# Pediatric Crohn's Disease Activity at Diagnosis, Its Influence on Pediatrician's Prescribing Behavior, and Clinical Outcome 5 Years Later

*Tamara Mesker, MD,* Patrick F. van Rheenen, MD, PhD,* Obbe F. Norbruis, MD,† Jan Uitentuis, MD,‡ Herman J. Waalkens, MD, PhD,§ Gieneke Gonera, MD,‖ Lidy A.T. van Overbeek, MD,¶ Joke Butler, MD,** and Edmond H.H.M. Rings, MD, PhD**

**Background:** No studies have been performed in which therapeutic regimens have been compared between mild and moderate-to-severe pediatric Crohn's disease (CD) at diagnosis. The aim was to analyze pediatric CD activity at diagnosis, its influence on pediatrician's prescribing behavior, and clinical outcome 5 years later.

**Methods:** In a retrospective multicenter study we divided pediatric CD patients at diagnosis into mild or moderate-severe disease. We compared initial therapies, duration of first remission, number of exacerbations, height-for-age and weight-for-height evolvement, and cumulative duration of systemic steroid use in a 5-year follow-up period.

**Results:** Forty-three children were included (25 with mild and 18 with moderate-severe disease). Aminosalicylate monotherapy was more frequently prescribed in the mild group (40% versus 17%; $P < 0.01$). The median duration of systemic steroid use was 18.3 months in the mild group and 10.4 months in the moderate-severe group ($P = 0.09$). Duration of first remission was 15.0 months in the mild group and 23.4 months in the moderate-severe group ($P = 0.16$). The mean number of exacerbations was 2.2 in the mild group and 1.8 in the moderate-severe group ($P = 0.28$).

**Conclusions:** CD patients with mild disease were treated with aminosalicylate monotherapy more frequently. These patients, however, tend to have more exacerbations, shorter duration of first remission, and longer total duration of systemic steroid use. Our data support the concept that severity of disease at diagnosis does not reliably predict subsequent clinical course. This study suggests that there is no indication that children with mild CD should be treated differently compared to children with moderate-severe disease.

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**Key Words:** Crohn's disease, PCDAI, treatment, outcome, remission

An important debate concerning the treatment of children with Crohn's disease (CD) is whether this should be "top-down" or "step-up."[1–3] The "top-down" approach is based on early use of immunomodulators or biologicals, with the aim of changing the course of the disease and avoiding complications.[3] However, patients run a higher risk of adverse effects of medication with this approach.[1] With the "step-up" method, treatment is progressively intensified over time. This approach ignores the opportunities to influence the natural course of disease.

Over the past few years, adult CD patients are increasingly treated more aggressively.[4] We have recently shown in pediatric CD that early introduction of immunomodulators is associated with a longer remission interval.[5] We did not evaluate the long-term outcome with respect to various initial therapies and did not correct for disease severity at diagnosis. Markowitz et al[6] showed that the addition of 6-mercaptopurine (immunomodulator) to a regimen of corticosteroids lessened the need for prednisone and improved maintenance of remission in a group of children with moderate-to-severe disease. To our knowledge no studies have been performed in which therapeutic regimens have been compared between mild and moderate-severe pediatric CD in children; however, pediatricians have the tendency to treat mild CD differently as compared to moderate-severe. We hypothesize that the severity of the

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From the *Department of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, †Department of Pediatrics, Isala Clinics, Location Sophia, Zwolle, The Netherlands, ‡Department of Pediatrics, Medical Center Leeuwarden, Leeuwarden, The Netherlands, §Department of Pediatrics, Martini Hospital, Groningen, The Netherlands, ‖Department of Pediatrics, Wilhelmina Hospital, Assen, The Netherlands, ¶Department of Pediatrics, Scheper Hospital, Emmen, The Netherlands, **Department of Pediatrics, Deventer Hospital Location Geertruida, Deventer, The Netherlands.

Reprints: Edmond H.H.M. Rings, MD, PhD, Department of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, P.O. Box 30.001, 9700 RB, Groningen, The Netherlands (e-mail: e.h.h.m.rings@bkk.umcg.nl)

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disease at diagnosis does not predict the subsequent clinical course. We evaluated whether disease severity at diagnosis as expressed by the Pediatric Crohn's Disease Activity Index (PCDAI) influenced prescribing behavior of pediatricians. We evaluated 1) initial therapies, 2) duration of first remission, 3) number of exacerbations, 4) height-for age and 5) weight-for-height evolvement, and 6) cumulative duration of systemic steroid use after 5 years follow-up.

## MATERIALS AND METHODS

### Patients and Centers

Data on consecutive newly diagnosed CD patients were retrospectively collected by a single researcher at 7 different hospitals in the northern part of the Netherlands. All except 1 (University Medical Center Groningen, UMCG) are general hospitals. UMCG is a tertiary care center. Patients were treated according to a shared treatment plan between the hospitals. Most pediatricians in the general hospital were trained as fellows in Pediatric Gastroenterology (4/6) and most had their training in the tertiary UMCG (3/6). Patients were eligible for inclusion in the study if their age was below 18 years at diagnosis. When the follow-up was less than 5 years, patients were excluded from analysis. Data were obtained between January 1, 1998, and December 31, 2007. The diagnosis of CD was based on standard clinical symptoms, endoscopic, radiographic, and histopathologic findings in accordance with the Porto criteria.[7]

### Data Collection

Medical records were reviewed and data were entered in a computerized database (MS Access 2003, Microsoft, Redmond, WA). Baseline characteristics included age, sex, weight, height, the presence of extraintestinal manifestations, disease location, and behavior (according to the Montreal Classification).[8] Height and weight were entered in Growth Analyser 3.5, a freely available computerized system to analyze anthropometric data using Dutch reference standards (2006 Dutch Growth Research Foundation, Rotterdam, the Netherlands). Severity of disease was assessed by extracting the PCDAI from the medical records. This is a validated, multi-item scoring system that comprises items on history, physical examination, and laboratory parameters.[9,10] The PCDAI score is responsive to short-term change and thereby used to indicate the response to treatment in time.[11] Laboratory parameters used to calculate the PCDAI score include serum albumin, hematocrit, and erythrocyte sedimentation rate (ESR). Hematocrit scores are gender- and age-specific.

All visits were recorded. PCDAI score, weight, height, drug prescription, adverse drug reactions, diagnostic procedures (radiologic, endoscopic), and surgical interventions (resection of bowel) were entered in the database. Prescribed drugs included corticosteroids, aminosalicylates (mesalazine or sulfasalazine), antibiotics (used for perianal disease only), immunomodulators (azathioprine, 6-mercaptopurine or cyclosporine), and biologicals (infliximab). Exclusive enteral nutrition was also considered a medical treatment option because of its effectiveness in treating pediatric CD.[12]

In case of missing data the abbreviated PCDAI or the clinical index was used.[9,13] The abbreviated PCDAI score can be calculated without knowing laboratory results. It is said to predict disease activity equally well as the full PCDAI.[13]

### Definitions

A PCDAI score of 11 to 30 points was defined as mild activity and a score over 30 points as moderate to severe disease activity. Remission was defined as a PCDAI score of 10 or less. Exacerbation (flare-up) was defined as an increase in PCDAI score above 10 points after a period of remission. Duration of first remission was calculated by subtracting the date of first exacerbation and the date of first remission. We evaluated 1) initial therapies, 2) the number of exacerbations, 3) duration of first remission in months, 4) height-for-age evolvement, 5) weight-for-height evolvement, and 6) total duration of systemic steroid use during 5 years of follow-up.

Growth and nutritional status were expressed as gender-specific height-for-age z-scores and weight-for-height z-scores. Growth failure at diagnosis was defined as height-for-age z-score of minus 1.64 (below the fifth percentile). Growth failure after 5 years of treatment was the difference between height-for-age z-scores at 5 years follow-up and at diagnosis. The same was done for weight-for-height to determine the nutritional status of patients after 5 years. There was no systematic registration in the medical charts regarding the onset of puberty.

### Statistical Analysis

Two groups of patients were distinguished at diagnosis based on the initial PCDAI score: mild disease activity (PCDAI $\leq$ 30) and moderate-severe disease activity (PCDAI $>$ 30). Data were analyzed in SPSS (v. 13.0, Chicago, IL). Student's *t*-tests and chi-square tests were used to compare baseline characteristics between groups. For nonparametric data the Mann–Whitney *U*-test was used. Time to event data were analyzed by Kaplan–Meier and log-rank test. The level of significance used was a *P*-value $< 0.05$.

**TABLE 1.** Patient Characteristics at Diagnosis

| | All Patients | PCDAI ≤ 30 | PCDAI > 30 |
|---|---|---|---|
| | $n = 43$ | $n = 25$ | $n = 18$ |
| PCDAI score, mean (SD) | 30.5 (12.9) | 21.7 (7.1) | 42.6 (8.5) |
| Male (%) | 28 (65) | 17 (68) | 11 (61) |
| Age in years, median (range)[a] | 13.2 (2.4–16.7) | 12.1 (2.4–14.8) | 14.3 (7.4–16.7) |
| Sites of initial CD involvement, *n* (%) | | | |
| Small bowel | 6 (14) | 3 (12) | 3 (17) |
| Small bowel and colon | 19 (44) | 12 (48) | 7 (39) |
| Colon | 18 (42) | 10 (40) | 8 (44) |
| Perianal disease | 9 (21) | 4 (16) | 5 (28) |
| Upper GI tract disease | 2 (5) | 0 (0) | 2 (11) |
| Extraintestinal manifestation[a] | 9 (21) | 2 (8) | 7 (39) |
| Disease behavior, *n* (%) | | | |
| Nonstricturing | 33 (77) | 21 (84) | 12 (67) |
| Stricturing | 1 (2) | 0 (0) | 1 (6) |
| Penetrating | 9 (21) | 4 (16) | 5 (28) |
| Z-score height for age, mean (SD)[a,b] | −0.22 (1.13) | 0.10 (1.02) | −0.72 (1.16) |
| Z-score weight for height, mean (SD)[b] | −0.80 (1.49) | −0.80 (1.68) | −0.81 (1.21) |

[a]Significant difference, $P < 0.05$.
[b]One patient with moderate-severe disease activity was excluded from assessment of height and weight because of short stature unrelated to CD.

## RESULTS

### Patient's Baseline Characteristics

A total of 43 patients with CD met the inclusion criteria and were included in this study. Twenty-eight males and 15 females with a median age of 13.2 years at onset (range 2.4–16.7) were included. Twenty-five patients presented with mild disease activity (PCDAI ≤ 30) and 18 patients with moderate-severe disease activity (PCDAI > 30). Seven patients were exclusively treated in the tertiary center and 7 patients were exclusively treated in general hospitals. The remaining 29 patients were treated in both the tertiary center and a general hospital according to a shared treatment plan.

The mild and moderate-severe groups were comparable in terms of gender, site of initial CD involvement, and disease behavior. The children in the moderate-severe group were significantly older at diagnosis, had significantly more extraintestinal manifestations, and had significantly lower height-for-age z-scores. Baseline data are shown in Table 1.

### Pediatrician's Prescribing Behavior

#### *Initial Treatment*

Tables 2 and 3 show the drugs and combination of drugs that were prescribed in the first 30 days after diagnosis. Aminosalicylates were the most frequently prescribed drugs immediately after diagnosis. Aminosalicylate monotherapy was more frequently prescribed in the mild group (10/25 [40%] versus 3/18 [17%] ($P = <0.01$). Azathioprine (an immunomodulator) was only rarely prescribed within the first month after diagnosis. Combinations of medication were often used to control disease activity. In our cohort 9 different combinations of treatment could be distinguished at first presentation.

#### *Systemic Steroid Use*

Systemic steroids were prescribed for controlling active CD in 26 (60%) patients. The median duration of total systemic steroid use was 14.3 months (interquartile range 7.3–20.8). In the mild disease group the median

**TABLE 2.** Initial Drug Treatment

| Medication, *n* (%) | All | PCDAI ≤ 30 | PCDAI > 30 |
|---|---|---|---|
| Aminosalicylates | 41 (95) | 25 (100) | 16 (89) |
| Systemic steroids | 26 (60) | 13 (52) | 13 (72) |
| Enteral nutrition therapy | 3 (7.0) | 2 (8.0) | 1 (5.6) |
| Antibiotics for perianal disease | 4 (9.3) | 0 (0) | 4 (22.2) |
| Immunomodulators | 2 (4.7) | 0 (0) | 2 (11.1) |

**TABLE 3.** Prescribed Drug Combination in the First Month After Diagnosis

| Medication, *n* (%) | All | PCDAI $\leq$ 30 | PCDAI $>$ 30 |
|---|---|---|---|
| Aminosalicylates + steroids | 21 (49) | 13 (52) | 8 (44.4) |
| Aminosalicylates + monotherapy* | 13 (30) | 10 (40) | 3 (16.7) |
| Aminosalicylates + steroids + antibiotics | 2 (4.7) | 0 (0) | 2 (11.1) |
| Aminosalicylates + enteral therapy | 2 (4.7) | 2 (8.0) | 0 (0) |
| Aminosalicylates + antibiotics | 1 (2.3) | 0 (0) | 1 (5.6) |
| Aminosalicylates + enteral therapy + antibiotics | 1 (2.3) | 0 (0) | 1 (5.6) |
| Aminosalicylates + steroids + immunomodulators | 1 (2.3) | 0 (0) | 1 (5.6) |
| Steroids + immunomodulators | 1 (2.3) | 0 (0) | 1 (5.6) |
| Steroids monotherapy | 1 (2.3) | 0 (0) | 1 (5.6) |

*Significant difference, $P < 0.01$.

duration (interquartile range) of total systemic steroids was 18.3 months (9.1–22.6) as compared to 10.4 months (5.5–17.9) in the moderate-severe group ($P = 0.09$). No significant correlations were found between height-for-age z-score and weight-for-height z-score after 5 years and total duration of systemic steroid use.

### *Time Until Introduction of Immunomodulators*

Overall, 16 of the 43 patients (37%) started with immunomodulators (in all cases azathioprine) within 1 year of CD diagnosis. Median time until introduction of immunomodulators was 18.9 months (95% confidence interval [CI] 13.8–24.0 months) for all patients. Seven patients in the mild group (44%) started with immunomodulators within 1 year and 9 patients in the moderate-severe group (56%) ($P = 0.20$, log-rank test). In the group that initially presented with mild disease the median time before introduction of immunomodulators was 18.9 months (95% CI 16.3–21.5) as compared to 12.0 months (95% CI 0–36.9) in the moderate-severe group ($P = 0.44$). There was no difference between both groups regarding introduction of immunomodulators. Introduction of immunomodulators was not correlated with duration of first remission ($r = 0.11$). Dosage of immunomodulators (azathioprine) in our cohort was 2–3 mg/kg/day.

In the mild group the mean PCDAI score before immunomodulators was 14.1 and after 10.3. In the moderate-severe group scores were 24.5 and 12.8. In the mild group, the median duration of total systemic steroid use was 7.3 months before introduction of immunomodulators and 12.3 months after introduction. For the moderate-severe group systemic steroid use was 4.7 months before and 8.3 months after introduction of immunomodulators.

### *Time Until Introduction of Biologicals*

In our cohort 7 patients required biologicals (in all cases infliximab) during their 5-year follow-up: 3 patients in the mild group and 4 in the moderate-severe group ($P > 0.05$).

The median time of introduction of biologicals was 53.3 months (95% CI 24.5–117.5) in the mild group and 8.0 months (95% CI 8.0–11.0) in the moderate-severe group ($P = 0.06$, log-rank test). One patient required infliximab because of no improvement on steroids or immunomodulators for nonperianal disease and 6 patients required biologicals for their fistulizing CD unresponsive to conventional therapy.

### *Enteral Therapy*

In our study period enteral nutrition therapy was just being introduced and was not yet considered first choice in treatment of pediatric CD.

### *Maintenance Therapy*

In the group with mild disease 7 patients (28.0%) were on aminosalicylate-only maintenance therapy in the first 4 years after diagnosis as compared to 4 patients (9.7%) in the moderate-severe group ($P = 0.74$). One patient in the moderate-severe group was not on any maintenance therapy.

### *Treatment Combinations After 5 Years*

Table 4 shows the drugs and drug combinations that were prescribed at 5 years after diagnosis of the disease. The table shows that most patients (69%) used immunomodulators (exclusively or in combination with other drugs) at the end of our study period.

## Outcome of Disease

### *Height and Weight*

In this study population, 4 patients (9.5%) had a height-for-age z-score of minus 1.64 at diagnosis; all patients were in the moderate-severe group. After 5 years of follow-up, 7 patients (16.7%) had growth impairment. In

**TABLE 4.** Prescribed Drug Combination After 5 Years of Follow-up

| Medication, *n* (%) | All | PCDAI $\leq$ 30 | PCDAI $>$ 30 |
|---|---|---|---|
| Immunomodulators | 12 (28) | 7 (28) | 5 (28) |
| Immunomodulators + aminosalicylates | 6 (14) | 2 (8) | 4 (22) |
| Immunomodulators + biologicals | 3 (7) | 2 (8) | 1 (5) |
| Immunomodulators + aminosalicylates + steroids | 4 (9) | 3 (12) | 1 (5) |
| Immunomodulators + steroids | 3 (7) | 2 (8) | 1 (5) |
| Immunomodulators + aminosalicylates + steroids + antibiotics | 1 (2) | 1 (4) | 0 (0) |
| Immunomodulators + enteral therapy | 1 (2) | 1 (4) | 0 (0) |
| Aminosalicylates only | 8 (19) | 6 (24) | 2 (11) |
| Biologicals only | 1 (2) | 0 (0) | 1 (5) |
| Immunomodulators + antibiotics | 3 (7) | 0 (0) | 2 (11) |
| No therapy | 2 (5) | 1 (4) | 1 (5) |

the mild group 3 patients (12.0%) had growth impairment after 5 years and in the moderate-severe group 4 patients (23.5%; $P = 0.41$). Table 5 shows the height-for-age and weight-for-height z-scores at diagnosis after 5 years follow-up and the difference as compared to the z-scores at presentation for all patients and for both groups. No significant difference was found in height-for-age and weight-for-height evolvement after 5 years between both groups ($P = 0.10$ and $P = 0.57$, respectively). Through the years the overall height-for-age z-score did not change much (−0.13 SD). Weight-for-height, however, improved markedly; almost 1 SD (+0.94).

Eleven out of 42 patients (26%) had weight-for-height z-scores of minus 1 after 5 years of follow-up. Seven patients were in the moderate-severe group (41%) and 4 patients from the mild group (16%; $P = 0.07$). Height-for-age z-scores were minus 2 in 3 patients (7.1%); 2 patients were from the moderate-severe group and 1 patient from the mild group.

### *Duration of Active Disease After Diagnosis*

Median duration of active disease after diagnosis was 2.4 months (95% CI 1.8–3.0). The mild group did not reach remission sooner than the moderate-severe group (1.9 months (95% CI 0.9–3.0) versus 2.5 months (95% CI 2.1–2.9) ($P = 0.20$).

### *Duration of First Remission*

Figure 1 shows that the duration of first remission was 15.0 months (95% CI 10.1–19.9) in the mild group, as compared to 23.4 months (95% CI 0.1–46.7) in the moderate-severe group ($P = 0.16$, log-rank test).

### *Number of Exacerbations*

The mean total number of exacerbations in the first 5 years of disease was 2.2 (SD 0.9) in the mild group as compared to 1.8 exacerbations (SD 1.0) in the moderate-severe group ($P = 0.28$).

**TABLE 5.** Patient's Weight and Height Status After 5 Years

| | At diagnosis | *P*-value | After 5 Years Follow-up | *P*-value | Difference |
|---|---|---|---|---|---|
| Height for age z score, mean (SD) | | | | | |
| All patients | −0.22 (1.13) | | −0.35 (1.18) | | −0.13 |
| PCDAI $\leq$ 30 | 0.10 (1.02) | | −0.07 (1.14) | | −0.17 |
| PCDAI $>$ 30 | −0.72 (1.16) | 0.02 | −0.68 (1.18) | 0.10 | 0.04 |
| Weight for height z score, mean (SD) | | | | | |
| All patients | −0.80 (1.49) | | 0.14 (1.16) | | 0.94 |
| PCDAI $\leq$ 30 | −0.80 (1.68) | | 0.03 (1.29) | | 0.83 |
| PCDAI $>$ 30 | −0.81 (1.21) | 0.98 | 0.25 (0.97) | 0.57 | 1.06 |

One patient with moderate-severe disease activity was omitted from assessment of height and weight because of short stature unrelated to CD.

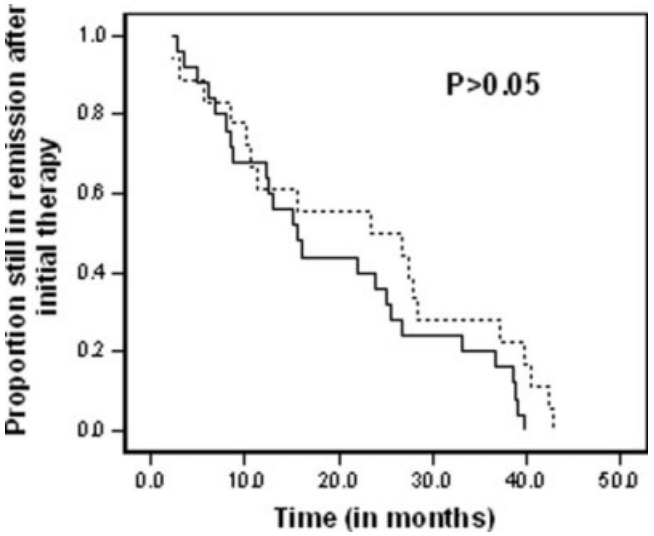


FIGURE 1. Proportion of CD patients still in remission after initial treatment in children with mild disease severity at diagnosis (solid line, PCDAI $\leq$ 30, $n = 25$) and moderately severe disease activity (broken line, PCDAI $>$ 30, $n = 18$).

### Activity of Disease During Follow-up

Both groups (mild and moderate-severe) had a mean total of 24 visits in 5 years. The mean PCDAI score during the follow-up period was calculated for both groups. The mean PCDAI score per visit was 11 (SD 3.5) in the mild group and 15 (SD 3.9) in the moderate-severe group ($P = 0.72$).

### Adverse Drug Reactions

Azathioprine- or mesalazine-induced pancreatitis was observed with an incidence of 7.0% in our cohort. One patient had a pancreatitis twice in our follow-up period, once associated with the use of mesalazine and the second time with azathioprine.

### Surgical Intervention

During follow-up, 12 (28%) patients had a resecting operation. Indication for surgery was obstructing or perforating disease. Median time until surgery was 38.7 months (95% CI 31.1–46.3) in the mild group versus 8.5 months (95% CI 0.0–30.5) in the moderate-severe group ($P = 0.98$, log-rank test). In the mild group ($n = 25$), 7 resecting operations (28%) were performed as compared to 5 (28%) in the moderate-severe group ($n = 18$) ($P = 0.99$).

## DISCUSSION

This study shows that pediatricians direct their therapies according to the severity of CD at diagnosis. Our data, however, support the concept that severity of disease at diagnosis does not reliably predict subsequent clinical course. Severity of CD at diagnosis in children should therefore not be a parameter to direct differential therapies in this disease.

Cutoff scores for disease activity and changes in disease activity are well-defined.[10] The groups mild and moderate-severe disease at diagnosis were classified in accordance with these validated cutoff scores. We used the PCDAI score to follow the patient's clinical course over time. The PCDAI has not been used as a predictor for long-term outcome in pediatric studies.[10] The PCDAI score does not reflect disease progression but is responsive to short-term change in disease activity. The PCDAI is therefore an indicator of change in the clinical status of patients. Changes in growth parameters are pertinent in the PCDAI.[10] However, other variables in the PCDAI are moment-dependent and do not give any information on progression of disease over time.

Treatment of pediatric CD patients is dependent on treatment guidelines and policies. We showed that in the period between 1998 and 2007 Dutch pediatricians tended to choose treatment with aminosalicylates, as advised in the 1994 Dutch consensus guidelines.[14] Nowadays, evidence-based treatment protocols no longer recommend aminosalicylates as initial therapy.[15] We used the cumulative duration of systemic steroids as an indicator for disease control. The steroid treatment regimen in the Netherlands has a maximum starting dose of 40 mg daily ($\approx$1–2 mg/kg bodyweight) with subsequent tapering as recommended by the Dutch consensus guidelines on treatment of inflammatory bowel disease.[15] According to these guidelines the total duration of steroid use to treat exacerbations should be $\approx$14 weeks. We found that systemic steroids were often prescribed for extended periods (median total duration of 14.3 months), indicating that the children in our study cohort did not receive effective maintenance therapy. Our study suggests that the use of less intensive therapies does not improve the clinical course in mild CD patients.

Children with moderate-severe disease activity at diagnosis had a significantly higher age than those with mild disease activity at presentation (14.3 versus 12.1 years), a greater prevalence of growth impairment (−0.72 versus 0.10 z-score), and more extraintestinal manifestations (39% versus 8%). Baseline characteristics of patients are comparable with patients in previous studies.[16] However, the difference in age between both groups cannot be explained. A possible explanation may be a longer patient–doctor's delay, which in turn leads to a higher disease activity score at diagnosis. Alternatively, this may be a reflection of the natural presentation of the disease during pediatric development, with a more severe presentation in older patients. A recent study, however, shows that children with moderate-severe disease activity at diagnosis had a mean age of 12.0 years (SD 2.4), unlike our findings.[17]

Children with CD often present with weight loss or poor weight gain and growth. Growth failure is common at presentation in CD and has been reported in up to 25%–

30% of CD children, depending on the definition of growth failure.[18] Of our patients, 9.5% presented with a height-for-age z-score of minus 1.64 z-score and all were patients in the moderate-severe group. After 5 years of follow-up 16.7% of the patients had a height-for-age z-score of minus 1.64. Overall, height-for-age showed no significant improvement after 5 years of follow-up. However, weight-for-height greatly improved over the period of 5 years in both groups, almost 1 SD overall. An inadequate nutritional status (low weight-for-height z-score) is widely recognized in CD and has been associated with increased morbidity in patients.[19] The findings of this study suggest that medical treatment in CD patients greatly improves their nutritional status after 5 years of follow-up. In this cohort, ultimate final height was minus 1 z-score in 26% and minus 2 z-score in 7.1% of the patients. These results are similar to findings in the study of Taminiau.[20]

In this study no data were collected for onset of puberty and pubertal development. Therefore, no separate analysis of height and weight according to onset of puberty could be made. This can influence our height z-score. It is known that severity of disease is usually greater in adolescents and once puberty has started the period of time available for recovering linear growth is almost none.[21] Also, target height could not be calculated because of missing data on parent's height.

We are aware of the limitations of this study; however, several strengths of this study may be appreciated: first, intercenter and interphysician variation in medical management and referral of CD patients has been observed in previous studies.[22,23] In our study this "bias" was filtered out by using patients from different centers, namely, a tertiary center and 6 nontertiary centers (general hospitals). It should be noted that the nontertiary group, consisting of patients exclusively treated in a nontertiary center for 5 years, was a very small sample. Only 7 patients were in the nontertiary group as compared to the 35 from the tertiary center. However, most children (29 patients) in the tertiary center were also seen in general hospitals during the 5-year follow-up as part of a shared care plan according to regional agreements. Second, the follow-up period (5 years) after diagnosis was identical for all patients. Studies have demonstrated that CD is more active during the first years of the disease.[24] By using identical follow-up times for both groups, a better comparison of the disease course is obtained between groups. Third, data collection was done by 1 researcher only, thereby minimizing subjective differences in scoring of the PCDAI.

The limitations of this study are: first, the relatively small number of patients included. A larger number of patients would have increased the validity of our conclusions. Even so, significant differences may then be found in this study setting. The major conclusion of this study, however, would not change with a larger sample size. Second, due to the retrospective character of this study, chart review was occasionally inadequate because of missing data. Third, psychosocial factors are omitted in the calculation of the PCDAI score. Factors such as anxiety and depression may influence patient's symptoms and thus bias the total PCDAI score and influence medication use. Social status, which plays an important role in compliance of therapy and lifestyle, especially in young adolescent children, has not been recorded.[25,26]

Fourth, it is unclear if the natural history of the disease, especially when comparing severity on presentation, would change if patients were treated by current standards of care.

In conclusion, with this retrospective multicenter study we show that pediatricians direct their initial therapies according to the severity of CD. Patients with mild disease at diagnosis were treated with aminosalicylate monotherapy more frequently in the Netherlands. These patients, however, tended to have more exacerbations, shorter duration of first remission, and longer total duration of systemic steroid use. Our data support the concept that severity of disease at diagnosis does not reliably predict subsequent clinical course. This study suggests that there is no indication that children with mild CD should be treated differently compared to children with moderate-severe disease.

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