE: RELATIONSHIP BETWEEN NATURE OF DISEASE AND OUTCOME

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AN EPIDEMIOLOGICAL STUDY OF PEDIATRIC-ONSET CROHN'S DISEASE: RELATIONSHIP BETWEEN NATURE OF DISEASE AND OUTCOME

By

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Abstract

Objective: To identify baseline variables predictive of severity of pediatric-onset Crohn's disease during the first year following diagnosis.

Study Design: Prospective inception cohort study.

Participants/Setting: Pediatric patients (aged <17 years) newly diagnosed with Crohn's disease at the Hospital for Sick Children, Toronto, Canada from July 1997 - May 2001.

Methods: The primary outcome variable was disease severity as measured by Physicians Global Assessment (quiescent/mild, moderate/severe). The influence of pre-selected baseline variables (gender, disease location, laboratory parameters, initial corticosteroid therapy, response to initial therapy and PCDAI scores) on disease severity was determined by multivariate analysis.

Results: In follow-up of 122 patients, 73 had quiescent/mild disease and 49 moderate/severe disease. Univariate analysis demonstrated moderate/severe disease was associated with low albumin ($p=0.004$), high PCDAI ($p<0.001$), initial hospitalization ($p=0.004$), initial corticosteroids use ($p=0.003$) and partial/no response to initial therapy ($p=0.028$). In multivariate regression analysis, PCDAI score was the best single predictor of subsequent disease severity ($p<0.001$, $R^2=0.16$).

Conclusion: Disease activity at diagnosis is predictive of disease severity during the first year in pediatric-onset Crohn's disease.

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I dedicate this thesis to my parents, William and Shirley, and to my wife Cheryl.

To my parents, who impressed upon me the importance of learning and created a home where all things became possible. They have been my role models and my heroes.

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Chapter 1 - INTRODUCTION

1.1 INTRODUCTION

Crohn's disease (CD) is an idiopathic chronic relapsing disorder of the gastrointestinal tract. It is a heterogeneous condition with considerable variability noted both in its phenotypic expression and clinical course. Up to 25 percent of cases present during childhood and adolescence (1) and can be associated with significant morbidity as manifested by debilitating symptoms, frequent hospitalizations, growth retardation and need for surgical interventions (2-4). Despite the wide range in clinical course, little work has been done to identify prognostic factors of disease severity.

In the subsequent pages, the current understanding of the etiology and epidemiology of Crohn's disease will be reviewed with a focus on pediatric-onset disease. Studies describing the clinical course and associated morbidity of Crohn's disease will be critically analyzed, so as to determine the spectrum of illness associated with this condition. Current therapeutic algorithms will be presented with emphasis placed on the evolution of new therapeutic paradigms and how treatment selection is determined in part by disease activity and severity. Finally, studies conducted to identify prognostic factors of disease severity will be reviewed, as such information may prove important in the selection of the most appropriate therapeutic modalities for any individual patient. This discussion will form the foundation for the argument defending the purpose of this thesis.

1.2 BACKROUND

1.2.1 Description of Crohn's Disease

Crohn's disease, together with ulcerative colitis (UC), accounts for the majority of cases of chronic intestinal inflammation occurring in humans. The etiology(s) has not been identified, though accumulated evidence supports a multi-variable model involving complex interactions between genetic and environmental factors (5-9). Recent research supports the theory that the underlying pathophysiology involves an inappropriate and ongoing activation of the mucosal immune system propagated by the normal luminal flora. This aberrant response most likely develops secondary to defects in both the barrier function of the intestinal epithelium and the mucosal immune system (10).

Crohn's disease is heterogeneous, encompassing a wide spectrum in its phenotypic expression. Classically, patients present with the triad of symptoms of diarrhea, abdominal pain and weight loss. However, many pediatric patients present with growth failure, pubertal delay, iron deficiency anemia, anorexia, perianal disease or arthritis as the predominant symptom (11).

The anatomical site of intestinal involvement also varies widely in Crohn's disease. Six hundred ninety-two children and adolescents were evaluated at the Hospital for Sick Children, Toronto from 1980-1999. Forty-one percent had macroscopic disease involving the small bowel only, 40 percent had ileocolonic disease, and 19 percent had disease limited to the colon (12). Barton et al (13) reported similar findings in pediatric-onset Crohn's disease (small bowel only 30%, large and small bowel 38%, colon only

28%). Similarly, 30-35 percent of adults are reported to have small bowel disease and 25-35 percent isolated colonic disease (14). Perianal disease and fistula formation occurs in one third of patients over time (15).

Unfortunately, no gold standard exists to confirm the diagnosis. Hence, Crohn's disease is currently defined empirically on the basis of compatible clinical, radiologic, endoscopic and histologic features, after the exclusion of other etiologies (16;17). Advancements in flexible endoscopy allow for easily obtainable biopsies, improving diagnostic accuracy. Despite this, differentiation between ulcerative colitis and isolated colonic Crohn's disease may initially be difficult in 10-15 percent of patients (18).

1.2.2 Epidemiology

The worldwide distribution of Crohn's disease and ulcerative colitis is similar, with the highest incidence rates reported in North America (7.0-14.6/100,000) and Northwestern Europe, especially Scandinavia (5.8-15.6/100,000) and the United Kingdom (3.8-22.1/100,000) (19-27). Bernstein et al (20) performed a population-based study (1989-1994) in the province of Manitoba and measured the incidence and prevalence rates for Crohn's disease to be 14.6/100,000 and 198.5/100,000 respectively.

The incidence of Crohn's disease peaks during the second decade of life, with a subsequent smaller rise during the fifth decade (19;28). Notably, up to 25 percent of cases clinically manifest in patients under the age of twenty (1). The majority of these present in late childhood and adolescence, though occurrence even during infancy has

been reported (29-33). Incidence rates of pediatric-onset Crohn's disease during the 1980's range from 1.7-2.5/100,000 and for ulcerative colitis from 0.7-4.3/100,000 (34-36). Bernstein et al (20) measured the incidence rate for Crohn's disease in children <10 years of age and between 10-19 years to be 0.7/100,000 and 12.7/100,000 respectively. The prevalence rate was found to be 1.77/100,000 and 55.8/100,000 for children <10 years old and between 10-19 years old respectively.

Epidemiological studies have documented changes in the incidence/prevalence of the inflammatory bowel disease (IBDs) over time. The incidence of Crohn's disease increased sharply in all age groups in most Western populations between the 1950's and the 1980's, while the incidence of ulcerative colitis did not change (37). A threefold rise in the incidence of Crohn's disease among Scottish children between 1968 and 1983 and a fourfold increase in the incidence of Crohn's disease in youth below age 19 in Sweden between 1959 and 1974 have been reported (3). Recently, Timmer et al observed a stable incidence of Crohn's disease in Germany from 1980 to 1995, but did note significantly more involvement of the sigmoid and rectum over this period (38).

The variations in incidence and prevalence rates reported among the different studies may relate to differences in the genetic and/or environmental risks of the populations analyzed. However, introduction of measurement bias in the study design could account for the observed variation. Measurement bias may occur at a number of levels, including population selection, disease definition, case ascertainment, method and quality of data selection, duration of assessment and statistical evaluation (19).

For instance, increased awareness of inflammatory bowel disease and improvements in diagnostic techniques, especially endoscopy, make it difficult to compare rates between studies over time (19). Variability in health care delivery, with limitation of diagnostic access to segments of the population may in part account for the lower incidence rates observed in developing countries (19;39). In general, data collection in prospective studies is of a higher quality than that of retrospective studies (40). In comparing incidence and prevalence rates between different regions, crude rates can be misleading due to the age dependency. As such standardized rates should be looked at, adjusting the crude rate for the population demographics (40).

It is important to adhere to several other principles when designing epidemiological studies of Crohn's disease. Most importantly, population-based studies are necessary to accurately estimate the incidence and prevalence of disease. Unfortunately, many early studies were hospital-based and were likely to underestimate incidence and prevalence but overestimate disease severity. The relatively long duration between onset of symptoms and diagnosis of inflammatory bowel disease will also lead to underestimation of incidence and prevalence during any given time period (19;41).

Consistently applied definitions of disease are also necessary. As no gold standard exists for the diagnosis of inflammatory bowel disease, misclassification and reclassification can be problematic. As previously noted, 10-15 percent of colitis cases are initially classified as 'indeterminate'; and up to 3 percent of patients with Crohn's disease or ulcerative colitis are reclassified during follow-up (19;42). Outcome variables

must be carefully selected. They must be validated and ideally standardized to facilitate comparisons among studies.

1.3 IMPACT OF DISEASE

1.3.1 Natural History/Clinical Course

Crohn's disease is characterized by a pattern of exacerbations and remissions. However, there is considerable intra-patient and inter-patient heterogeneity in its clinical course. The spectrum ranges from one of relatively mild symptoms with infrequent exacerbations to chronic unremitting disease activity that is refractory to treatment. The basis of the heterogeneity is unknown but may relate to different etiologies and/or disease modifiers, either environmental and/or genetic.

Truelove et al (43) reported on the clinical course and prognosis of Crohn's disease in a cohort retrospectively assembled using diagnostic codes from two regional hospitals in Oxford, Britain from 1938-1970. Three hundred and three patients with Crohn's disease were originally identified, of which 82 were excluded due to inadequate records. One hundred sixty-six were newly diagnosed patients, the remainder being referred for management of established disease. Of the 166 newly diagnosed patients the mean duration of follow-up was 9.1 years. Twenty-eight patients (12.7%) were less than 20 years of age at diagnosis. Due to the prolonged period of recruitment, therapy regiments changed quite significantly in the cohort. During the earlier years, treatment consisted of vitamin supplements, control of diarrhea and correction of anemia. Specific measures were introduced in the 1950s with the use of sulphasalazine and corticosteroids.

Practices with these therapies varied widely, with differing doses and lengths of treatment. Immunosuppressives drugs were used very infrequently during the time frame of this study. Diagnostic criteria also differed from those currently employed, and were based upon a compatible clinical complex with definite radiological, operative or histological evidence to support the diagnosis.

Relapse rate was not assessed. Seventy-four percent of new cases underwent surgery during follow-up. Local problems included fistula formation (14.5%), abscess (10.2%), intestinal obstruction (5.4%), perforation (1.2%) and carcinoma (2.4%). Twelve patients died from problems of Crohn's and 5 others from probable problems of Crohn's disease. The cumulative mortality rate for newly diagnosed Crohn's disease patients over a 15-year follow-up was 18.0 percent, compared to 8.1 percent for age and sex matched controls. Age did not appear to have any effect on prognosis in terms of survival over a five-year period, though females had a cumulative fatality rate of 4.6 percent over 5 years compared to 0.6 percent for males (newly diagnosed cases). Statistical comparisons were not made.

While the study did illustrate the clinical course with respect to surgical intervention and mortality relatively well, weaknesses of this study included imprecise diagnostic criteria and failure to assess relapse and remission rates. Forty-six patients (20.8%) did not have histology collected and this may have lead to inaccurate diagnoses. Eight-two patients (27%) were not analyzed secondary to inadequate records and this is a potential source of bias in assessing clinical outcomes. Furthermore, the study was

retrospective and assembled over a period of 32 years during which time treatment regimens changed dramatically and differed significantly from those currently used. As such, the applicability of this data to present populations is tenuous. Moreover, the study primarily described adult-onset disease, which may preclude its generalization to pediatric-onset disease.

In a separate study, Munkholm et al (44) described the clinical course of inflammatory bowel disease in a regional inception cohort of 373 Crohn's disease patients diagnosed in Copenhagen County, Denmark from 1962-1973. Only two patients were excluded due to inadequate data. Patients were followed up regularly from diagnosis with a mean follow-up of 8.5 years (range 0-26 years). Diagnosis was standardized and patients were treated with combinations of sulphasalazine, corticosteroids and surgery. Immunosuppressants were infrequently used during this study period.

Disease activity was assessed for each year, based on the maximal activity during that year. Disease activity was categorized as no activity, low activity or moderate/high activity (Table 1.1). Additionally, disease course during the previous year was categorized as relapse-free, chronic-intermittent or chronic continuous (**Table 1.1**).

Eighty percent of patients had high activity in the initial year of diagnosis. In subsequent years, approximately 30 percent had high activity, 15 percent low activity and 55 percent were in clinical remission. No differences were noted between those patients

Table 1.1 Disease Activity and Disease Course Definitions, Munkholm et al (44)

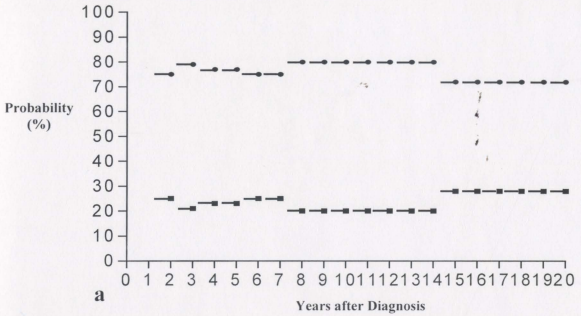
Outcome	Definition
Disease Activity	
- No Activity	</= 2 stools/day and no blood or pus in the stools. No abdominal pains and no systemic symptoms such as fever or weight loss
- Low Activity	<5 and >2 stools/day and/or blood or pus in the stools and/or mild abdominal pain less than daily; no systemic symptoms such as fever or weight loss
- Moderate/High Activity	> 4 stools/day and/or passage of blood or pus daily and/or abdominal pains either severe or daily, with (high) or without (moderate) systemic symptoms such as fever or weight loss
Disease Course	
- Relapse Free Course	No clinical activity in any year after the year of diagnosis
- Chronic Intermittent Course	Either a) years with intermittent activity – that is, remission for more than 1 month (without corticosteroid treatment) or b) years without disease activity between years with activity
- Chronic Continuous Course	Continuous activity within and during each year of follow-up

with relapses and those in remission with regard to age, gender, year of diagnosis, localization of Crohn's disease or histological evidence of disease.

While individual patients changed from year to year between relapse and remission, disease activity in the preceding year was related to that in the subsequent year. Seventy to 80 percent of patients with active disease in one year were observed to have active disease in the following year. Likewise, approximately 80 percent of patients in remission remained so the following year (**Figure 1.1**).

The strengths of this study are its large sample size and the fact that it is population-based thus eliminating referral bias. Importantly the treatment was standardized. Unfortunately, the sample size was collected over a period of 25 years prior to the use of immunosuppressive therapy. Thus, the results may not be applicable to present day practice where immunosuppressive are more frequently used. Additionally, the study was predominantly adult based and therefore may not be representative of pediatric-onset disease. Finally, the study did not attempt to identify baseline predictive factors such as disease activity and initial response to therapy.

More recently, Faubion et al (45) studied a population-based inception cohort of 171 patients diagnosed with Crohn's disease in Olmsted County from 1970-1993 to assess the outcomes during a one-year period in the 74 patients (43.3%) requiring the initiation of systemic corticosteroids. Immediate outcomes were assessed at thirty days and one year following the initiation of corticosteroids (**Table 1.2**).



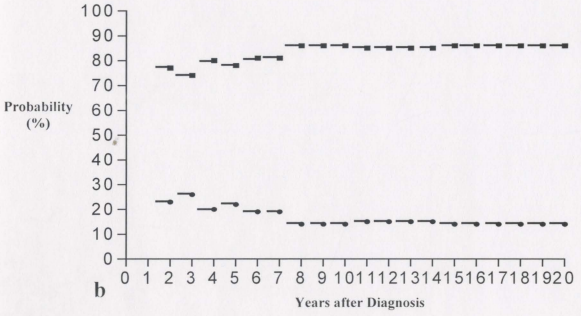


Figure 1.1 One-year probabilities of active disease (—●) or remission (—■) the following year, provided: active disease the previous year (1.1a) or remission the previous year (1.1b). A Markov analysis (41).

Table 1.2 Disease Activity and Disease Course Definitions, Faubion et al (45)

Outcome	Definition
Immediate Outcome	
- Complete Remission	Total regression of clinical symptoms (</= 2 stools/day; no blood, pus or mucus in feces; and no abdominal pain, fever, weight loss or extraintestinal symptoms).
- Partial Remission	Regression of clinical symptoms (</= 4 stools/day; blood, pus, mucus in feces; or abdominal pain; or all 4 less than daily and no systemic symptoms, such as fever or weight loss).
- No Response	No regression of clinical symptoms.
One-Year Outcome	
- Prolonged Response	Maintenance of complete or partial remission after steroid therapy was completed. Patients who required subsequent courses of steroids but maintained complete or partial response and were steroid free at the end of 1 year were included in the prolonged response outcome group.
- Steroid-Dependent	Continued steroid therapy at year-end caused by relapse after steroids were discontinued or caused by relapse at dose reduction impeding discontinuation of steroid therapy. Patients who required surgical resection (see below) and were also steroid dependent at 1 year were counted in the surgical resection group.
- Surgical Resection	Relapse within 1 year after steroid therapy was initiated, resulting in surgical resection.

Forty-three patients (58%; 95% CI, 46%-69%) were in complete remission, 19 (26%; 95% CI, 16%-37%) were in partial remission and 12 (16%; 95% CI, 9%-27%) had no response after 30 days. Age, gender, interval to corticosteroid therapy from diagnosis or disease extent were not associated with immediate outcome. Concomitant therapy with mesalamine or sulfasalazine however, was a statistically significant predictor of immediate outcome (OR 0.35 for combined partial or complete response, 95%CI 0.13-0.96, p=0.04).

One year after initiation of corticosteroid therapy, 24 patients (32%; 95% CI, 22%-44%) had sustained a prolonged response, 21 (28%; 95% CI, 19%-40%) were corticosteroid dependent, 28 (38%; 95% CI, 27%-50%) had undergone surgical resection and one (1%) was lost to follow-up. No risk factor was identified to be predictive of one-year outcome following the initiation of corticosteroid therapy.

Strengths of this study are the well-defined outcome variables and that it is population-based. The number of patients lost to follow-up was low (1 patient). As the study was conducted on patients diagnosed and treated before 1994, the use of immunosuppressive therapy on the outcome of disease could not be assessed as only two (3%) Crohn's disease patients had received immunosuppressants. Furthermore, the cohort was not solely composed of patients with newly diagnosed disease.

In another study, Moum et al (46) described the clinical course of Crohn's disease patients during the first year following diagnosis. Two hundred and thirty two patients

were diagnosed with Crohn's disease from 1990 - 1993, and represented a population-based cohort in southeast Norway. Two hundred and twenty two of these patients were followed prospectively for a mean of 16.2 months (range: 12-23 months). Relapse was defined as a change in the clinical status of the patient that entailed more aggressive medical treatment or surgery, whereas remission was defined as recovery from the initial treatment without clinical relapse until the end of follow-up.

The cumulative relapse rate between the time of diagnosis and 12 months follow-up was 47 percent. Of those who did not have sustained remission during follow-up, 23 percent had greater than two relapses with 10 percent experiencing a chronic relapsing course (> 5 relapses).

No differences were noted in the relapse rate based on disease location (colonic only, small bowel only or small and large bowel disease), gender (p= 0.912), duration of symptoms prior to diagnosis (p=0.834), or age (</= 50 years, >50 years, p=0.878). Risk of surgery was not related to age, however patients with small bowel involvement only had a higher risk of surgery compared to those with colon only disease (p=0.021). No difference in rate of relapse or surgery was noted between smokers and non-smokers.

The strong points of this study are its relatively large sample size, uniform criterion for diagnosis and therapy, low drop out rate (10 patients), prospective design and population-based recruitment. The major weakness is its outcome variable of relapse and that many relapses may have gone undetected if the patients did not present

themselves for evaluation. Again, the study is predominantly adult based. Unfortunately the authors did not report on the number of pediatric patients included in the study, but it was likely low as the median age was 30 years, interquartile range 22.5-47.5 (47). Furthermore, the authors did not evaluate the relationship between disease activity at diagnosis and relapse rate. The ability to extrapolate this information to current practices is limited since immunosuppressants including azathioprine were not used as maintenance therapy in this study.

In a fifth study, Griffiths et al (48) reported on the two-year clinical course of a prospectively compiled cohort of 100 consecutive, pre-pubertal patients with newly diagnosed Crohn's disease from 1980 - 1988 in Toronto, Canada. Disease severity was assessed during each year as; quiescent (no gastrointestinal or extraintestinal symptoms reported; normal complete blood count and erythrocyte sedimentation rate), mild (some symptoms but not needing prednisone treatment), moderate (intermittent symptomatic exacerbations warranting prednisone or nutritional therapy) and severe (chronic unremitting symptoms warranting prednisone or alternate treatment). Influence of disease severity on linear growth velocity was also assessed.

Fourteen patients had quiescent, 54 mild, 23 moderate and 9 severe disease activity during the first year following diagnosis. Similarly, 23 patients had quiescent, 42 mild, 25 moderate, and 9 severe disease activity during the second year following diagnosis. Disease severity was determined to be a significant factor influencing growth velocity during both the first and second years following diagnosis ($p<0.01$).

The strengths of this study include the relatively large sample size, uniform diagnostic and outcome criterion, low-drop out rate (1 patient) and evidence that it represented a population based sample. It was unique to the other studies in that a pediatric cohort was assembled. While it clearly described the clinical course of pediatric-onset Crohn's disease in the pre-immunosuppressant era, the results may not be readily extrapolated to the present day. Furthermore, the study was not designed to evaluate factors predictive of disease severity.

1.3.2 Morbidity

While inflammatory bowel disease has a low mortality rate (though some investigators have reported it to be higher than that of the general population (49)) the chronic nature of this disease can result in significant morbidity (50). The morbidity results from complications of the disease and/or therapy.

Complications of Crohn's disease include the development of arthritis/arthralgias in 15 percent of patients (51), cutaneous manifestations (erythema nodosum, pyroderma gangrenosum) (52), acute uveitis (51;52), urinary stones (53) and hypercoagulability with development of deep vein thrombosis, pulmonary emboli and cerebrovascular disease (54). Decreased bone mineral density is also a recognized complication of Crohn's disease with osteopenic levels present in 25 percent of newly diagnosed children with Crohn's disease (55;56).

Crohn's disease is associated with an increased risk for colorectal cancer (57;58). In addition, Bernstein et al (58) in a population-based study demonstrated an increased incidence rates ratio for carcinoma of the small bowel in Crohn's disease patients (17.4; 95% CI, 4.16-72.9). There is conflicting data as to whether Crohn's disease is associated with an increased risk of lymphoma (59). Bernstein et al (58) calculated an increased rates ratio for lymphoma in males with Crohn's disease (3.63; 95% CI, 1.53-8.62). In contrast, a more recent cohort study from the United Kingdom of 6605 patients with Crohn's disease followed for 3.7+/-2.4 years did not show an increased risk for lymphoma (60), though follow-up may have been too short to adequately assess this.

Additionally, two unique aspects of childhood Crohn's disease may increase the risk for morbidity in pediatric patients. First, the need for children and young adolescents to rapidly accrue lean body mass for growth and development makes them particularly vulnerable to the adverse nutritional consequences of chronic inflammation (61). Malnutrition and growth impairment are frequently observed problems of childhood Crohn's disease (48;62). Second, development of Crohn's disease at an early age carries the fundamental implication of a long life ahead with an increased risk of long-term complications (63).

Crohn's disease is also associated with significant financial costs, both directly from medical and surgical therapies and indirectly through lost days of work. In 1999, Silverstein et al (50) estimated the lifetime costs of medical therapy for a representative patient with Crohn's disease to be US$ 125 404 using mean charges and US$ 39 906 using median charges.

As illustrated in **Table 1.3**, the therapies used in Crohn's disease are also associated with significant adverse effects that may further add to the morbidity experienced by Crohn's disease patients. The need for surgical intervention is also high, with up to 80 percent of patients requiring surgical resection within the first three years following diagnosis (64). Unfortunately, recurrence is common, with greater than 80 percent having endoscopic recurrence and more than one third experiencing symptomatic recurrence within three years following resection (65). As a result many patients require multiple operations with the associated complications and morbidity.

Table 1.3 Side-Effect Profile of Crohn's Disease Therapies

Drug	Side-Effect Profile
Sulphasalazine	Nausea, vomiting, headaches, mild hemolysis, fever, Stevens-Johnson syndrome, pulmonary fibrosis, hepatotoxicity, agranulocytosis, reversible impairment of male fertility, exacerbation of colitic symptoms, reduced folate absorption
5-ASA	Fever, rash, exacerbation of colitic symptoms, acute pancreatitis
Antibiotics	Nausea, vomiting, increased antimicrobial resistance
Oral prednisone	Acne, moon facies, hirsutism, cutaneous striae, pseudotumor cerebri, steroid psychosis, proximal myopathy, hypercalcuria, aseptic necrosis of femoral head, osteopenia, growth delay, cataracts, hyperglycemia, Addisonian crisis
Azathioprine/6-mp (adjunctive to steroids)	Fever, pancreatitis, nausea, vomiting, leukopenia, thrombocytopenia, infection, hepatitis
Methotrexate (adjunctive to steroids)	Nausea, increased liver enzymes, impaired folate metabolism, hypersensitivity pneumonitis

1.4 THERAPY

1.4.1 Therapeutic Goals

At present there is no cure for Crohn's disease. As such, the goals of treatment are to induce remission and subsequently maintain remission while minimizing therapeutic complications and optimizing patient quality of life (66,67). A wide variety of medications are currently available with proven efficacy for induction and/or maintenance of clinical remission (**Tables 1.4 and 1.5**). In general, these include medications with anti-inflammatory properties, immunosuppressant properties and those with both.

1.4.2 Current Treatment Paradigms

The variable natural history of Crohn's disease and the possibility of spontaneous remissions and exacerbations make treatment selection difficult. Initial treatment algorithms currently advocate a 'step-up' approach (**Figure 1.2**), basing the selection of therapy primarily on disease activity. Less potent medications such as antibiotics and 5-aminosalicylates are used for milder disease activity. More potent medications such as systemic corticosteroids and enteral nutrition are reserved for moderate-severe disease activity. Immunomodulating pharmacotherapy with azathioprine, 6-mercaptupurine (6-mp), methotrexate or tacrolimus (FK506) are introduced later for intractable or relapsing symptoms. Surgical intervention is used for those patients with medically refractory disease or complications such as fistulization and/or stenosis.

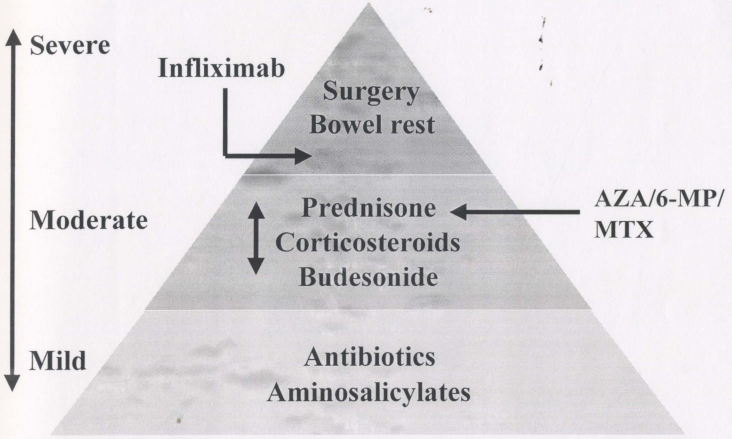
More recently, novel medications with specificity for intermediate metabolites in the inflammatory cascade have been developed, and include infliximab (an anti-

Table 1.4 Induction of Remission in Crohn's Disease (11;68;69)

Drug	Dose	Response (%)
5-ASA	4 g/d	43
Antibiotics	?	40-50
Oral prednisone	1-2mg/kg (60mg)	60-78
Azathioprine/6-mp (adjunctive to steroids)	AZA 2-3 mg/kg/day 6-mp 1.5mg/kg/day	36-65
Methotrexate (adjunctive to steroids)	25 mg/wk im/sc	39-54
Enteral Nutrition	-	50-75%
Placebo	-	8-50

Table 1.5 Maintenance of Remission in Crohn's Disease (68-70)

Drug	Dose	Response (%)
5-ASA	1.5 - 4 g/d	25-69
Oral prednisone	-	No Benefit
Azathioprine/6-mp	2.5(1.5) mg/kg/day	40-85
Methotrexate (methotrexate responders)	15 mg/wk	39-54
Placebo	-	35-64



Adapted from Hanauer. http://www.medscape.com

Figure 1.2 Conventional 'Bottom-Up' Therapeutic Paradigm

TNF-alpha chimeric antibody) and etanercept (a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1). Such therapies are currently reserved for patients who have had an unsatisfactory response to conventional immunosuppressants.

1.4.3 Early Introduction of Immunosuppressive Therapy?

With increased understanding of the pathogenesis of Crohn's disease, researchers hope to improve its clinical course and decrease morbidity. While several studies (70-74) have established a benefit for immunosuppressive agents in inducing and maintaining remission in steroid-dependent and refractory Crohn's disease, more recently researchers have sought to study the effect of the early introduction of immunosuppressants on clinical course.

Markowitz et al (75) in a double-blinded trial, prospectively randomized newly diagnosed pediatric-onset Crohn's disease patients who were to be started on systemic corticosteroids to receive either concomitant therapy with 6-mercaptopurine (n=27) or placebo (n=28). Moderate-severe disease was defined as partial Harvey-Bradshaw (HB) index >/=5. Remission was defined as 2 successive monthly total HB scores of <3, and relapse as 2 successive scores (obtained no closer than 1 week apart) of >/=4.

Remission was induced in 89 percent of patients in both groups. Of interest, over a follow-up period of up to 548 days, 9 percent of remitters in the 6-mercaptopurine

group relapsed as compared to 47 percent of controls ($p=0.007$) (**Figure 1.3**). Furthermore, in the 6-mercaptopurine group, the duration of steroid use was shorter ($p<0.001$) and the cumulative steroid dose lower at 6, 12 and 18 months ($p<0.01$).

In a separate study, Kugathasan et al enrolled fifteen children (6-18 years) with medically-refractory Crohn's disease into a prospective open-label trial to receive a single 5mg/kg dose of infliximab (76). Medically-refractory disease was defined as the inability to tolerate steroid taper, disease activity measured on the Pediatric Crohn's Disease Activity Index (PCDAI) as a score >/=30 and no improvements despite the use of immunomodulatory therapy (6-mp, methotrexate and/or cyclosporine A) for >/=4 months. Clinical relapse was defined as the need for additional medical or surgical therapy to treat the Crohn's and an increase in the PCDAI score by at least 15 points.

By week four following infliximab administration, fourteen patients (93.3%) had improved (decrease in PCDAI </=25 points). Interestingly, of the responders, six (42.9%) had early disease (defined as disease duration <2 years from the time of diagnosis), and eight (57.1%) had late disease. Three (50%) of patients with early disease maintained clinical response through the 12-month trial period compared to none of the eight children with late disease.

There are a number of concerns with both studies. In the study by Markowitz et al, ten patients (15.4%) that were originally randomized were not included in the analysis (7 changed their minds before therapy was initiated; 2 did not keep sufficient follow-up

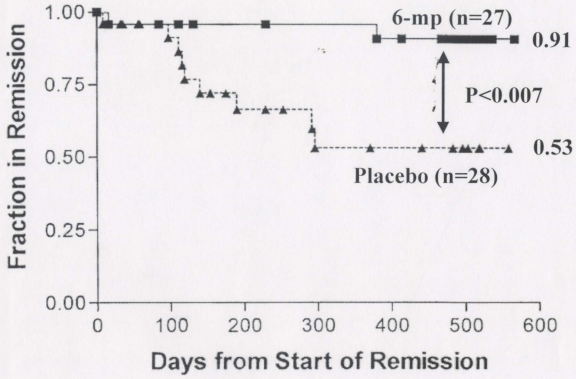


Figure 1.3 Effect of Early Introduction of Azathioprine in Childhood Crohn's Disease (62)

appointments; 1 was withdrawn for non-compliance to therapy). In addition, only 78 percent (21/27) of patients in the 6-mp group and 39 percent (11/28) of controls completed the full 18-month trial. The primary reason for withdrawal was treatment failure (3 6-mp subjects, 15 controls). Both of these factors raise concerns that the results may contain bias secondary to the high withdrawal rates. Furthermore, the study by Kugathasan et al was under-powered (15 patients) preventing generalization of the observations. It was also an open-label study without a control group for comparison. For these reasons the study is particularly vulnerable to bias.

These issues not withstanding, both studies provide preliminary evidence that the use of immunomodulatory medication in patients with moderate-severe, recent-onset Crohn's disease may prolong the duration of clinical remission. The reason for this observation is not known, though data does exist to indicate that the cytokine profile may differ in recent-onset and long-standing Crohn's disease (77). Furthermore, Kugathasan et al demonstrated that mucosal T cells isolated from children with early Crohn's disease were more susceptible to immunomodualtion with IL-12 then were those from children with late Crohn's disease (78). Similarly, Giannini demonstrated that the early use of methotrexate resulted in improved clinical outcome and decreased need for steroids in patients with rheumatoid arthritis (79). All of this data suggests that patients with Crohn's disease (and other immune-mediated diseases) may respond better to early use of immunomodulatory therapies and that the response may be attenuated when used in long-standing disease.

1.4.4 Future Treatment Paradigms

The previous data support the concept that the early introduction of immunosuppressants in Crohn's disease can alter its clinical course by prolonging the duration of remission. This data, along with the introduction of new medications such as infliximab, a chimeric monoclonal anti-TNFalpha antibody, has led many to re-think the current 'step-up' treatment paradigm. Researchers have proposed that a 'step down' therapeutic paradigm (**Figure 1.4**) with the early introduction of immunosuppressants may lead to better clinical outcomes and decreased morbidity.

A major concern with such an approach is that many patients with Crohn's disease who would have a relatively mild clinical course would be exposed to the potential adverse effects of immunomodulator therapy. The issue then is to identify those patients with Crohn's disease that would have a more severe clinical course and therefore may have a more favourable risk:benefit ratio for the early institution of immunomodulator therapy.

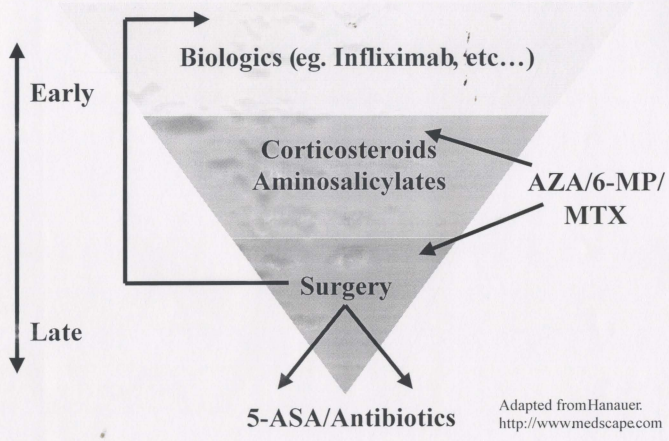


Figure 1.4 Proposed 'Top Down' Therapeutic Paradigm

1.5 PROGNOSTIC INDICATORS OF DISEASE SEVERITY

As previously cited in Section 1.2.1, a number of studies (43-46) have attempted to identify prognostic factors in Crohn's disease. However, no factor at diagnosis was consistently found to be prognostic of future disease outcome.

Truelove et al (43) found that female gender was associated with a higher incidence of mortality over a five-year period as compared to males (4.6% versus 0.6%). Unfortunately, no statistical analysis was performed. Age was not found to be associated with mortality.

Munkholm et al (44) determined that disease activity in any one year was related to the disease activity in subsequent years. They did not however find any relationship between disease course and such variables as gender, age, year of diagnosis, localization of Crohn's disease or histological evidence of disease.

Faubion et al (45) found no relationship between age, gender, interval to corticosteroid therapy from diagnosis or disease extent to the clinical course over a one year period from initial use of corticosteroids. Furthermore, Moum et al (46) determined that relapse rate was not associated with age, gender, duration of symptoms prior to diagnosis or disease location.

Unfortunately all of these studies had significant limitations. First, all were reported on cohorts assembled prior to 1994 when treatment with immunosuppressives

was uncommon. This limits their applicability to present day populations. Second, as all the cohorts were predominantly adult based, the data may not be generalizable to childhood-onset Crohn's disease. Third, the outcome variables of remission and relapse were not standardized therefore limiting the ability to make comparisons between the studies. Furthermore, while the Munkholm (44) study did show a relationship between disease activity in one year with that in subsequent years, no study has evaluated the ability of markers of disease activity, including ESR and albumin, to predict disease severity.

MEDLINE searches failed to identify any study analyzing for the presence of prognostic factors in pediatric-onset Crohn's disease. Of interest, however, Hyams et al (80) published on the clinical course of 171 pediatric patients (age 1.5-17.7 years) with newly diagnosed ulcerative colitis retrospectively compiled from two North American centers from 1975-1994. Forty-three percent had mild disease at presentation (</= 4 stools/day, the presence of blood in the stool less than daily, and no systemic symptoms such as fever or weight loss). Fifty-seven percent experienced moderate/severe disease (>/= 5 stools/day, and the daily presence of blood, with or without the presence of systemic symptoms). Of note, mild disease activity was associated with a significantly lower risk of colectomy ($p<0.03$) compared to those with moderate/severe disease, at one-year (1% versus 9%) and five-year (8% versus 26%) follow-up. This data indicates that in ulcerative colitis, disease activity at diagnosis is predictive of disease severity, as defined by need for colectomy.

Chapter 2 - RATIONALE AND OBJECTIVES

2.1 STUDY RATIONALE

As discussed, few studies have attempted to ascertain epidemiological trends or to characterize the natural history of pediatric Crohn's disease. A well designed study in which baseline characteristics are correlated with subsequent disease pattern and outcomes would help optimize initial treatment recommendations for individual patients.

2.2 POST-HOC ANALYSIS

Prior to conducting a study to identify baseline variables of disease severity, it was decided to assess the relationship between disease severity from year to year in pediatric-onset disease. A cohort of patients with Crohn's disease had previously been assembled at the Hospital for Sick Children, Toronto, Canada to assess the clinical course and growth of Crohn's disease in pre-pubertal children (62). For this thesis, data collected for that study was used to perform a post-hoc analysis with the primary purpose to evaluate the relationship between disease severity during subsequent years.

One hundred sixty-six consecutive Crohn's disease patients (108 males) at Tanner stage I (n=146) and Tanner stage II (n=17) of pubertal development were followed at the Hospital for Sick Children, Inflammatory Bowel Disease Clinic, from January 1990 - December 1999. These patients were identified using a prospectively maintained database of all patients with inflammatory bowel disease seen at the Inflammatory Bowel Disease clinic at the Hospital for Sick Children, Toronto since 1980. At each year for up

to five years of follow-up, patients were classified as having either quiescent, mild, moderate or severe disease (**Table 2.1**) (48).

This annual severity assessment was feasible because of customary follow-up practices in the Inflammatory Bowel Disease clinic. At follow-up visits standardized forms, originally designed to allow regular computation of the Pediatric Crohn's Disease Activity Index (PCDAI), are routinely used to record gastrointestinal symptoms (abdominal pain, diarrhea, weight loss, anorexia, etc.) and extra-intestinal manifestations and treatments. Complete blood count, serum albumin and ESR are regularly measured.

Prior to analysis, attempts were made to ascertain if this cohort represented a population-based study. In the Toronto Census Metropolitan Area, no pediatric gastroenterologist practiced outside of the Hospital for Sick Children prior to 1997 and general pediatricians did not independently manage such patients. In 1997, a survey was mailed out to all practicing adult gastroenterologist in the Toronto Census Metropolitan Area (**Appendix A**) who were listed in the 1997 Membership Directory of the Canadian Association of Gastroenterology (81). The gastroenterologists were asked to provide data on the number of pediatric patients with inflammatory bowel disease that they followed independently of the Hospital for Sick Children for the period of 1980-1990 and 1991-1997. The response rate was 58 percent. Of those gastroenterologists who saw patients less than 15 years of age, none saw more than two patients. If the gastroenterologists who responded to the questionnaire are representative of others in the community, these findings would indicate that the inflammatory bowel disease database captured 95 percent

Table 2.1 Global Assessment of Disease Severity

Severity	Definition
Quiescent	No intestinal (diarrhea, bleeding, abdominal pain) or extraintestinal symptoms reported; normal CBC and ESR
Mild	Some symptoms, but not requiring corticosteroid, enteral nutrition or surgical treatment
Moderate (Exacerbations with remissions)	Symptomatic exacerbations warranting corticosteroid, enteral nutrition or surgical treatment alternating with the occurrence of symptom free intervals of at least one months duration, excluding when the patient received corticosteroid, enteral nutrition or surgical therapy
Severe (Chronically active)	Chronic unremitting symptoms warranting corticosteroid, enteral nutrition or surgical therapy; or the presence of corticosteroids or enteral nutrition at least 50% of the time and recurrence of symptoms when corticosteroids or enteral nutrition is stopped

of children less than 15 years of age at diagnosis in the Toronto Census Metropolitan Area, thus closely approximating a population based cohort. As such, only those patients who resided in the Toronto Census Metropolitan Area and were less than 15 years of age at diagnosis (n=83) were included in the post-hoc analysis of this cohort.

Chi-square analysis and Spearman correlation were performed to assess the relationship between disease severity in any one year with disease severity in subsequent years.

Of these 83 patients the mean age at diagnosis was 10.8 +/- 2.0 years. Twenty-three (27.7%) were female. Twenty-eight (33.7%) had disease limited to the small bowel only, 40 (48.2%) had disease involving both the large and small bowel and 15 (18.1%) had isolated colonic disease. Systemic corticosteroids were used as the initial therapy in 62.7 percent of patients and 71.1 percent of patients required at least one course of systemic corticosteroids during the first year following diagnosis.

During the first year following diagnosis, 18 (21.7%) patients had quiescent disease, 25 (30.1%) mild disease, 23 (27.7%) moderate (intermittent exacerbations) and 17 (20.5%) had severe (chronically active) disease. As demonstrated in **Figure 2.1**, the proportion of patients in each category was similar over each year of follow-up.

As illustrated in **Figure 2.2** and **Table 2.2**, disease severity in any one year was related to that observed in the preceding years. In other words, patients with

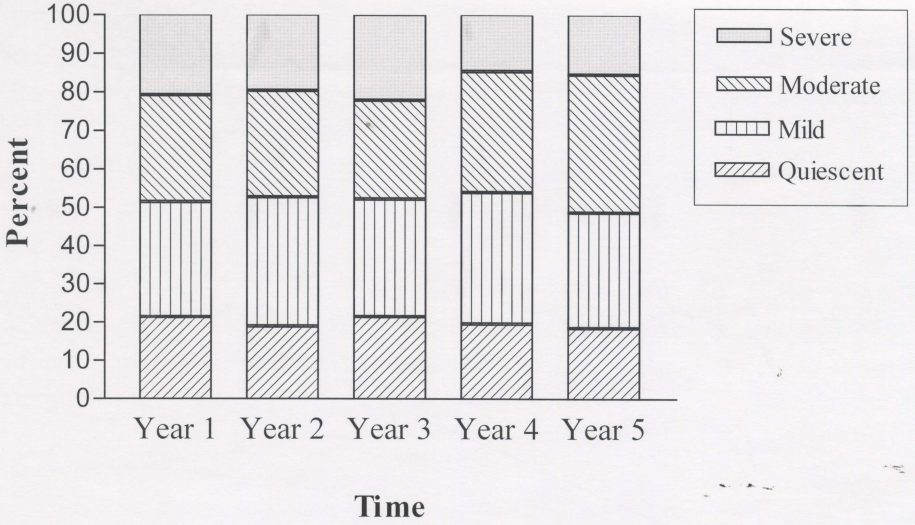


Figure 2.1 Percentage of Patients with Quiescent, Mild, Moderate and Severe Disease During Each Year After Diagnosis.

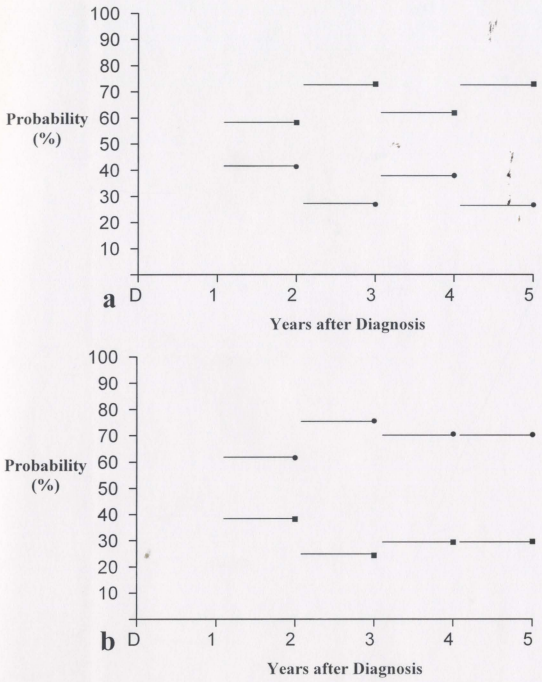


Figure 2.2 One-year probabilities of moderate/severe disease (—■) or quiescent/mild disease (—•) the following year, provided: moderate/severe disease the previous year (2.2a) or quiescent/mild disease the previous year (2.2b).

Table 2.2 Post-Hoc Analysis: Relationship between disease severity in any one year with subsequent years

Initial Year	Subsequent Year	n	χ^2	p	r Spearman	p
1	2	83	27.82	0.0282	0.4334	<0.0001
1	3	78	18.67	0.0042	0.2476	0.0289
1	4	70	28.78	<0.0007	0.2950	0.0132
1	5	53	32.60	0.0002	0.4626	0.0005
1	Over all	83	37.09	<0.0001	0.5447	<0.0001
2	3	78	44.78	<0.0001	0.5112	<0.0001
2	4	70	21.57	0.0103	0.2979	0.0123
2	5	53	14.88	0.0943	0.4047	0.0027
2	Over all	83	48.37	<0.0001	0.5835	<0.0001
3	4	70	43.11	<0.0001	0.5054	<0.0001
3	5	53	23.54	0.0051	0.4194	0.0018
3	Over all	78	61.15	<0.0001	0.5818	<0.0001
4	5	53	45.16	<0.0001	0.6039	<0.0001
4	Over all	70	43.69	<0.0001	0.4311	0.0002
5	Over all	53	33.03	0.0001	0.4963	0.0002

moderate/severe disease in one year were more likely to have moderate/severe disease in subsequent years. The converse was also true, in that those with quiescent/mild disease were more likely to continue to have quiescent/mild disease in the subsequent year. Fifty-eight percent of patients with moderate/severe disease over the first year following diagnosis were more likely to continue to have a moderate/severe disease over the second year. Likewise, 62 percent of patients with quiescent/mild disease over the first year after diagnosis continued to have a quiescent/mild disease during the second year.

The data from the post-hoc analysis clearly demonstrated a relationship between disease severity in consecutive years, which was similar to that described by Munkholm et al (44). However, it is recognized that there does exist significant variability in disease severity that is not explained by prior disease pattern. With this data suggesting a relationship between disease severity from year to year, and the data from Hyams et al (80) demonstrating that disease activity at diagnosis is predictive of colectomy in ulcerative colitis, it is natural to pose the following question. Is disease activity at diagnosis predictive of future disease severity in pediatric-onset Crohn's disease?

2.3 STUDY HYPOTHESIS

Patients with high disease activity at diagnosis are more likely to have a more severe disease course over the first year following diagnosis.

2.4 STUDY OBJECTIVES

1) To determine if disease activity at diagnosis is predictive of severity of pediatric-onset Crohn's disease during the first year following diagnosis.

2) To identify baseline factors predictive of disease severity.

3) To document the clinical course of pediatric Crohn's disease for an inception cohort during the first year following diagnosis.

4) To assess the influence of early immunosuppressive therapy on disease severity.

Chapter 3 - STUDY METHODOLOGY

3.1 STUDY DESIGN

3.1.1 Study Design

An inception cohort composed of pediatric patients with newly diagnosed Crohn's disease was assembled at the inflammatory bowel disease clinic, Hospital for Sick Children, Toronto. Recruitment was facilitated by the inflammatory bowel disease database that has been prospectively maintained on all patients with inflammatory bowel disease followed through the Hospital for Sick Children since 1980.

3.1.2 Study Population

The target population was children and adolescents at the time of their initial diagnosis of Crohn's disease at the Hospital for Sick Children, Toronto. Patients were prospectively recruited from July 1997 to May 2001. Follow-up continued for one year following diagnosis, with the last follow-up occurring in May 2002.

3.1.3 Inclusion/Exclusion Criteria

Inclusion criteria:

1. A new diagnosis of Crohn's disease (**Appendix B**); a diagnosis of Crohn's disease was made if a potential case met at least two of the following criteria:

    - clinical history of abdominal pain, weight loss, malaise, diarrhea, and/or rectal bleeding for at least 2 months;

    - endoscopic findings of mucosal cobblestoning, linear ulceration, skip areas, or perianal disease;

- radiological findings of stricture, fistula, mucosal cobblestoning, or ulceration;

- macroscopic appearance of bowel wall induration, mesenteric lymphadenopathy, and "creeping fat" at laparotomy; or

- pathological findings of transmural inflammation and/or epithelioid granulomas.

These criteria were identical to those used in previous studies (21;82).

2. Age < 17 years.

3. Availability of required baseline information.

4. Informed consent obtained for prospectively recruited subjects.

Exclusion criteria:

1. Patients with ulcerative colitis; the diagnostic criteria for ulcerative colitis was the presence of at least two of the following four criteria: (21;82)

- clinical history of diarrhea, stools containing blood and pus, or both

- macroscopic appearance at endoscopy, with continuous mucosal inflammation affecting the rectum in continuity with some or all of the colon with granulated friable mucosa or ulcerations, or both

- histological signs of inflammation

- no suspicion of Crohn's disease on small-bowel roentgenography, ileoscopy, or biopsy

2. Patients with indeterminate colitis; a diagnosis of indeterminate colitis was made if endoscopy and histopathology were either inconclusive or divergent with regard to the diagnosis of Crohn's disease or ulcerative colitis (21).

3. Patients with any co-morbid condition, including but not limited to hepatic, renal, cardiovascular, neurological, or psychiatric diseases that were determined to be of clinical relevance for the purposes of this thesis. Specifically, any co-morbid illness that had a significant impact on disease severity would be excluded. (Of note, no patients were excluded for this reason)

3.2 STUDY OUTLINE

A one-year follow-up study was conducted as outlined in **Figure 3.1**.

Baseline characteristics measured at diagnosis included: age; gender; duration of symptoms; date of diagnosis; family history of IBD; current medications; height; weight; signs on physical examination; Tanner pubertal stage; stool cultures; albumin; ESR; platelet count; hemoglobin; radiological findings; endoscopy findings; and pathology. Pediatric Crohn's Disease Activity Index (PCDAI) scores were calculated on all patients. Crohn's Disease Endoscopic Index of Severity (CDEIS) scores were collected on patients diagnosed between August 2000 and May 2001.

Follow-up data was collected at six weeks, six months and one year after initial diagnosis. Data was also collected during intermittent hospitalizations. Data collected included: frequency and consistency of bowel movements; presence of blood and mucus in stools; abdominal pain; current medications; growth parameters; Tanner stage; albumin; ESR; platelet count; hemoglobin; and PCDAI scores. Response to initial therapy was collected only at 6 weeks. IMPACT (quality of life) scores were collected at 6 and 12 months in those patients >/=10 years old from August 2000 to May 2001.

Follow-up data was collected where possible in the GI outpatient clinic and during hospitalizations. For patients unable to attend follow-up clinics, arrangements were made for the patients' family physician or pediatrician to collect the required information.

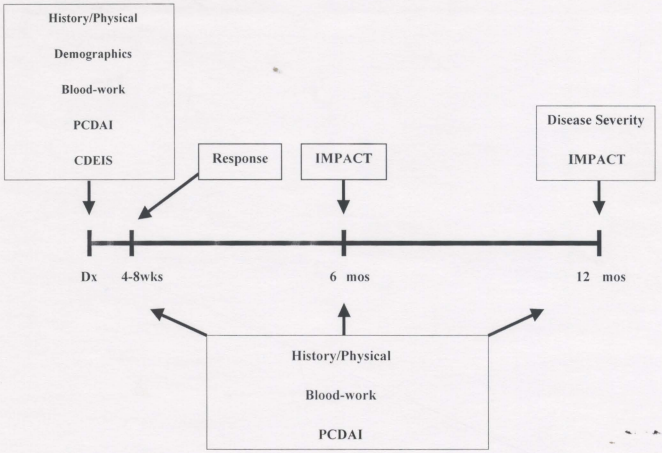


Figure 3.1 Study Protocol

3.3 MEASUREMENT/VARIABLES

3.3.1 Index Measurements

Disease activity for Crohn's disease was measured using the Pediatric Crohn's Disease Activity Index (PCDAI) (**Appendix C**) (83). The PCDAI is a multi-item instrument that was specifically developed as an objective measure of disease activity in pediatric patients with Crohn's disease (83). The PCDAI consists of 11 criteria, assessing three main categories: symptoms, laboratory markers of inflammation, and physical examination findings including an evaluation of growth velocity. Scores range from 0 - 100 in increments of 2.5. Higher scores reflect more active disease. A PCDAI value >30 correlates with moderate and severe disease activity and a value <15 with inactive disease (84). The PCDAI has been validated and has been demonstrated to be more feasible and to more accurately reflect disease activity in children than does the adult patient derived Crohn's Disease Activity Index (CDAI) (84). More recently, it has been demonstrated that the PCDAI is responsive to short-term changes in disease activity (85).

For patients recruited between August 2000 and May 2001, the CDEIS was collected at the initial colonoscopy (if performed prior initiation of therapy) to grade the macroscopic severity of disease. The score is based on the presence of deep or superficial ulceration, the proportion of ulcerated surface and the presence of ulcerated or non-ulcerated stenosis in five separate regions (rectum, sigmoid and left colon, transverse colon, right colon and ileum) (86). Scores range from 0 - 44 with higher scores reflecting more severe involvement. The CDEIS has been validated for use in adults by a prospective multi-center study (86). It is reproducible and responsive (86).

Unfortunately, correlation with clinical and laboratory indexes (including hemoglobin, ESR, stool frequency, CDAI - Crohn's Disease Activity Index) and with prognosis appears to be poor (86-90).

For each colonoscopy, two independent evaluations were completed. The consultant gastroenterologist or gastroenterology fellow performing the colonoscopy completed one CDEIS assessment. Another examiner (JC) performed a second assessment of the CDEIS either at the time of the colonoscopy or afterwards by reviewing videotapes. In addition, both reviewers completed a 10cm visual analog scale (VAS) to indicate their assessment of the endoscopic severity. While the CDEIS has not been specifically validated for use in pediatric patients, as the endoscopic findings of Crohn's disease has not been shown to be appreciably different between children and adults, it was judged that use of this index was acceptable for purposes of this thesis.

Clinical response to initial therapy was assessed at the 6-week follow-up visit. Clinical response was classified into 1 of 3 categories (45).

The categories were:

1. Complete remission: defined as total regression of clinical symptoms (</= 2 bowel movements/day; no blood, pus, or mucus in feces; and no abdominal pain, fever, weight loss or extraintestinal symptoms.
2. Partial clinical remission: defined as regression of clinical symptoms (</= 4 stools/day; blood, pus, mucus in feces; or abdominal pain; or all four less than daily and no systemic symptoms, such as fever or weight loss).

3. No response: defined as no regression of clinical symptoms.

Quality of life was assessed at the 6 and 12 month visits (between August 2000 and May 2002) by patient completion of the IMPACT questionnaire (91;92) (**Appendix D**). The IMPACT questionnaire was developed and validated as a disease specific measure of quality of life for use in pediatric patients (late childhood and adolescences) with inflammatory bowel (91). It is a self-administered questionnaire composed of 33 questions encompassing six domains: bowel (6 concerns), body image (3 concerns), functional/social impairment (11 concerns), emotional impairment (11 concerns), tests/treatments (3 concerns), and systemic impairment (2 concerns). A 10cm visual analog scale is employed to capture the response for each question. Each component is equally weighted and composite scores range from 0 - 231 with higher scores reflecting a better quality of life.

3.3.2 Outcome Variable - Definition

The primary outcome variable of disease severity was determined by a physicians' global assessment of disease course over the preceding year, excluding the immediate two months after therapy was initiated, as defined in **Table 2.1**. Versions of this classification system had been used successfully in previous studies (48;80;91). Disease severity was sub-divided into four groups; quiescent, mild, moderate (exacerbations with remissions) and severe (chronically active disease). In general terms, categorization of disease severity was based upon symptom pattern (duration and severity of symptoms)

and the potency of therapy required (specifically the need for prolonged or repeated systemic corticosteroids, enteral nutrition or surgical resection).

Prior to proceeding, it is important to differentiate between the explanatory variable of disease activity as measured by PCDAI and the primary outcome variable of disease severity. Disease activity is a reflection of inflammation at one point in time. In contrast, disease severity is a multi-dimensional concept. It is often derived from the physician and/or patient making a composite assessment of multiple attributes including, disease activity, sequelae of disease, and its treatment and health states (i.e. perceived quality of life) over a period of time. Prior to study commencement, no validated measure of disease severity in pediatrics Crohn's disease had been published. For purposes of this study, the assessment of disease severity was based on the physicians' global assessment of severity, as defined in **Table 2.1**.

3.3.3 Outcome Variable - Validation

In the absence of a previously validated measurement of disease severity in pediatric-onset Crohn's disease, this thesis was designed to concurrently validate the outcome measure of disease severity as defined in **Table 2.1**. As previously discussed, validated outcome variables are an essential component of clinical studies.

Outcome measures should be demonstrated to adhere to four properties: feasibility, reliability, validity and responsiveness (93).

1) Feasibility refers to the ease in which a measurement can be made.

2) Reliability of a measurement refers to its reproducibility (93). That is, the measurement of an unchanged entity on different occasions by the same observer (intra-rater reliability) or by different observers (inter-rater reliability) produce similar results.

3) Validity is concerned with how well an instrument measures what it was designed to measure (93). A number of approaches are employed to assess validity, but in the absence of a clearly defined external criterion ('gold standard') the process of construct validation is necessary (91;93;94). In construct validation, hypotheses are developed *a priori* based on how it is felt the measure should act. The measure is then tested against these hypotheses to determine if it is acting in the predicted manner.

4) Responsiveness refers to the ability of a measure to detect change in an entity over time.

3.4 SAMPLE SIZE

As this study was designed to enable construction of a multivariate regression model to determine the relationship between 5 to 9 baseline variables with disease outcome (moderate/severe disease), a minimum of 45 patients (cases) was required. This was based on the need for 5-10 patients with moderate/severe disease per baseline variable analyzed (94;95).

3.5 ANALYSIS

3.5.1 Variables

Explanatory variables

Baseline variables to be evaluated as prognostic indicators of disease severity included categorical variables: gender, disease location, initial hospitalization, initial systemic corticosteroid use and response to initial therapy at six weeks; and continuous variables: albumin, ESR, CDEIS (patients recruited from August 2000 to May 2001) and PCDAI score.

The laboratory variables (ESR, albumin), the index scores (PCDAI, CDEIS) and the categorical variables (initial hospitalization, initial systemic corticosteroid use, response to initial therapy) were pre-selected for analysis as they were felt to be surrogate markers of disease activity. These were also variables that could be objectively measured and easily collected in both a research and clinical setting. Disease location and gender were also pre-selected for inclusion as they were felt to be possible important

demographic factors affecting disease severity. Age was not analyzed due to the narrow age range of patients that were recruited. Explanatory variables were limited in the primary analysis to those listed above, as these variables were felt to likely be clinically relevant (as opposed to being solely statistically relevant) and thus more applicable physiologically for inclusion into a logistic regression model (96). Furthermore, it was pre-determined to limit the number of explanatory variables in the primary analysis to reduce the chance of type I errors. This not withstanding, secondary analysis was performed on several other variables (baseline platelets, duration of symptoms prior to diagnosis and positive family history of IBD) to identify other possible predictive factors.

Outcome Variable

The primary outcome variable of interest is disease severity (quiescent, mild, moderate - exacerbations alternating with remission, and severe - chronically active disease) as defined previously in **Table 2.1**. The four categories of the primary outcome variable were condensed into two groups prior to analysis. Quiescent disease was grouped together with mild disease and moderate (exacerbations with remissions) disease was grouped together with severe (chronically active) disease. The contraction of the outcome variables into two groups (mild/quiescent and moderate/severe) was justified on the basis that it was clinically more relevant to identify those patients with moderate/severe disease from those with quiescent/mild disease, as it is collectively the moderate/severe disease group that received the more aggressive treatments and therefore may arguably have a more favourable risk:benefit ratio for the early introduction of immuno-modulators.

Assessment of Liner Growth

Height was measured at each visit using a wall-mounted stadiometer. Heights were converted to z-scores with data sets used to construct the Centers for Disease Control and Prevention (CDC) 2000 growth charts (97). A z-score is the deviation of the height for an individual from the mean height of the reference population divided by the standard deviation for the reference population.

3.5.2 Validation of Primary Outcome Variable

Validation of the primary outcome variable was conducted by demonstrating adherence to the properties of feasibility, reliability and validity:

Feasibility: Testing was conducted by evaluating the ease with which the observers were able to grade disease severity in the cases. The presence of incomplete assessments was also recorded.

Reliability: Evaluation of both inter-rater and intra-rater reliability of the outcome variable was performed. Intra-rater reliability was assessed by having one examiner (JC) assign the disease severity grade at two separate times, separated by several months. This was possible as the outcome variable of disease severity was retrospectively assigned, allowing the examiner (JC) to review the records and re-assign the grade while blinded to his original assessment. Inter-rater reliability was assessed by having two examiners (JC, AG) independently assign the disease severity grade to each case.

Validity: Assessment was conducted by constructing hypothesis on disease severity *a priori*, as outlined in **Table 3.1**. As disease severity is likely to be dependent on many factors, hypothesis were constructed by choosing variables (duration of hospitalization, number of hospitalizations, quality of life (IMPACT scores), disease activity over time (mean of PCDAI scores measured at 6 and 12 months) and linear growth) that were postulated to be correlates of disease severity. Importantly, the outcome measure of disease severity utilized in this study was defined independently of the variables chosen for construct validation.

Responsiveness: The responsiveness of the outcome measure for disease severity was not determined. As the outcome variable was designed to assess disease severity over the one-year period examined in this study, it was not possible to test responsiveness within the context of this thesis. To assess for responsiveness, it would have been necessary to extend the study interval to two years. In the context of this thesis, failure to demonstrate responsiveness of the outcome variable was not felt to be limiting, as this property was not required for purposes of this study.

Table 3.1 Construct Hypothesis for Validation of Primary Outcome Variable

Construct Hypothesis
1. Duration of hospitalization should be **longer** in patients with moderate/severe disease.
2. Number of hospitalizations should be **higher** in patients with moderate/severe disease.
3. IMPACT scores should be **lower** in patients with moderate/severe disease.
4. Linear growth should be **lower** in patients with moderate/severe disease.
5. Mean PCDAI scores should be **higher** in patients with moderate/severe disease.

3.5.3 Statistical Analyses

Analyses were initially performed using the two-category (mild/quiescent and moderate/severe) primary outcome variable, for reasons justified previously. A second analysis was conducted with the primary outcome variable divided into the four separate categories (quiescent, mild, moderate, severe).

Univariate Analyses

To identify risk factors for moderate/severe disease, univariate analyses were initially performed using the selected baseline variables. Fisher's exact test was used for categorical variables and the unpaired Student's t-test for normally distributed continuous variables. Mann Whitney U (MWU) test was used for continuous variables that were not normally distributed. Testing for normality was performed. Data was evaluated for kurtosis and skewness. Levene's test was used to examine for equality of variances. For the four-category outcome variable, chi-square analyses were used for categorical variables and ANOVA for continuous variables. Nonparametric tests were used if testing failed to ensure the assumption of a normal distribution.

Mulitvariable logistic regression

Baseline characteristics found to be associated with poor outcome at a level of significance </= 0.05 were entered into a multivariate logistic regression model. It was decided to include gender into the multivariate model, even if non-significant by univariate analysis, as it is an important demographic factor. A backward regression model was developed to predict poor outcome (moderate/severe disease) at one-year

follow-up. Risk factors were sequentially removed from the model based on two criteria: the variable was not a statistically significant predictor of poor outcome at the $p<0.05$ level, and removal of the variable resulted in a reduction of the area under the receiver operating characteristic (ROC) curve by <0.03. First level multiplicative interaction terms were studied. Explanatory variables were assessed for multicollinearity in each model. Possibility of a high multicollinearity problem was suggested if the correlation coefficient was >/= 0.8 (98). Data was reviewed for the presence of standardized residuals >2.58, 0.01 significance level. Models were evaluated using percent concordance, Nagelkerke R^2, and Hosmer and Lemeshow's goodness-of-fit test. The area under the ROC curve, a commonly used measure of the predictive power of a statistical model, was assessed.

Ordinal logistic regression analyses were used for the four-category outcome variable.

Validation of outcome variable

Reliability: Kappa statistic was used to calculate both intra-rater and inter-rater agreement for the outcome variable disease severity. Testing was performed for both the contracted two-category form (quiescent/mild and moderate/severe) and for the four-category form (quiescent, mild, moderate, and severe). Kappa statistic was selected as the most appropriate test to use as the outcome variable was of the categorical ordinal type (99). A kappa statistic >0.80 represents excellent agreement, 0.60 – 0.80 substantial agreement, 0.40 - 0.60 moderate agreement and <0.40 poor to fair agreement (99;100).

Validity: Testing of the construct hypothesis was performed using univariate analysis. Fisher's exact test was used for categorical variables and the unpaired Student's t-test for normally distributed continuous variables. The Mann-Whitney U test was used for continuous variables that were not normally distributed. For the four-category outcome variable, chi-square analyses were used for categorical variables and ANOVA for continuous variables. A strong correlation was defined as $r>0.5$, a moderate correlation $r>0.4$ and a mild or weak correlation $r>0.3$. Analyses were conducted using parametric techniques. Nonparametric tests were used if testing failed to ensure the assumption of a normal distribution.

CDEIS agreement

Intra-class correlation (ICC) was used to evaluate agreement between the two examiners for both the CDEIS and the visual analog scores (VAS). Inter-rater reliability was analyzed using ICC Model 2 (repeated measures ANOVA) for single measurements, with raters selected as the independent variable (99). As a general guideline, ICC >0.75 is indicative of good reliability and <0.75 of poor to moderate reliability. It has been suggested, that the ICC should exceed 0.90 for clinical measurements (99). Pearson's correlation was used to evaluate the correlation between CDEIS and visual analog scores (VAS) for each observer.

Data management

Data was stored in Microsoft Excel 97. All analyses were performed using the statistical package SPSS 11.0 - 12.0 for windows and/or SAS Version 8.10 for windows. Statistical significance was determined at a two-tailed level of 0.05. Statistical support was provided through consultation with statisticians at the Faculty of Medicine, University of Toronto and the Research Institute, Hospital for Sick Children.

3.6 ETHICAL CONSIDERATIONS

Approval was obtained from the Research Ethics Board (Hospital for Sick Children), prior to implementation. Patients, parents and legal guardians were informed of the purpose of the study, expected length of participation and the anticipated involvement of the patient in the study. Patients, parents and legal guardians were informed of their right to refuse participation and to withdraw their child from the study at any time. In the event of refusing participation, patients, parents and legal guardians were reassured that their health care services would not be affected in any way. Verbal and written consent for participation in the prospective trial was obtained prior to enrolment. Patient rights (including confidentiality) were protected for all information entered into the database. Data were stored in secured locations and electronic data was password protected. All analyses arising from this study are available to the patients, parents or legal guardians at their request.

3.7 FUTURE BENEFIT

The ability to predict those children with Crohn's disease who will do poorly could have significant clinical applications. Health care providers, patients and their families could use this information to provide an overview of the anticipated clinical course. Additionally, it may help select the most appropriate candidates for enrolment in future studies assessing the early use of immunosuppressive therapies.

Chapter 4 - RESULTS

4.1 DESCRIPTIVE STATISTICS

One hundred sixty-one Crohn's disease patients less than 17 years of age at diagnosis were assessed at the Hospital for Sick Children, Toronto between July 1997 and May 2001. Of these patients, 21 did not meet the inclusion/exclusion criteria of this study. Twenty were removed due to inadequate baseline data as the initial diagnosis was made outside the Hospital for Sick Children and one patient refused to participate. Eight others were lost to follow-up prior to 8 months after diagnosis, precluding assignment of the outcome variable. As such, 132 patients were entered into this study, of which 122 patients (92.4%) had complete baseline and follow-up data available for analysis. (Separate analyses were done on the set of 122 patients with complete data and the set of 132 of which 10 cases were missing some baseline data).

Of the 122 patients with complete data, 44 (36.1%) were female and the average age at diagnosis was 13.10 +/- 2.37 years. At the end of the first year following diagnosis, 35 (28.7%) had quiescent disease, 38 (31.2%) mild disease, 29 (23.8%) moderate disease (intermittent exacerbations) and 20 (16.4%) severe disease (chronically active) **(Figure 4.1)**.

Thirty patients (24.6%) had disease involving the large bowel only, 62 patients (50.8%) had disease of both the small and large bowel, 28 patients (23.0%) had disease of the small bowel only and 2 patients (1.6%) had isolated perianal disease.

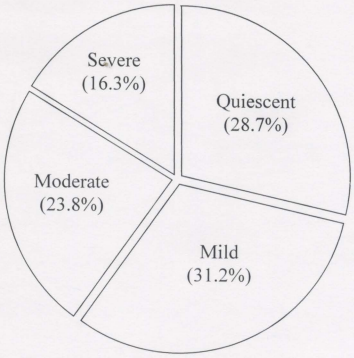


Figure 4.1 Percentage of Patients with Quiescent, Mild, Moderate and Severe Disease During the First year Following Diagnosis.

For initial treatment, 61 patients (50.0%) received systemic corticosteroids, 57 (46.7%) antibiotic treatment (ciprofloxacin and/or metronidazole), 43 (35.2%) 5-ASA/sulphasalazine, 5 (4.1%) budesonide, 7 (5.7%) azathioprine and 11 (9.0%) enteral nutrition. Over the first year, 69 (56.6%) received at least one course of steroids and 37 (30.3%) were started on immunosuppressant therapy (34 azathioprine, 2 methotrexate and 1 both). Fourteen patients (11.5%) underwent surgical intervention (4 ileocecal resection, 2 subtotal colectomy, 2 drainage of intra-abdominal abscess, 3 diversional ileostomies, 2 incision and drainage of perianal abscess, 1 perianal fistulectomy).

As previously stated, in the initial analysis, patients with quiescent and mild disease were grouped together as were those with moderate and severe disease. Overall, 49 patients (40.2%) had moderate/severe disease over the first year of follow-up. This was comparable to that observed in our post-hoc analysis where 43.4 percent of patients had moderate/severe disease over the first year of follow-up.

4.2 DEMOGRAPHICS OF PATIENTS WITH INCOMPLETE DATA

Eighteen enrolled patients had insufficient data to enable analyses. Eight subjects had insufficient follow-up to assess the primary outcome of disease severity and ten subjects had incomplete baseline data. As demonstrated in **Tables 4.1 and 4.2**, these patients had similar baseline demographics to those analyzed.

Table 4.1 Baseline Demographics of Patients with Incomplete Data: Categorical Variables

Variable	Lost Follow-up (n=18)	Complete Sets (n=122)	p Value (2-sided) Fisher
Female Gender	6	44	1.000
Initial Hospitalization	9	43	0.297
Initial Steroids	10	61	0.802
Initial Response (Complete vs Partial/No Response)	11 (n=15)	86	1.000
Disease Location			
Small Bowel Only	8	28	0.079
Small/Large Bowel	7	62	0.451
Large Bowel Only	2	30	0.247

Table 4.2 Baseline Demographics of Patients with Incomplete Data: Continuous Variables

Variable	Lost Follow-up (n=18)	Complete Sets (n=122)	p Value (2-sided) Student t	P Value Mann-Whitney U
Age at Diagnosis (years)	12.52 (2.55)	13.10 (2.37)	0.337	0.332
Baseline ESR (mm/hr)	37.00 (18.72)	48.25 (24.51)	0.125	0.118
Baseline PCDAI	37.83 (13.29)	37.70 (14.71)	0.974	0.899
Baseline Albumin (g/L)	32.79 (4.71)	32.39 (5.01)	0.778	0.986
Baseline Platelets (10^9/L)	423.60 (157.20)	445.90 (127.70)	0.547	0.723

Mean (SD)

4.3 UNIVARIATE ANALYSIS

Fisher's exact test for categorical variables showed no significant association between disease severity and gender (p=0.701) or disease location, small bowel only (p=0.827), small and large bowel (p=0.465) and large bowel only (p=0.207) **(Table 4.3)**. Initial steroid usage (p=0.003) **(Figure 4.2)**, initial hospitalization (p=0.004) **(Figure 4.3)** and partial/no response following initial induction therapy (p=0.028) **(Figure 4.4)** were associated with moderate/severe disease over the first year after diagnosis.

Student's t-test was performed on continuous variables, assuming a normal distribution **(Table 4.4)**. Hypoalbuminemia (p=0.043) **(Figure 4.5)** and elevated baseline PCDAI scores (p<0.0001) **(Figure 4.6)** were significantly associated with moderate/severe disease over the course of the first year following diagnosis. Age at diagnosis (p=0.292) and initial ESR (p=0.073) were not associated with disease severity.

Analysis of the data using the four-category outcome variable obtained similar results, as did analysis using all patients (n=132) **(Appendix E)**.

Secondary analysis failed to identify an association with disease severity and positive family history of IBD (p=0.0687), baseline platelet count (p=0.324) or duration of symptoms prior to diagnosis (p=0.582).

In addition, baseline PCDAI scores were not associated with disease location (p=0.624) nor with duration of symptoms prior to diagnosis (p=0.470).

Table 4.3 Univariate Analysis: Categorical Variables

Variable	Quiescent/Mild Disease (n=73)	Moderate/Severe Disease (n=49)	p Value (Fisher 2-sided)	Relative Risk	95% Confidence Interval
Female Gender	25	19	0.701	1.123	0.723 - 1.743
Initial Hospitalization	18	25	0.004	1.914	1.258 – 2.910
Initial Steroids	28	33	0.003	2.063	1.276 – 3.334
Initial Response (Partial/No Response vs Complete Response)	16	20	0.028	1.648	1.087 – 2.498
Disease Location					
Small Bowel Only	16	12	0.827	1.089	0.663 – 1.788
Small/Large Bowel	35	27	0.465	1.188	0.767 – 1.838
Large Bowel Only	21	9	0.207	0.690	0.381 – 1.250
Positive Family History of IBD	20 (n=68)	16 (n=48)	0.687	1.080	0.767 – 1.521

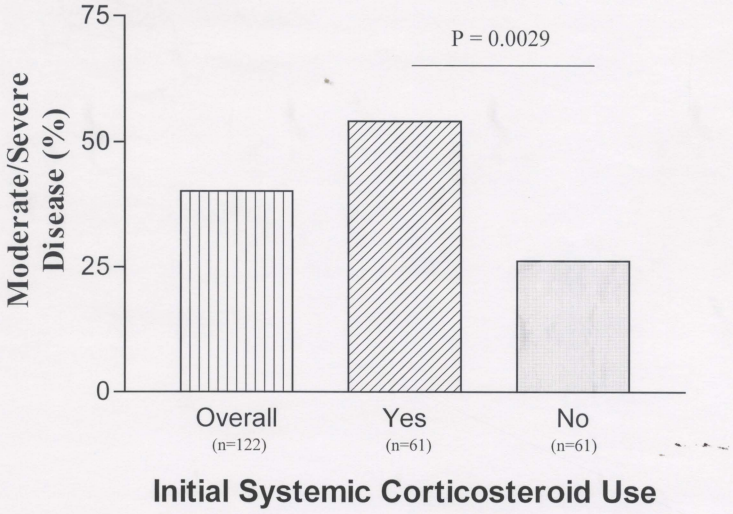


Figure 4.2 Disease Severity and Initial Corticosteroid Use

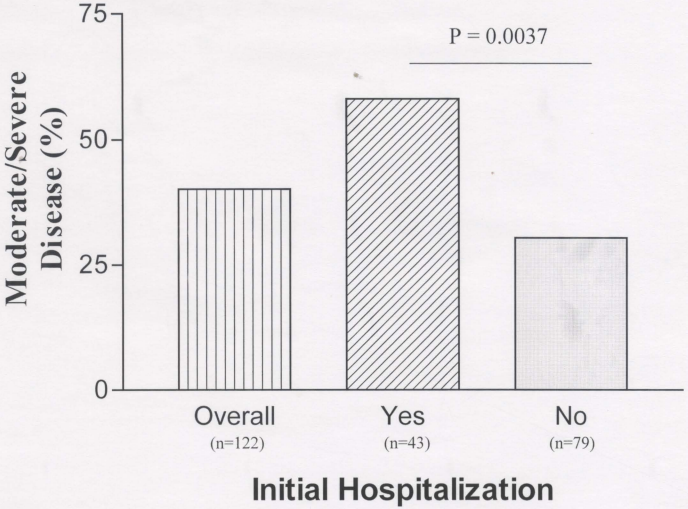


Figure 4.3 Disease Severity and Initial Hospitalization

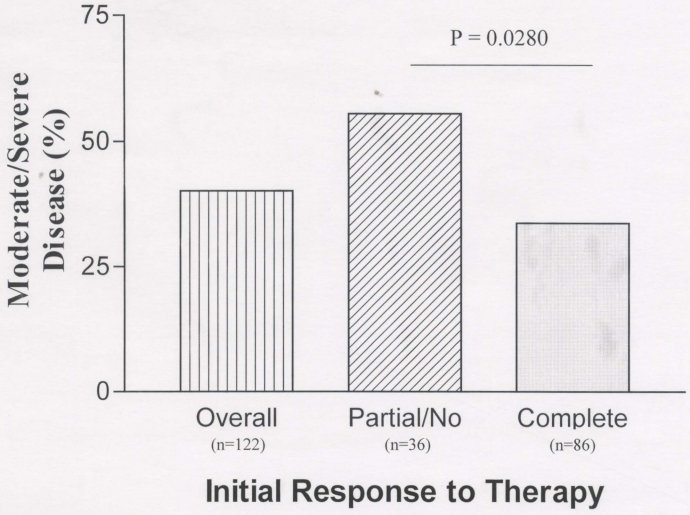


Figure 4.4 Disease Severity and Initial Response to Therapy

Table 4.4 Univariate Analysis: Continuous Variables

Variable	Quiescent/Mild Disease (n=73)	Moderate/Severe Disease (n=49)	p Value
Age at Diagnosis (years)	12.92 (2.50)	13.38 (2.15)	0.292
Baseline ESR (mm/hr)	45.00 (21.03)	53.10 (28.47)	0.073
Baseline Albumin (g/L)	33.44 (4.88)	30.83 (4.83)	0.004
Baseline PCDAI	33.53 (12.69)	43.93 (15.43)	<0.001
Baseline Platelets (10^9/L)	436.51 (133.19)	459.84 (118.90)	0.324
Duration of Symptoms (months)	9.58 (11.35)	8.43 (11.12)	0.582

Mean (SD)

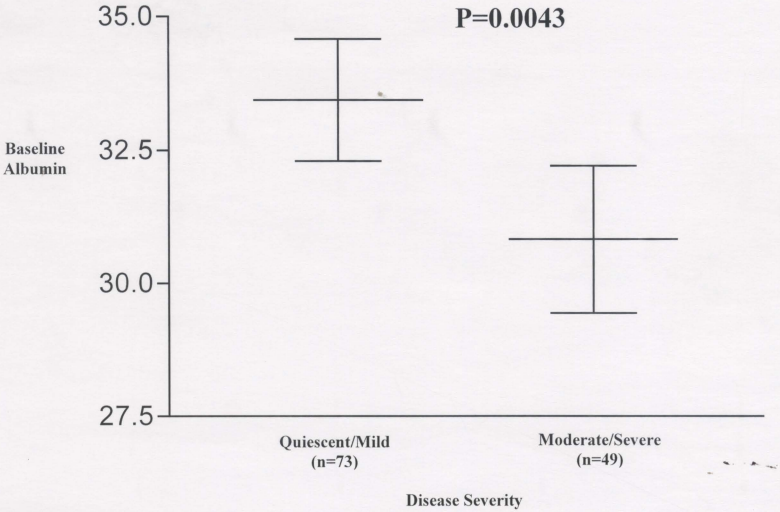


Figure 4.5 Plot of baseline albumin for quiescent/mild and moderate/severe disease. Bars indicate 95% confidence interval for mean albumin levels.

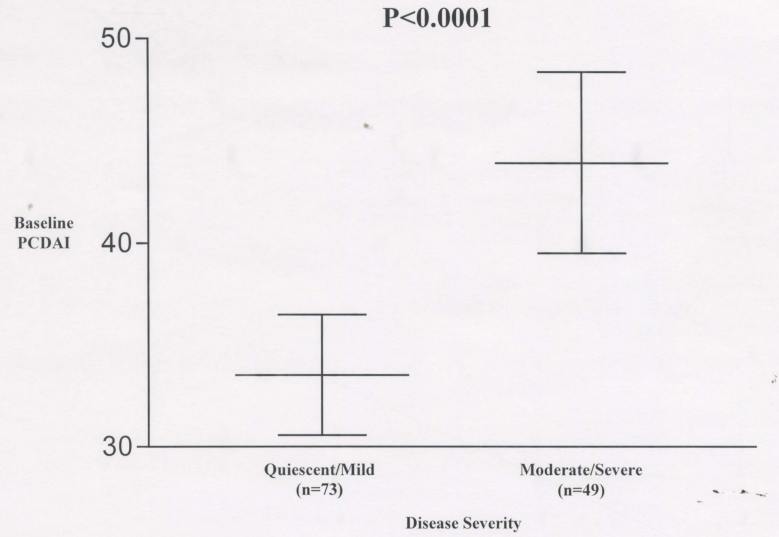


Figure 4.6 Plot of baseline PCDAI scores for quiescent/mild and moderate/severe disease. Bars indicate 95% confidence interval for mean of baseline PCDAI scores.

4.4 MULTIVARIATE LOGISTIC REGRESSION MODELS

Mulitvariate logistic regression models using backward stepwise selection were constructed. All variables that were significant in the univariate analysis at a level of p</=0.05 were entered. Gender was added to the model, despite not being significant in the univariate analysis, as it is an important demographic factor. No interaction terms were significant. As illustrated in **Table 4.5,** baseline PCDAI scores is the best single variable predictive of future disease severity over the first year following diagnosis, accounting for 16.3% of the variability of the model. It is also the only variable that remained statistically significant in the multivariate analysis. This compares to the full model (including all five variables and gender) which accounts for 23.0% of the variability. Model 4, which contains three variables (baseline PCDAI, initial corticosteroid use and response to initial therapy), was the best simplified model accounting for 21.6% of the variability. However, this model contained two covariates (initial corticosteroid use and response to initial therapy) which were not found to be significant in the multivariate regression analysis.

The presence of multicollinearity between the variables was evaluated for each model. As demonstrated in **Table 4.6** the correlation coefficients for the explanatory variables in each model ranged from -0.382 to +0.482.

ROC curves were constructed for each of the models listed in **Table 4.5** and are plotted in **Figure 4.7** for models 1, 4 and 6. The area under the curve ranged from 0.744 to 0.688 as noted in **Table 4.7**.

Table 4.5 Multivariate Analysis: Logistic Regression Models

Model	Covariate	Regression Coefficient	Standard Error	p Value	Odds Ratio	95% CI	Percent Concordant	Nagelkerke R^2
1	Intercept	-1.340	2.173	0.537	0.262		70.5	0.230
	PCDAI	0.029	0.021	0.157	1.030	0.989 - 1.072		
	Albumin	-0.028	0.051	0.579	0.972	0.880 - 1.074		
	Initial Hospital (Yes)	0.510	0.459	0.267	1.665	0.677 - 4.092		
	Initial Steroids (Yes)	0.714	0.449	0.112	2.041	0.847 - 4.922		
	Initial Response (Partial/No Response)	0.641	0.455	0.159	1.898	0.778 - 4.629		
	Gender (Male)	-0.076	0.426	0.858	1.079	0.468 - 2.487		
2	Intercept	-1.426	2.117	0.500	0.240		69.7	0.230
	PCDAI	0.029	0.021	0.154	1.030	0.989 - 1.072		
	Albumin	-0.027	0.050	0.588	0.973	0.881 - 1.074		
	Initial Hospital (Yes)	0.515	0.458	0.260	1.674	0.683 - 4.104		
	Initial Steroids (Yes)	0.713	0.449	0.112	2.040	0.846 - 4.915		
	Initial Response (Partial/No Response)	0.651	0.452	0.150	1.917	0.791 - 4.644		
3	Intercept	-2.520	0.666	<0.001	0.080		68.9	0.227
	PCDAI	0.035	0.018	0.056	1.035	0.999 - 1.073		
	Initial Hospital (Yes)	0.494	0.455	0.278	1.639	0.671 - 4.002		
	Initial Steroids (Yes)	0.733	0.446	0.101	2.081	0.867 - 4.991		
	Initial Response (Partial/No Response)	0.672	0.450	0.135	1.958	0.811 - 4.727		
4	Intercept	-2.623	0.662	<0.001	0.073		71.3	0.216
	PCDAI	0.041	0.017	0.016	1.042	1.008 - 1.078		
	Initial Steroids (Yes)	0.742	0.443	0.094	2.100	0.881 - 5.004		
	Initial Response (Partial/No Response)	0.780	0.436	0.074	2.182	0.928 - 5.127		

Table 4.5 Multivariate Analysis: Logistic Regression Models continued

Model	Covariate	Regression Coefficient	Standard Error	p Value	Odds Ratio	95% CI	Percent Concordant	Nagelkerke R^2
5	Intercept	-2.649	0.654	<0.001	0.071		68.9	0.189
	PCDAI	0.053	0.016	0.001	1.054	1.022 - 1.087		
	Initial Response (Partial/No Response)	0.712	0.413	0.098	2.038	0.876 - 4.738		
6	Intercept	-2.531	0.636	<0.001	0.080		67.2	0.163
	PCDAI	0.055	0.016	<0.001	1.057	1.025 - 1.090		

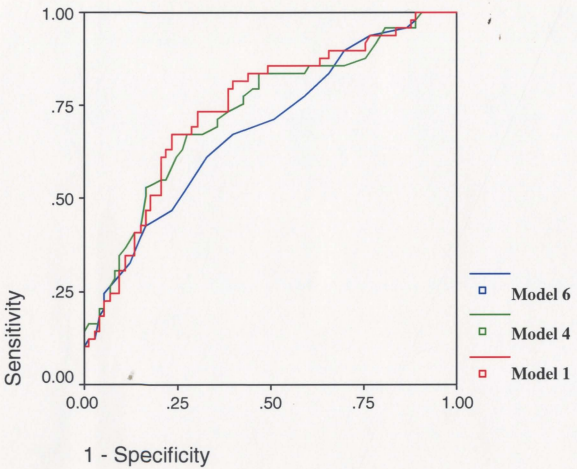


Figure 4.7 Receiver Operating Characteristic Curves of Multivariate Models 1, 4 and 6.
Model 1: baseline PCDAI, initial steroids, initial response, initial hospitalization, baseline albumin, gender;
Model 4: baseline PCDAI, initial steroids, initial response;
Model 6: baseline PCDAI

Table 4.6 Correlation Coefficients

	PCDAI	Response	Initial Steroids	Initial Hosp	Albumin	Gender
PCDAI	-	.024	-.288	-.320	.482	.057
Response	.024	-	.124	-.201	.093	.118
Initial Steroids	-.288	.124	-	-.008	.070	-.014
Initial Hosp	-.320	-.201	-.008	-	-.087	.066
Albumin	-.482	.093	.070	-.087	-	.091
Gender	.057	.118	-.014	.066	.091	-
PCDAI	-	.017	-.287	-.324	.479	
Response	.017	-	.127	-.211	.083	
Initial Steroids	-.287	.127	-	-.007	.072	
Initial Hosp	-.324	-.211	-.007	-	-.094	
Albumin	.479	.083	.072	-.094	-	
PCDAI	-	-.026	-.365	-.317		
Response	-.026	-	.117	-.209		
Initial Steroids	-.365	.117	-	-.003		
Initial Hosp	-.317	-.209	-.003	-		
PCDAI	-	-.089	-.382			
Response	-.089	-	.121			
Initial Steroids	-.382	.121	-			
PCDAI	-	-.054				
Response	-.054	-				

Table 4.7 Area Under the Curve of Multivariate Models

Model	AUC	Standard Error	Asymptotic significance[1]	Asymptotic 95% CI
1	0.744	0.046	<0.001	0.654 - 0.834
2	0.738	0.046	<0.001	0.648 - 0.829
3	0.736	0.046	<0.001	0.645 - 0.827
4	0.733	0.047	<0.001	0.641 - 0.825
5	0.711	0.048	<0.001	0.617 - 0.806
6	0.688	0.049	<0.001	0.592 - 0.783

[1]Null hypothesis: true area = 0.5

Hosmer and Lemeshow's goodness-of-fit test statistic for all the models ranged between 0.303 and 0.900, and was in support of well-fitting models. Examination of standard residuals failed to identify any outliers.

The estimated odds ratio (moderate/severe disease) for the model containing only PCDAI as a predictive factor was 1.057 (95% CI, 1.025-1.090) per 2.5 units PCDAI. The odds ratio (moderate/severe disease) for each change in PCDAI ranged from 2.41 to 18.17 **(Figure 4.8)**. The odds ratio for moderate/severe disease was highest for PCDAI scores >15, >62.5 and >65 at 11.17, 18.17 and 14.54 respectively.

Subsequent analysis of the data stratifying the outcome variable into four groups showed similar results, with baseline PCDAI being the best single independent prognostic factor of disease severity **(Appendix F)**.

4.5 CDEIS SCORES

CDEIS scores were prospectively collected and recorded independently on 13 patients. Nine patients had quiescent/mild disease and four had moderate/severe disease. The intraclass correlation as a measure of inter-rater reliability was 0.948 (95% CI, 0.840-0.984) and 0.891 (95% CI, 0.636-0.967) for CDEIS and visual analog scores (VAS) respectively. Pearson correlation for the VAS and CDEIS scores were 0.792 ($p<0.01$) and 0.801 ($P<0.01$) for those ranked by JC and the other raters, respectively. The CDEIS score was not associated with disease severity over the first year following diagnosis ($p=0.877$) nor was the VAS ($p=0.534$).

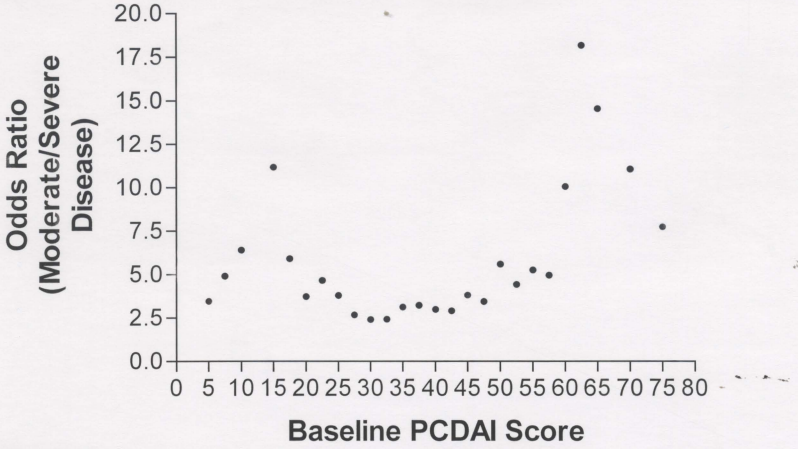


Figure 4.8 Odds Ratio for Each Change of PCDAI Score

Of note, administration of the CDEIS was conducted only from August 2000 through May 2001. During this period, the CDEIS was completed in 13 (of 16 eligible) patients, representing an 81.3% collection rate. Of the 3 patients who did not complete a CDEIS evaluation, 1 patient had initial colonoscopy performed at an outside hospital and 2 patients did not undergo colonoscopy prior to treatment.

4.6 VALIDATION OF PRIMARY OUTCOME VARIABLE

As previously discussed, no validated instrument of disease severity in Crohn's disease was available prior to commencement of this study. The primary outcome variable chosen was similar to those used in other studies on pediatric Crohn's disease (48;80;91). This study was designed to concomitantly validate the outcome variable by evaluating how well it compared with other surrogate markers of disease severity that were not included in the outcome variable definition. Total days hospitalized, number of hospitalizations, IMPACT scores, linear growth and mean PCDAI scores were pre-selected as likely markers of disease severity.

Correlation of the *a priori* constructs are reported in **Table 4.7**.

The average duration of hospitalization was longer for patients with moderate/severe disease compared to quiescent/mild disease (14.8+/-16.5 vs 5.1+/-12.5 days, p=0.001). If the hospitalization at diagnosis was removed from the analysis, the average duration of hospitalization for patients with moderate/severe disease remained longer compared to quiescent/mild disease (7.9+/-12.1 vs 1.5+/-6.09 days, $p<0.001$). Furthermore, patients with moderate/severe disease averaged more hospitalizations compared to patients with quiescent/mild disease (1.2+/-1.3 vs 0.5+/-0.8, $p<0.001$).

Total days hospitalized ($p<0.001$), days hospitalized after diagnosis ($p<0.001$) and total number of hospitalizations ($p<0.001$) were all significantly associated with more severe disease when analyzing with the four-category outcome variable (**Appendix G**).

Table 4.7 Construct Validity Testing

Construct	Analysis	r	p
Disease severity should reflect total length of hospitalization	Correlation between disease severity and total length of hospitalization	0.35	<0.0001
Disease severity should reflect length of hospitalization, excluding hospitalization at diagnosis	Correlation between disease severity and total length of hospitalization, excluding hospitalization at diagnosis	0.41	<0.0001
Disease severity should reflect number of hospitalizations	Correlation between disease severity and number of hospitalizations	0.34	0.0001
Disease severity should reflect quality of life, as measured by IMPACT scores at one year after diagnosis	Correlation between disease severity and quality of life, as measured by IMPACT scores at one year after diagnosis	-0.39	0.043
Disease severity should reflect quality of life, as measured by IMPACT scores at six months after diagnosis	Correlation between disease severity and quality of life, as measured by IMPACT scores at six months after diagnosis	-0.73	0.001
Disease severity should reflect disease activity over time, as measured by mean PCDAI scores at 6 and 12 months	Correlation between disease severity and disease activity over time, as measured by mean PCDAI scores at 6 and 12 months	0.36	0.0005
Disease severity should reflect linear growth, as measured by change in z-scores from end of first year and diagnosis	Correlation between disease severity and linear growth, as measured by change in z-scores from end of first year and diagnosis	-0.18	0.044

IMPACT scores were completed at six months after diagnosis in 18 patients, of which 10 patients had moderate/severe disease and 8 had quiescent/mild disease. The average IMPACT score for moderate/severe disease was significantly lower compared with quiescent/mild disease (152.9+/-25.6 vs 197.2+/-19.0, p=0.001).

Similarly, IMPACT questionnaires were completed at one year after diagnosis in 27 patients, of which 14 patients had moderate/severe disease and 13 quiescent/mild disease. The average IMPACT score for patients with moderate/severe disease tended to be lower compared to quiescent/mild disease (154.9+/-40.1 vs 179.5+/-29.9, p=0.084).

There were a number of reasons why only a proportion of the patients had IMPACT scores calculated. First, due to its design, the IMPACT questionnaire was not administered to children <10 years of age. Second, administration of the IMPACT questionnaire was conducted only from August 2000 through to May 2002. As such, 18 patients completed the 6-month questionnaire of 21 eligible patients (85.7%); and 27 patients completed the 12-month questionnaire of 43 eligible patients (62.8%).

Analysis of IMPACT scores was not performed with the four-category outcome variable due to insufficient numbers in some groups.

PCDAI scores were collected at the 6 weeks, 6 months and 12 months visits. For purposes of this analysis, the association of the average PCDAI scores collected from the 6 and 12-month visits to disease severity was assessed. The average PCDAI score was

higher for the group with moderate/severe disease (15.9+/-11.7, n=36) compared to the group with quiescent/mild disease (8.0+/-7.3, n=53) (p=0.001) **(Figure 4.9)**. (Not all patients had bloodwork collected at both the 6 and 12 month visits, thus precluding calculation of the mean PCDAI score in those patients).

Similarly, higher mean PCDAI scores were associated with more severe disease ($p<0.001$) when analyzing using the four-category outcome variable **(Appendix G)**.

Height was measured at all visits and converted to z-scores. The height z-scores were low at baseline and one-year follow-up in both the moderate/severe and quiescent/mild groups. The baseline height z-scores for moderate/severe disease was comparable to quiescent/mild disease (–0.708+/-1.038 vs –0.632+/-1.259, p=0.726) (r=-0.060, p=0.51); as were those at one-year follow-up, moderate/severe disease and quiescent/mild (–0.762+/-1.083 vs –0.486+/-1.112, p=0.1763) (r=-0.14, p=0.13). Of note, the change in z-scores between one-year follow-up and baseline were significantly lower for patients with moderate/severe disease compared to those with quiescent/mild disease (–0.054+/-0.381 vs 0.146+/-0.571, p=0.045) (r=-0.18, p=0.044). Similar results were obtained when analyzing height with the four-category outcome variable, though the association between disease severity and change in z-scores did not quite reach significance (p=0.065) (r=-0.16, p=0.082) **(Appendix G)**.

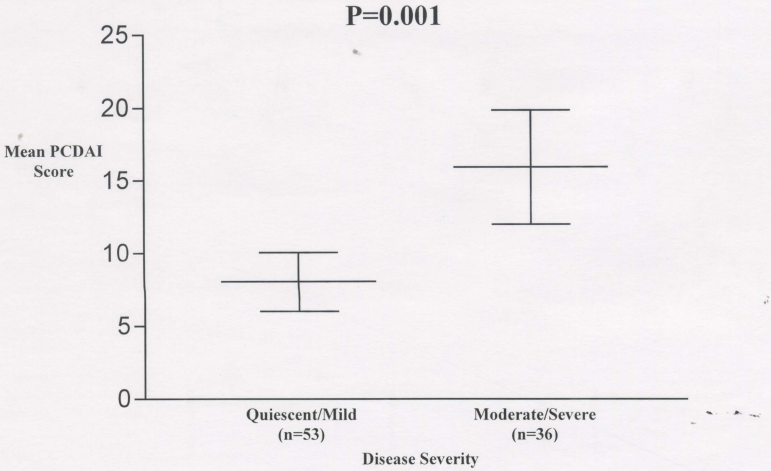


Figure 4.9 Plot of mean PCDAI scores (measured at 6 and 12 months) for quiescent/mild and moderate/severe disease. Bars indicate 95% confidence interval for mean scores.

Reliability

Kappa statistic for intra-rater agreement was 0.898 and 0.856 for the two-category and four-category disease severity outcome variable respectively. Similarly, kappa statistic for inter-rater agreement was 0.900 and 0.846 for the two-category and four-category disease severity outcome variable respectively.

For the four-category variable, thirteen (10.7%) responses were disconcordant with intra-rater assessment and nineteen (15.6%) were disconcordant with inter-rater assessment. Of the disconcordant response for intra-rater assessment, twelve (92.3%) were separate by only one category and one (7.2%) was separated by two categories. Similarly, of the disconcordant responses for inter-rater assessment, seventeen (89.5%) differed by only one category and two (10.5%) differed by two categories. When reduced to a two-category outcome variable, six (4.9%) responses remained disconcordant for both the intra-rater and inter-rater assessments.

Feasibility

Both raters (JC, AG) reported that the outcome variable definition was easy to use and they were each able to provide an outcome variable assignment for all the cases.

4.7 CASE-CONTROL STUDY: EARLY IMMUNMODULATOR USE

As previously discussed, several studies (75;76) presented data demonstrating that early use of immunosuppressive therapy in pediatric-onset Crohn's disease leads to improved outcomes. To further assess this, the thesis cohort was utilized to conduct a case-control analysis on those patients who were started on immunsuppressant therapy within the first 30 days of diagnosis, randomly matching each case with seven controls. As the baseline PCDAI was identified to be the primary prognostic factor for disease severity over the course of the first year, cases and controls were matched for baseline PCDAI.

Immunomodulator therapy was started on seven patients (6 azathioprine, 1 methotrexate) within the first 30 days of diagnosis. As demonstrated in **Table 4.9**, cases and controls were similar for baseline PCDAI, baseline ESR, baseline albumin, age at diagnosis, gender, and disease location (ileum, colon).

Five patients (71.4%) of those receiving immunomodulator therapy within 30 days of diagnosis had a quiescent/mild disease course over the following year as compared to 25 (51.0%) controls (p=0.431).

Similarly, immunomodulator therapy was initiated on 11 patients (10 azathioprine, 1 methotrexate) within 90 days of diagnosis. A case-control analysis matching for baseline PCDAI was conducted, randomly matching each case to 3 controls.

Table 4.9 Early Immunomodulation Therapy (<30days): Baseline Characteristics

Variable	Immunomodulator (n=7)	No Immunomodulator (n=49)	p Value (Student's T)	p Value (Mann Whitney U)
Baseline PCDAI	47.86 (12.11)	46.53 (12.98)	0.800	0.610
Baseline ESR (mm/hr)	65.71 (20.62)	56.12 (24.88)	0.336	0.282
Baseline Albumin (g/L)	29.86 (4.45)	30.56 (4.19)	0.681	0.716
Age at Diagnosis (years)	12.46 (2.25)	13.64 (2.24)	0.197	0.185
Female Gender	3	18	1.00 (Fisher)	
Ileal Involvement	4	33	0.679 (Fisher)	
Colon Involvement	6	29	0.237 (Fisher)	

Mean (SD)

As demonstrated in **Table 4.10**, cases and controls were similar for baseline PCDAI, ESR, albumin, age at diagnosis, gender and disease location (ileum, colon).

Six patients (54.5%) of those receiving immunomodulator therapy within 90 days of diagnosis had a quiescent/mild disease course over the following year as compared to 13 (39.4%) of controls (p=0.489).

Table 4.10 Early Immunomodulation Therapy (<90days): Baseline Characterisitcs

Variable	Immunomodulator (n=11)	No Immunomodulator (n=33)	p Value (Student's T)	p Value (Mann Whitney U)
Baseline PCDAI	49.55 (10.89)	49.24 (13.98)	0.948	0.708
Baseline ESR (mm/hr)	63.91 (19.57)	53.58 (26.09)	0.236	0.130
Baseline Albumin (g/L)	28.82 (4.45)	29.91 (4.84)	0.499	0.574
Age at Diagnosis (years)	13.15 (2.32)	13.36 (1.95)	0.787	1.000
Female Gender	5	10	0.468 (Fisher)	
Ileal Involvement	6	20	0.738 (Fisher)	
Colon Involvement	10	22	0.240 (Fisher)	

Mean (SD)

Chapter 5 - DISCUSSION

5.1 DISCUSSION

This thesis clearly illustrates the wide inter-patient heterogeneity in the clinical course of Crohn's disease, with 59.8 percent of patients having quiescent/mild disease and 40.2 percent having moderate/severe disease. This spectrum of disease severity is similar to that observed in the post-hoc analysis (51.8% quiescent/mild) and the Munkholm study (55% mild) (44).

Additionally, the data demonstrates the considerable intra-patient variability in the clinical course of Crohn's disease, as many patients alternate between quiescent/mild disease and moderate/severe disease. However, importantly the post-hoc analysis clearly indicates a relationship between disease severity from year to year, as patients with quiescent/mild disease in any one year are more likely to continue to have quiescent/mild disease in the following year. Likewise, those patients with moderate/severe disease in any given year are at higher risk of having moderate/severe disease in subsequent years. These results are similar to those published by Munkholm et al (44).

The data supports the hypothesis that disease activity at diagnosis is predictive of disease severity. Patients with high disease activity at the time of diagnosis were clearly shown to be at increased risk for a moderate/severe course over the subsequent year. Several variables used to estimate disease activity were predictive of subsequent disease severity, including PCDAI, albumin level, initial corticosteroid use, initial hospitalization and initial response to therapy. Multivariate analysis indicated that baseline PCDAI

score was the best single factor predictive of disease severity. The highest odds ratios were found at both ends of the PCDAI scale (>15, >62.5 and >65), demonstrating that very low scores (</=15) were most predictive of quiescent/mild disease over the first year and very high scores (>62.5) were most predictive of moderate/severe disease.

While this study identifies several clinical parameters which have value in predicting disease severity, only a small proportion of the variability (Nagelkerke R^2=0.230) was explained by the full six-variable logistic regression model. For this reason, one cannot reliably use this model to predict outcome for individual cases. However, the data provides evidence to support targeting patients with higher disease activity for early immunosuppressant therapy, as these patients are at increased risk to experience a more severe clinical course. This is supportive of the study by Markowitz et al (75) who selected patients with moderate-severe disease activity at baseline for early introduction of immunosuppressive therapy.

The model that includes baseline PCDAI, initial corticosteroid therapy and response to initial therapy is superior in its predictive ability to the model using only baseline PCDAI (Nagelkerke R^2 0.216 and 0.163 respectively). However, as many subjective factors, including patient, parent and physician biases can influence the choice of initial therapy and thus response, the model using PCDAI alone is arguably the best objective model to employ, albeit with some loss of predictive power. Additionally, this was the only model that did not contain non-significant covariates in the multiple regression analyses. Furthermore, it is important to emphasize that the prognostic ability

of all the models should be verified against other similar prospectively assembled cohorts.

The importance of an appropriate and valid outcome variable in conducting clinical trials cannot be over emphasized. For this reason, great attention was paid to defining the primary outcome variable of disease severity. These criteria were objectively defined, based upon symptom pattern and the potency of medication, specifically the need for corticosteroids, enteral nutrition or surgery.

Versions of the outcome variable had been used in other studies studies (48;80;91) but had not been systematically evaluated. Therefore, validation of the primary outcome variable for feasibility, construct validity and reliability was conducted within the study design. Both scorers rated the outcome variable classification as easy to use. Construct validity was demonstrated by proving significant association of moderate/severe disease with longer hospitalization, greater number of hospitalizations, impairment of linear growth, higher mean PCDAI scores and lower IMPACT scores at 6 months. There was also a trend towards lower IMPACT scores at 12 months. Of note, Otley et al (91) also demonstrated a relationship between more severe disease (similar definition of disease severity) and lower IMPACT scores. Griffiths et al (48) reported a similar significant association between more severe disease (similar definition of disease severity) and impaired linear growth.

Furthermore, both intra-rater and inter-rater reliability were strong as evaluated by high kappa statistic for each (0.898 and 0.856 respectively for the two-category variable; 0.900 and 0.846 respectively for the four-category variable). Not surprisingly, with the four-category variable, most of the disconcordant responses for both intra-rater and inter-rater assessments were separated by only one category (92.3% and 89.5%, respectively). This indicates that most of the disagreement occurred among consecutive categories.

As is evident, the correlation coefficients in the construct validity assessment tended to be in the mild to moderate range ($0.3 < |r| < 0.5$). That is to be expected since our outcome variable of disease severity is multidimensional and should not be expected to have high correlation with anyone of the independent variables used to validate it. That it did behave in the predicted manner, albeit with mild to moderate correlation, to the *a priori* constructs (each measuring a different entity), is evidence in support of the measure's multi-dimensional validity.

Contraction of the outcome variable into two-categories from four-categories was justified on the basis that the moderate and severe disease groups were more similar then dissimilar, as were the quiescent and mild disease groups. The moderate and severe disease groups both experienced significant symptoms and received the more aggressive therapies compared to the quiescent and mild disease groups. As such, it was judged to be more relevant clinically to combine the moderate and severe disease groups into one, as the risk/benefit ratio for the early introduction of immunosuppressive therapies may be more favorable for this group. As the reliability of a scale decreases as fewer categories

are used (93), analyses were performed with both the two-category and four-category variable to check for any adverse effect with using the contracted form as the primary outcome measure. As was shown, similar results were observed. The finding of similar results between the two-category and four-category outcome variable further supports the choice of using the two-category outcome variable as it is a simplified version that provides similar clinically significant discrimination.

The case-control analysis did not demonstrate a significant reduction in disease severity in the group receiving early immunosuppressive therapy. However the number of patients receiving immunomodulator therapy within 30 (n=7) and 90 (n=11) days of diagnosis was small. Thus this analysis was under-powered to detect a statistical difference. However, the study does reveal a trend towards a higher proportion of patients experiencing quiescent/mild disease in the early immunosuppressant groups compared to the matched controls (71.4% vs 51.0%, </=30days; 54.5% vs 39.4%, </=90 days). This trend was in support of the findings from the randomized controlled trial of Markowitz et al (75), where patients with moderate-severe disease activity at diagnosis who received 6-mercaptopurine had better outcomes then those who did not.

5.2 STUDY STRENGTHS

The maintenance of a prospectively compiled database was essential for both the post-hoc analysis and the thesis cohort study to be completed. Due to referral patterns the post-hoc analysis very closely approximated population-based data for childhood Crohn's disease. As such, the influence of referral bias was low and the data from this study

should accurately reflect the clinical course of childhood Crohn's disease. Furthermore, the high rate of follow-up in the thesis cohort study was important in ensuring the generalisability of the analyses.

As no gold standard exists for the diagnosis of Crohn's disease, misclassification and reclassification can be problematic. As noted, 10-15 percent of colitis cases are initially classified as 'indeterminate', and up to 3 percent of patients with Crohn's disease or ulcerative colitis are reclassified during follow-up (19;42). While this is a potential problem with all studies in inflammatory bowel disease, the application in this study of accepted definitions of Crohn's disease, ulcerative colitis and indeterminate colitis should have minimized the possibility of misclassification.

The validation of the primary outcome variable was very important in ensuring the accuracy and generalisability of this study.

Eighteen patients were not included in the initial analysis secondary to having incomplete data (eight were lost to follow-up and ten had incomplete baseline data collected). There were no appreciable differences in the baseline demographic data of the 18 patients with incomplete data and the 122 analyzed. As such, exclusion of these patients from the analysis should not be expected to appreciably affect the conclusions. As a further test, all analyses were conducted on the cohort of 132 patients (comprised of the 122 patients and the 10 with incomplete baseline data). The results were similar.

5.3 STUDY LIMITATIONS

Disease location was not found to be associated with future disease severity in our study. Munkholm et al (44) also found no association between disease location and disease course. However, it is important to note that our analysis was performed on relatively small numbers (particularly perianal disease - 2 patients) and thus a larger sample size may have detected a difference. Similarly, the small number of completed CDEIS (n=13) and IMPACT (n=18 and n= 27 at 6 and 12 months respectively) scores could have resulted in type II error in the analysis. Therefore, caution must be used in the interpretation of these results.

As this study was conducted in a tertiary care referral hospital it is likely that a higher percentage of patients with more severe disease were represented in the thesis cohort than would be expected in the normal population. While this referral bias would represent a significant methodological error for a natural history study, it should have minimal impact on the cohort study designed to identify prognostic factors, since the inflammatory bowel disease clinic at the Hospital for Sick Children also provides primary care to Crohn's disease patients in the region. Thus, the entire spectrum of disease severity in pediatric Crohn's disease would have been represented in the study group.

5.4 DIRECTIONS FOR FUTURE RESEARCH

This study examined factors predictive of disease severity only over the first year following diagnosis. Future studies should assess the presence of prognostic factors for a longer period of time.

As stated, the multivariate regression models explained only a small proportion of the variability in disease severity. Identification of other prognostic variables would increase the prognostic ability of these models. As our understanding of the pathophysiology of Crohn's disease evolves, future studies should examine the predictive value of other entities including TNF-alpha levels, baseline titers for ASCA/ANCA and mutations of associated genes, such as NOD2/CARD15. Furthermore, such studies should also evaluate clinical variables that were not evaluated in this study (including exposure to breast-feeding, smoking history and presence of anemia). As Crohn's disease is heterogeneous, future work will need to focus on identifying parameters to allow stratification of patients into individual treatment groups based upon their disease characteristics and predicted behaviour. Additional work should be done to identify prognostic factors in adult-onset Crohn's disease.

When conducting clinical trials it is imperative to have well defined and appropriate outcome measures. The outcome measures should be standardized to facilitate comparisons among different studies. To this end, validation of the primary outcome variable was performed in this study. However, the disease severity classification used in this study should be further validated against other independently compiled cohorts.

Future work should also be done to improve the assessment of disease severity. Disease severity is a multi-dimensional concept and such a measure should incorporate a

variety of factors including symptoms, impact on daily life, emotional and social disturbances, potency of therapy and complications of therapy over time. This may best be assessed through the development and validation of an index measure, as constructed through the process of item generation, reduction and selection. Such measures will need to be rigorously validated in a manner similar to that performed in this study. Other constructs should be incorporated in addition to the ones employed in this study, including correlation with school/work days missed, and impact on each patient's emotional well-being. Assessment by both patients/parents and physicians should be included. Similarly, future work should address the need to develop other outcome measures to be employed in clinical trials including assessments of severity of mucosal inflammation and healing.

Future investigation must focus on the role of early immunomodulator therapy in Crohn's disease. While Markowitz et al (75) provided preliminary evidence to support the early use of immunomodulator therapy, other groups must confirm their observation. This would most appropriately be performed within the setting of multi-center randomized control trials targeting first those patients with high disease activity. Finally, it is essential that well-defined outcome variables of disease severity be employed, similar to those used in this study.

Appendix A

1997 Toronto Census Metropolitan Area Jurisdictions

Ajax
Aurora
Bradford West Gwillimbury
Brampton
Caledon
East Gwillimbury
Georgina
Georgina Island First Nation
Halton Hills
King
Markham
Milton
Mississauga
Mono
New Tecumseth
Newmarket
Oakville
Orangeville
Pickering
Richmond Hill
Toronto
Uxbridge
Vaughan
Whitchurch-Stouffville

Appendix B

Criteria for Diagnosis of Crohn's Disease (16)

Exclusion:

- Infections (microbiology, including *Yersinia* antibodies when appropriate)
- Ischemia (predisposing factors, distribution of disease, histology)
- Irradiation (history)
- Lymphoma/carcinoma (previous coeliac disease, suggestive radiologic features, prognosis)

Inclusion:

a) Mouth to anus
- Chronic granulomatous lesion of the lip or buccal mucosal (inspection, biopsy)
- Pyloro-duodenal disease (radiology, endoscopy, biopsy)
- Small-bowel disease (radiology, endoscopy, specimen)
- Chronic anal lesion (clinical, examination, biopsy)

b) Discontinuous
- Lesions separated by normal mucosa, which may be widely separate, or 'skip lesions' along the length or around the circumference, or discrete ulcers (endoscopy, radiology, specimen)

c) Transmural
- Fissuring ulcers (radiology, specimen)
- Abscess (clinical imaging)
- Fistula (clinical, imaging)

d) Fibrosis
- Stricture (to be distinguished from carcinoma or concentric muscular thickening in UC), which can be asymmetric and multiple (endoscopy, radiology, specimen)

e) Lymphoid
- Biopsy of small apthoid ulcer or showing lymphoid aggregates

f) Mucin
- Retention of colonic mucin on biopsy in the presence of active inflammation (biopsy, specimen)

g) Granulomata
- Not present in all cases of Crohn's disease, distinguish from caseating granulomata of tuberculosis, foreign-body granulomata, or other causes (biopsy, specimen)

Appendix C Pediatric Crohn's Disease Activity Index[1]

HISTORY (Recall, 1 week)

Abdominal pain: None _____ (0)
Mild – Brief, does not interfere with activities _____ (5)
Mod/severe – daily, longer lasting, affects activities, nocturnal _____ (10)

Stools: (per day)
0-1 liquid stools, no blood _____ (0)
Up to 2 semi-formed with small blood, or 2-5 liquid _____ (5)
Gross bleeding, or >/= 6 liquid, or nocturnal diarrhea _____ (10)

Patient functioning, General Well-Being (Recall, 1 week)

No limitation of activities, well _____ (0)
Occasional difficulty in maintaining age appropriate activities,
Below par _____ (5)
Frequent limitation of activity, very poor _____ (10)

LABORATORY

HCT (%) **<10 yrs:** >33 ___(0) **11-14 M:** >/= 35 ___(0)
28-32 ___(2.5) 30-34 ___(2.5)
<28 ___(5) <30 ___(5)

11-19 F: >/= 34 ___(0) **15-19 M:** >/= 37 ___(0)
29-33 ___(2.5) 32-36 ___(2.5)
<29 ___(5) <32 ___(5)

ESR (mm/hr) <20 _____ (0)
20-50 _____ (2.5)
>50 _____ (5)

Albumin (g/dl) >/=3.5 _____ (0)
3.1-3.4 _____ (5)
</=3.0 _____ (10)

EXAMINATION

Weight

Weight gain or voluntary weight stable/loss _____ (0)
Involuntary weight stable, weight loss 1-9% _____ (5)
Weight loss >/= 10% _____ (10)

Height

At Diagnosis:
<1 channel decrease _____ (0)
>/=1, <2 channel decrease _____ (5)
>2 channel decrease _____ (10)

or

Follow-up:[2]
Height velocity >/= -1 SD _____ (0)
Height velocity < -1 SD, > -2 SD _____ (5)
Height velocity </= -2 SD _____ (10)

Abdomen

No tenderness, no masses _____ (0)
Tenderness, or mass without tenderness _____ (5)
Tenderness, involuntary guarding, definite mass _____ (10)

Perirectal disease

None, asymptomatic tags _____ (0)
1-2 indolent fistula, scant drainage, no tenderness _____ (5)
Active fistula, drainage, tenderness, or abscess _____ (10)

Extra-intestinal Manifestations

(Fever >/= 38.5 °C for 3 days over past week, definite arthritis,
Uveitis, e. nodosum, p. gangrenosum)
None _____ (0)
One _____ (5)
>/= Two _____ (10)

TOTAL SCORE _____

[1] Hyams JS et al. Development and validation of a pediatric Crohn's disease activity index. JPGN 1991; **12**:439-447.

[2] Tanner JM, Davies PSW. Clinical longitudinal standard height and height velocity for North American children. J Ped 1985; **107**:317-329.

Appendix D

IMPACT Questionaire

INSTRUCTIONS

On the next few pages you will find questions about many different issues. Some of these questions are about physical symptoms; other deal with emotions or worries. Underneath each question is a line. There is an answer A at one end of the line and an answer B at the other. Please put a mark anywhere on the line to show where your feelings lie. You can put your mark at A, at B, or anywhere in between, wherever fits best with your answer.

Here is an example:

How much do you like school?

A **B**

I hate school. I love school.

You can put a mark on the line anywhere you want; wherever fits best with how you feel about school.

The instructions for all the questions that follow will be the same, but the points A and B will have different meanings depending on the question.

Question 1: Put a mark anywhere on the line to tell how much your stomach has been hurting recently.

A	B
My stomach has been hurting so much, the pain is as bad as it has ever been, and comes all the time; it's really hard to deal with.	I haven't had any stomach cramps at all recently.

Question 2: Taking pills or medications is usually part of the treatment of IBD. Put a mark on the line to show how you feel about having to take medications.

A	B
I hate taking medications and I get really upset and bothered about having to take them.	I really don't mind at all when I have to take medications.

Question 3: Some kids find that they get more stomach pain or diarrhea when they eat certain foods. Put a mark on the line to show how eating affects you.

A	B
I can hardly eat anything at all; whenever I eat, I get pain or I'm running to the bathroom.	Nothing upsets my stomach; I can eat anything I want.

Question 4: Your IBD may have been completely under control for a long time, or you may have had flare-ups of symptoms. Do you worry about flare-ups? Put a mark on the line to show how much you worry about having a flare-up.

A	B
Even if I'm feeling better I can't enjoy it, because I can't trust it to last. I'm always afraid of getting sick again.	I never worry about having a flare-up.

Question 5: Your doctor and nurse have told you that medications and other treatments are used to keep your bowel condition under control, but not actually cure it. Put a mark on the line to show how you feel about this.

A	B
IBD is going to be with me all my life; it's horrible having something that's lifelong. I can't stop thinking about that.	I know that there isn't a cure for IBD yet but I never worry about that.

Question 6: Sometimes IBD (especially Crohn's disease) can affect your growth in height. Put a mark on the line to show how you feel about your growth.

A	B
Being short is really awful for me. If only I could be taller.	I am perfectly happy with my height.

Question 7: Some kids and teenagers have trouble gaining weight because of IBD, but others find they gain too much weight. Put a mark on the line to show how much you feel about your weight.

A	B
I'm miserable because of my weight. If only I could change it.	I'm perfectly happy with my weight.

Question 8: Some kids feel that IBD or the drugs sometimes used to treat it affect the way they look. Put a mark on the line to show how you feel about the way you look.

A	B
I think I look awful.	I'm perfectly happy with the way I look.

Question 9: Do you have enough energy to do the things you want to do?

A	B
I never have energy to do anything; I'm so tired all the time.	I have lots of energy; I can do as much as my friends can do without getting tired.

Question 10: Do you feel you have to give up or miss out on things you would like to do such as hobbies, just playing, going to parties or other special things?

A	B
I always have to stay out of things; I feel like I'm missing out on everything.	I can do all the things I like as much as I want. I don't feel my bowel condition gets in the way at all.

Question 11: How much does your bowel condition get in the way of going to school normally?

A	B
I can't attend school normally at all; I'm always having to stay home.	I never have to miss school because of my bowel condition.

Question 12: How much are you bothered by having diarrhea or gas?

A	B
My life seems to be spent in the bathroom; I'm always having to go to the bathroom or pass gas.	I don't have any problems with loose stools or gas.

Question 13: Some kids tell us they worry about health problems they might have in the future or bowel surgery they might need in the future. Are these things you worry about?

A	B
It's horrible always worrying about what might happen to me in the future because of this bowel condition.	I never worry about such things. It's not an issue for me.

Question 14: Do you feel it's unfair that you have IBD?

A	B
It's totally unfair that I have IBD; I feel really bitter about it all the time.	I'd rather I hadn't developed IBD, but I never spend time thinking it's unfair.

Question 15: Do you feel frustrated or angry about your bowel condition?

A	B
I feel very frustrated about my bowel condition; it makes me feel very angry all the time.	I don't feel angry or frustrated about my bowel condition at all.

Question 16: Sometimes other people might try to set restrictions or rules about what you eat or about other things that you would like to do. Do you feel that there are too many restrictions on you because of your IBD?

A	B
I have so many restrictions placed on me; it feels as if it's not my life.	I don't feel as if I have a lot of extra rules.

Question 17: How has your bowel condition affected your family?

A	B
I hate what my bowel condition has done to our family.	My family has handled my bowel condition very well. It has made us a stronger family.

Question 18: Do you feel embarrassed about your bowel symptoms? (For example about having to use a public washroom or going to the washroom a lot or passing gas).

A	B
I do almost anything to avoid using a washroom when people are around; You can't imagine how embarrassing it is to always have to use the washroom.	I don't feel I have any reason to be embarrassed; that's not something that bothers me.

Question 19: Being young is a time for having fun. Does your bowel condition get in the way?

A	B
I can't remember the last time I had fun; I feel like I'm always missing out on just having fun.	I have lots of fun times.

Question 20: Do you think your bowel condition makes it harder for you to make and have friends?

A	B
It's hard for me to make friends; I feel as if I don't have any.	I have good friends; we spend a lot of time together.

Question 21: How much are you bothered by bleeding with a bowel movement?

A	B
I'm very upset or scared by the bleeding I have been having.	That's not a problem. I may pass blood, but it's nothing I worry about.

Question 22: How much do you worry about having an accident and not making it to the washroom?

A	B
That's my worst fear. I often don't go out because of it. I can't go anywhere without knowing exactly where the washrooms are.	I don't have to get to the washroom fast; that's not a problem for me.

Question 23: How much do you feel sick to your stomach?

A	B
I feel like I'm always sick to my stomach.	I never feel sick to my stomach.

Question 24: Does your bowel condition leave you feeling stressed out?

A	B
I'm really stressed out; I've had about all I can take.	I don't feel stressed; I'm pretty relaxed.

Question 25: Do you worry about tests, investigations or treatments you have for your bowel condition? (For example Xrays, blood tests, IV's, colonoscopies).

A	B
I worry for days ahead of time about tests and treatments I have to have.	These things don't bother me. I don't worry about them.

Question 26: Do you think about your life when you are grown up? Do you worry that your bowel condition will get in the way of you having the job you want, or getting married and having a family?

A	B
I used to have a lot of hopes and dreams about what I would do in the future; but now there's no point.	I'm pretty hopeful about the future; I don't worry about those things.

Question 27: Do you feel kids treat you as different because of your bowel condition? Do you feel teased or not understood?

A	B
Kids treat me like some sort of freak; they talk about me behind my back or tease me.	I'm not treated any differently than anyone else.

Question 28: Do you feel generally happy with your life, or have you been feeling sad and depressed?

A	B
I feel very down and depressed.	I feel very happy with my life.

Question 29: Do you worry that your bowel condition gets in the way of going out on dates or having a boyfriend or girlfriend?

A	B
That's something that bothers me a lot; I feel as if no one would ever want to go out with me. I know that a date wouldn't go well, if I had one.	I don't have any problem with that; I have a good social life.

Question 30: Do you keep your bowel condition a secret from other people?

A	B
I'd never tell anyone I have IBD; I'd do anything to keep it secret.	I don't mind people knowing that I have IBD; it's nothing to be ashamed of.

Question 31: Do you have problems traveling or going away for a holiday because of your IBD?

A	B
I couldn't have a holiday. I'd just have to stay home. Traveling would be awful.	I don't have any problems traveling or going on holiday.

Question 32: How do you feel in general?

A	B
I just don't feel well at all. I'm not up for much.	I feel generally very well.

Question 33: Does your bowel condition get in the way of playing sports the way you would like to?

A	B
I would love to play sports, but I can't at all because of my bowel condition.	That's not a problem for me. I can play and enjoy sports if I want to. My bowel condition doesn't interfere at all.

Appendix E

Univariate Analysis

Table E-1a Univariate Analysis: Categorical Variables (Complete Set [n=122]/4)

Variable	Disease Severity				P Value (2-sided)	Chi-Square
	I (n=35)	II (n=38)	III (n=29)	IV (n=20)		
Female Gender	10	15	9	10	0.385	3.046
Initial Hospitalization (Yes)	6	12	12	13	0.004	13.486
Initial Steroids (Yes)	14	14	20	13	0.019	10.004
Initial Response (Partial/No Response vs Complete Response)	2	14	22	7	<0.001	23.023
Disease Location						
Small Bowel Only	8	8	8	4	0.913	0.528
Small/Large Bowel	14	21	17	10	0.449	2.651
Large Bowel Only	13	8	3	6	0.081	6.720
Positive Family History of IBD	8 (n=32)	12 (n=36)	13 (n=29)	3 (n=19)	0.153	5.274

I-quiescent, II-mild, III-moderate, IV-severe.

Table E-1b Univariate Analysis: Continuous Variables (Complete Set [n=122]/4)

Variable	Disease Severity				p Value	r^2
	I (n=35)	II (=38)	III (n=29)	IV (n=20)		
Age at Diagnosis (years)	12.76 (2.82)	13.07 (2.19)	13.48 (1.93)	13.23 (2.49)	0.684	0.013
Baseline ESR (mm/hr)	45.83 (23.12)	44.24 (19.18)	49.45 (28.62)	58.40 (28.13)	0.183	0.040
Baseline Albumin (g/L)	33.77 (4.43)	33.13 (5.30)	31.86 (4.71)	29.33 (4.71)	0.009	0.094
Baseline PCDAI	33.07 (14.73)	33.95 (10.65)	42.24 (16.29)	46.38 (14.13)	<0.001	0.129
Baseline Platelets (10^9/L)	440.60 (135.03)	432.74 (133.17)	465.17 (114.54)	452.10 (127.58)	0.764	0.010
Duration of Symptoms (months)	11.13 (13.91)	8.14 (8.30)	9.78 (11.36)	6.48 (10.73)	0.459	-

Mean (SD)
I-quiescent, II-mild, III-moderate, IV-severe.

Table E-2a Univariate Analysis: Categorical Variables (All Set [n=132]/2)

Variable	Quiescent/Mild Disease (n=78)	Moderate/Severe Disease (n=54)	P Value (2-sided)	Relative Risk	95% Confidence Interval
Female Gender	28	20	1.000	1.029	0.674 – 1.572
Initial Hospitalization	19	28	0.002	1.948	1.309 – 2.898
Initial Steroids	29	36	0.001	2.062	1.313 – 3.237
Initial Response (Partial/No Response vs Complete Response)	17	22	0.021	1.639	1.106 – 2.427
Disease Location					
Small Bowel Only	18	13	1.000	1.033	0.641 – 1.664
Small/Large Bowel	38	30	0.482	1.176	0.777 – 1.780
Large Bowel Only	21	9	0.207	0.680	0.377 – 1.225
Positive Family History of IBD	22(n=73)	17 (n=53)	0.847	1.039	0.749 – 1.442)

Table E-2b Univariate Analysis: Continuous Variables (All Set [n=132]/2)

Variable	Quiescent/Mild Disease n, x (SD)	Moderate/Severe Disease n, x (SD)	p Value (if Variances equal)	p Variances not equal
Age at Diagnosis (years)	78, 12.73 (2.63)	54, 13.43 (2.07)	0.104	0.0903
Baseline ESR (mm/hr)	76, 44.58 (20.73)	50, 53.00 (28.19)	0.056	0.073
Baseline Albumin (g/L)	77, 33.32 (4.89)	51, 30.95 (4.79)	0.008	0.008
Baseline PCDAI	76 33.55 (12.70)	51, 43.48 (15.57)	<0.001	<0.001
Baseline Platelets (10^9/L)	77, 433,43 (137.93)	51, 459.59 (116.50)	0.267	0.251
Duration of Symptoms (months)	78, 9.96 (11.91)	54, 8.74 (11.07)	0.552	0.547

Table E-3a Univariate Analysis: Categorical Variables (All Set [n=132]/4)

Variable	Disease Severity I (n=38)	II (n=40)	III (n=33)	IV (n=21)	p Value (2-sided)	Chi-Square
Female Gender	13	15	10	10	0.621	1.772
Initial Hospitalization	7	12	15	13	0.004	13.173
Initial Steroids	14	15	23	13	0.010	11.416
Initial Response (Partial/No Response vs Complete Response)	3	14	8	14	<0.001	23.476
Disease Location						
Small Bowel Only	8	10	9	4	0.880	0.670
Small/Large Bowel	17	21	20	10	0.586	1.934
Large Bowel Only	13	8	3	6	0.074	6.925
Positive Family History of IBD	10 (n=35)	12 (n=38)	13 (n=33)	4 (n=20)	0.508	2.323

I-quiescent, II-mild, III-moderate, IV-severe.

Table E-3b Univariate Analysis: Continuous Variables (All Set [n=132]/4)

Variable	Disease Severity				p Value	r^2
	I n, x (SD)	II n, x (SD)	III n, x (SD)	IV n, x (SD)		
Age at Diagnosis (years)	38, 12.66 (2.75)	40, 12.78 (2.54)	33, 13.54 (1.83)	21, 13.24 (2.43)	0.411	0.022
Baseline ESR (mm/hr)	37, 45.08 (22.71)	39, 44.10 (18.94)	30, 49.40 (28.12)	20, 58.40 (28.13)	0.148	0.043
Baseline Albumin (g/L)	37, 33.73 (4.53)	40, 32.95 (5.23)	31, 32.00 (4.61)	20, 29.33 (4.71)	0.010	0.087
Baseline PCDAI	36, 32.85 (14.58)	40, 34.19 (10.88)	31, 41.61 (16.39)	20, 46.38 (14.13)	0.001	0.122
Baseline Platelets (10^9/L)	38, 444.53 (130.35)	39, 422.62 (145.82)	31, 464.42 (110.69)	20, 452.10 (127.58)	0.599	0.015
Duration of Symptoms (months)	38, 11.75 (14.71)	40, 8.26 (8.27)	33, 9.65 (11.10)	21, 7.31 (11.14)	0.450	-

I-quiescent, II-mild, III-moderate, IV-severe.

Appendix F – Multivariate Analysis

Table F Mulivariate Analysis: Logistic Regression Models (Complete Set [n=122]/4)

Covariate	Regression Coefficient	Standard Error	p Value	Odds Ratio	95% CI	Percent Concordant
Intercept	2.157	1.744	0.216			71.1
Intercept 2	0.599	1.733	0.119			
Intercept 3	-0.872	1.737	0.252			
PCDAI	0.019	0.016	1.310	1.018	0.987 – 1.052	
Albumin	-0.043	0.042	1.073	0.958	0.883 – 1.040	
Initial Hospital (Yes)	0.344	0.199	2.991	1.990	0.913 – 4.334	
Initial Steroids (Yes)	0.182	0.191	0.904	1.437	0.680 – 3.038	
Initial Response (Partial/No Response)	0.578	0.196	8.700	3.177	1.474 – 6.850	
Intercept	0.188	0.555	0.735			69.7
Intercept 2	-1.344	0.567	0.018			
Intercept 3	-2.799	0.610	<0.001			
PCDAI	0.0330	0.013	0.012	1.033	1.007 – 1.073	
Initial Hospital (Yes)	0.3195	0.198	0.106	1.894	0.873 – 4.110	
Initial Response (Partial/No Response)	0.5880	0.194	0.003	3.241	1.512 – 6.946	
Intercept	-0.176	0.500	0.724			67.3
Intercept 2	-1.685	0.521	0.001			
Intercept 3	-3.119	0.574	<0.001			
PCDAI	0.040	0.012	0.001	1.041	1.016 – 1.066	
Initial Response (Partial/No Response)	0.654	0.191	0.001	3.699	1.748 – 7.828	
Intercept	-0.628	0.470	0.181			60.8
Intercept 2	-2.051	0.500	<0.001			
Intercept 3	-3.407	0.560	<0.001			
PCDAI	0.044	0.012	0.003	1.045	1.020 – 1.070	

Appendix G – Validation Analysis: Hospitalization

Table G-1 Construct validity testing (4 Category)

Construct	Analysis	r	p
Disease severity should reflect total length of hospitalization	Correlation between disease severity and total length of hospitalization	0.43	<0.0001
Disease severity should reflect length of hospitalization, excluding hospitalization at diagnosis	Correlation between disease severity and total length of hospitalization, excluding hospitalization at diagnosis	0.47	<0.0001
Disease severity should reflect number of hospitalizations	Correlation between disease severity and number of hospitalizations	0.43	<0.0001
Disease severity should reflect quality of life, as measured by IMPACT scores at one year after diagnosis	Correlation between disease severity and quality of life, as measured by IMPACT scores at one year after diagnosis	-0.39	0.043
Disease severity should reflect quality of life, as measured by IMPACT scores at six months after diagnosis	Correlation between disease severity and quality of life, as measured by IMPACT scores at six months after diagnosis	-0.59	0.010
Disease severity should reflect disease activity over time, as measured by mean PCDAI scores at 6 and 12 months	Correlation between disease severity and disease activity over time, as measured by mean PCDAI scores at 6 and 12 months	0.49	<0.0001
Disease severity should reflect linear growth, as measured by change in z-scores from end of first year and diagnosis	Correlation between disease severity and linear growth, as measured by change in z-scores from end of first year and diagnosis	-0.16	0.082

Table G-2 Validation Analysis: Hospitalization

Variable	Disease Severity				F	p Value
	I (n=35)	II (n=38)	III (n=29)	IV (n=20)		
Total Days Hospitalized	1.97 (5.61)	8.00 (16.11)	11.14 (14.75)	20.10 (17.82)	7.527	<0.001
Days Hospitalized Excluding Hospitalization at Diagnosis	0.00 (0.00)	2.95 (8.25)	5.83 (10.65)	10.85 (13.77)	6.923	<0.001
Number of Hospitalizations	0.17 (0.38)	0.71 (1.04)	1.07 (1.33)	1.45 (1.19)	7.927	<0.001

Mean (SD)
I-quiescent, II-mild, III-moderate, IV-severe

Table G-3 Validation Analysis: Mean PCDAI Scores

Variable	Disease Severity				F	p Value
	I (n=28)	II (n=25)	III (n=21)	IV (n=15)		
Mean PCDAI Scores (6 and 12 months)	4.24 (3.42)	12.30 (8.12)	13.93 (10.01)	18.67 (13.51)	10.435	<0.001

Mean (SD)
I-quiescent, II-mild, III-moderate, IV-severe

Table G-4 Validation Analysis: Growth

Variable	Disease Severity				F	p Value
	I (n=35)	II (n=38)	III (n=29)	IV (n=20)		
Height at Diagnosis (z-score)	-0.48 (1.09)	-0.77 (1.40)	-0.71 (0.86)	-0.70 (1.28)	0.399	0.754
Height at One Year (z-score)	-0.28 (1.03)	-0.67 (1.17)	-0.85 (0.82)	-0.63 (1.39)	1.537	0.208
Change in Height Over One Year (Delta z-score)	0.20 (0.51)	0.10 (0.62)	-0.14 (0.30)	0.07 (0.51)	2.471	0.065

Mean (SD)
I-quiescent, II-mild, III-moderate, IV-severe

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