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# Long-Term Prognosis for Childhood Constipation: Clinical Outcomes in Adulthood



**WHAT'S KNOWN ON THIS SUBJECT:** Long-term follow-up studies involving children with functional constipation are scarce, but results suggest that symptoms may persist for many years. Information about outcomes at adult age is lacking.



**WHAT THIS STUDY ADDS:** In this study, we examine the long-term prognosis for children with constipation when they reach adult age, and we identify prognostic factors associated with poor and good clinical outcomes.

## abstract

**OBJECTIVES:** This study examines long-term prognoses for children with constipation in adulthood and identifies prognostic factors associated with clinical outcomes.

**METHODS:** In a Dutch tertiary hospital, children (5–18 years of age) who were diagnosed as having functional constipation were eligible for inclusion. After a 6-week treatment protocol, prospective follow-up evaluations were conducted at 6 and 12 months and annually thereafter. Good clinical outcomes were defined as  $\geq 3$  bowel movements per week for  $\geq 4$  weeks, with  $\leq 2$  fecal incontinence episodes per month, irrespective of laxative use.

**RESULTS:** A total of 401 children (260 boys; median age: 8 years [interquartile range: 6–9 years]) were included, with a median follow-up period of 11 years (interquartile range: 9–13 years). The dropout rate during follow-up was 15%. Good clinical outcomes were achieved by 80% of patients at 16 years of age. Thereafter, this proportion remained constant at 75%. Poor clinical outcomes at adult age were associated with: older age at onset (odds ratio [OR]: 1.15 [95% confidence interval [CI]: 1.02–1.30];  $P = .04$ ), longer delay between onset and first visit to our outpatient clinic (OR: 1.24 [95% CI: 1.10–1.40];  $P = .001$ ), and lower defecation frequency at study entry (OR: 0.92 [95% CI: 0.84–1.00];  $P = .03$ ).

**CONCLUSIONS:** One-fourth of children with functional constipation continued to experience symptoms at adult age. Certain risk factors for poor clinical outcomes in adulthood were identified. Referral to a specialized clinic should be considered at an early stage for children who are unresponsive to first-line treatment. *Pediatrics* 2010;126:e156–e162

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### KEY WORDS

functional constipation, childhood, follow-up, outcome, adulthood, prognosis

### ABBREVIATIONS

GEE—generalized estimating equation

OR—odds ratio

CI—confidence interval

IBS—irritable bowel syndrome

IQR—interquartile range

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Functional constipation is a common disorder among children, accounting for ~3% of visits to pediatric clinics and even 10% to 25% of visits to pediatric gastroenterology clinics.<sup>1-4</sup> The general belief that functional constipation is self-limiting<sup>5,6</sup> was not supported by several long-term follow-up studies.<sup>7-12</sup> Persistence of symptoms was reported for 30% to 52% of children in studies with  $\geq 5$  years of follow-up monitoring.<sup>7-9,11,12</sup> Children with chronic symptoms of functional constipation suffer from lower quality of life, as found through children's self-reports and parents' proxy measurements.<sup>13,14</sup>

To date, data are scarce regarding the prognosis for childhood constipation when patients reach adult age. Follow-up monitoring of a large cohort of children with constipation in our pediatric gastrointestinal clinic showed that symptoms persisted for one-third of children at  $\geq 16$  years of age.<sup>12</sup> Results were imprecise, however, because only one-fourth of the included children reached 16 years of age in that study. A small retrospective study found that the frequency of constipation among adults with a history of childhood constipation was not different from that of control subjects (25% vs 23.5%).<sup>15</sup> However, Khan et al<sup>15</sup> reported that childhood constipation seemed to be a predictor of irritable bowel syndrome (IBS) in adulthood. With longer follow-up data for our cohort now being available, our aim was to evaluate whether our previous findings on the long-term outcomes of children with constipation would be sustained. Furthermore, we wanted to determine which clinical characteristics at the time of first presentation to the pediatric gastrointestinal outpatient clinic were associated with persistence of constipation in adulthood.

## METHODS

### Patients

All patients who participated in one of the clinical studies on childhood constipation between 1991 and 1999 were eligible for inclusion.<sup>16,17</sup> In those studies, functional constipation was defined as the presence of  $\geq 2$  of the following 4 criteria: defecation frequency of  $< 3$  times per week;  $\geq 2$  episodes of fecal incontinence per week; passage of very large amounts of stool at least once every 7 to 30 days; or a palpable abdominal or rectal mass on physical examination. Only patients  $\geq 5$  years of age who had received laxative treatment for  $\geq 2$  months before the initial presentation were included. Children with organic causes of constipation or mental retardation and children using drugs that influence gastrointestinal function, other than laxatives, were excluded.

### Follow-up Monitoring and Data Collection

After the last visit of the initially intensive, 6- to 8-week treatment protocol, follow-up evaluations were conducted for each patient at 6 months and annually until 2005. Between 2005 and 2007, every patient who was still in the cohort was contacted once more. Follow-up evaluations were conducted during an outpatient clinic visit or by telephone when the child had been discharged from the outpatient clinic. If telephone contact failed, then an explanatory letter was mailed to the patient's current address. This letter contained study information, an invitation to contact the pediatric gastrointestinal department for follow-up evaluation, and a nonresponse form that could be returned in a prestamped, addressed envelope. Subjects who indicated at any point during the follow-up period that they no longer wished to participate in this follow-up cohort were contacted no further. If the ad-

dress proved wrong, then the investigators tried to obtain new contact details from the patient's last known general practitioner or from municipal archives where the patient was last registered.

During each follow-up interview, a standardized questionnaire was used to obtain information regarding current clinical outcome. Data concerning defecation frequency, stool consistency and size, painful defecation, fecal incontinence frequency, abdominal pain, and laxative use were based on the 6-week period before the follow-up evaluation. In addition to this 6-week period, all relapses between the previous and current follow-up evaluations were documented.

### Definitions of Clinical Outcomes

A good clinical outcome during the follow-up period was defined as defecation frequency of  $\geq 3$  times per week for a period of  $\geq 4$  weeks and  $< 2$  episodes of fecal incontinence per month, with no use of laxatives in the previous 4 weeks (category 1). For more-detailed assessments of clinical outcomes, 3 additional categories were defined, that is, a group of children with good clinical outcomes with the use of laxatives (category 2) and 2 groups with poor clinical outcomes, either without (category 3) or with (category 4) the use of laxatives. A child was considered to have experienced a relapse when the defecation frequency decreased to  $< 3$  times per week and/or fecal incontinence frequency increased to more than once per fortnight after an initially good clinical outcome.

### Statistical Analyses

Baseline characteristics of the cohort are reported in a descriptive way. Comparisons between patients with complete follow-up data and those who dropped out were conducted with

Mann-Whitney *U* tests for continuous outcomes and with  $\chi^2$  tests for dichotomous outcomes. For each of the fixed follow-up times, the distribution of patients in the 4 defined categories of clinical outcomes was computed.

Generalized estimating equation (GEE) models were used to gain insight into the association between clinical characteristics and clinical outcomes at adult age.<sup>18</sup> In the GEE analysis, the 4 clinical outcome categories were reduced to a binary outcome, that is, good clinical outcome (categories 1 and 2) versus poor clinical outcome (categories 3 and 4). To take into account the possible fluctuation of constipation symptoms from year to year, adult age was defined as 16 to 18 years of age. Therefore, all observations available for each patient in this age range were included. A limited set of predefined baseline factors, including gender, age at onset of constipation, delay (ie, time between onset and first presentation to our pediatric gastrointestinal outpatient clinic), and defecation frequency and fecal incontinence frequency at first presentation to the outpatient clinic, was entered into the model without any additional selection strategy. These candidate factors were selected on the basis of previous research findings and our own interest. A multivariate GEE model was used, and results were expressed with 95% confidence intervals (CIs) and corresponding  $\chi^2$  test results. In addition, the frequency and timing of relapses for patients with good clinical outcomes at adult age were presented in a Kaplan-Meier curve.

Statistical analyses were performed by using SPSS 12.0.2 (SPSS, Chicago, IL) and SAS 9.1 (SAS Institute, Cary, NC). Statistical significance was accepted at  $P < .05$ .

## RESULTS

### Baseline Characteristics and Completeness of Follow-up Data

Between 1991 and 1999, a total of 416 patients with functional constipation were included in the 2 clinical studies. Of this cohort, 15 children were excluded from follow-up study because of incorrect inclusion in the research protocols. Therefore, a total of 401 children with functional constipation (65% male; median age at entry: 8 years [interquartile range [IQR]: 6–9 years]) were included in the present study. The median duration of follow-up monitoring was 11 years (IQR: 9–13 years). Baseline characteristics are presented in Table 1.

During this follow-up study, there was a drop-out rate of 15% ( $n = 62$ ). Of the remaining 339 patients (85%), 244 patients (72%) reached the age of 18 years. Loss to follow-up monitoring occurred for the following reasons: (1) no contact information could be retrieved ( $n = 14$ ); (2) there was no response to a written invitation to contact the pediatric gastrointestinal department for follow-up evaluation ( $n = 33$ ); (3) the subject declined further participation ( $n = 7$ ); (4) the subject had died in a car accident ( $n = 1$ );

or (5) other reasons ( $n = 7$ ). The subjects who dropped out differed from the patients who remained in the follow-up study with respect to age at the first visit to the outpatient clinic, with median ages of 7 years (IQR: 6–9 years) and 8 years (IQR: 7–10 years;  $P = .01$ ), respectively. No other differences in baseline characteristics were found (data not shown).

### Clinical Outcomes During Follow-up Period

The distribution of patients in the 4 defined clinical outcome categories for each follow-up year is shown in Fig 1. After 1 year, 50% of children achieved good clinical outcomes, with 11% of those children still using laxatives. Thereafter, a gradual increase in the proportion of patients with clinical success was seen, from 64% at the 5-year follow-up evaluation to 81% at the 10-year follow-up evaluation. By that time, only 4% of patients were still being treated with laxatives, with 3% achieving good clinical outcomes and 1% poor clinical outcomes. After 10 years, the overall success rates were generally stable at ~80%.

Clinical outcomes according to biological age are depicted in Fig 2. During childhood, a steady increase in good clinical outcomes was found, from 50% at the age of 5 years to 80% at the age of 16 years. Thereafter, success rates at adult age remained constant at ~75%. Laxative use at the age of 18 years was limited to 10 patients with good clinical outcomes and 1 patient with a poor clinical outcome.

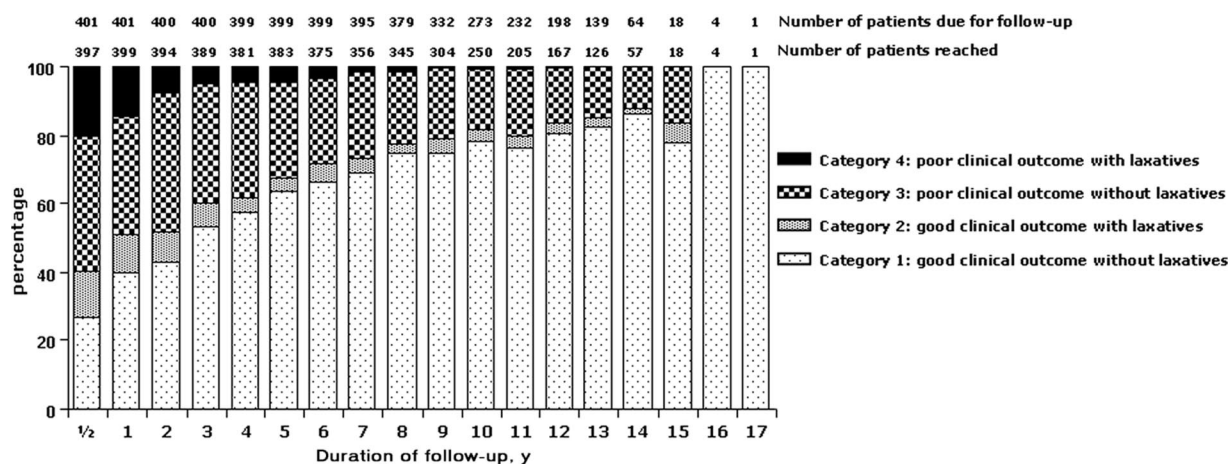
### Prognostic Factors for Persistence of Constipation at Adult Age

A total of 333 patients achieved the age of 16 years. Of those patients, 302 (63% male) were reached for follow-up evaluation. All 816 follow-up evaluations for these patients between 16 and 18 years of age were included in the mul-

**TABLE 1** Baseline Characteristics ( $N = 401$ )

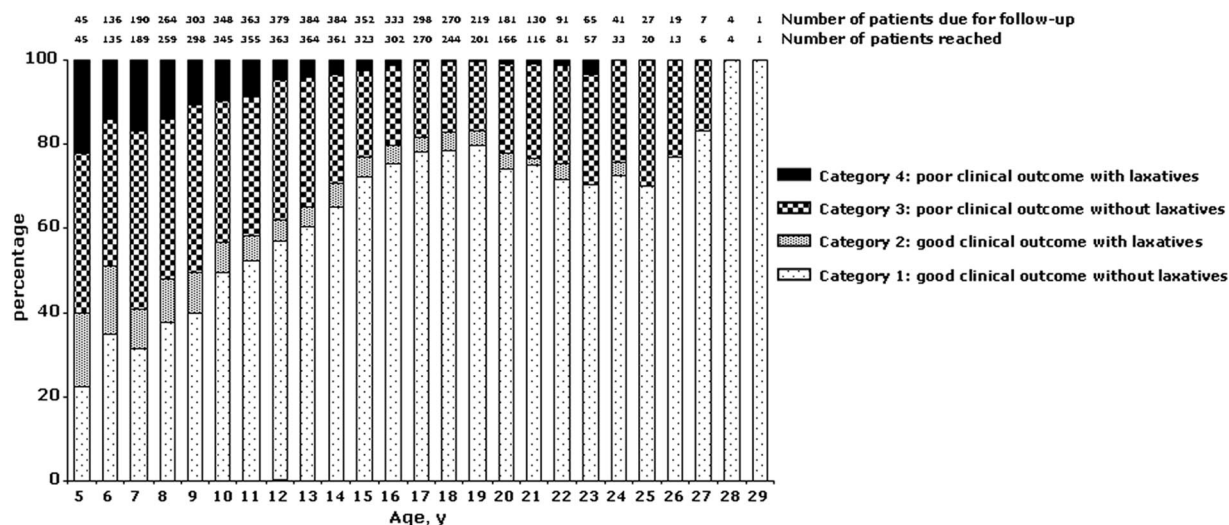
Age, median (IQR), y	8 (6–9)
Gender, %	
Male	65
Female	35
Age of onset, median (IQR), y	3 (0–4)
Defecation frequency	
Median (IQR), times per wk	2 (1–4)
<3 times per wk, %	71
Fecal incontinence frequency	
Median (IQR), times per wk	10 (5–21)
$\geq 2$ times per wk, %	89
No fecal incontinence, %	8
Large stools, %	68
Hard stools, %	40
Painful defecation, %	47
Abdominal pain, %	54
Abdominal scybalus, %	22
Rectal scybalus, %	30
Positive family history findings, %	14





**FIGURE 1**

Clinical outcomes of patients according to follow-up year, divided into the 4 defined outcome categories. Numbers in the upper row above the bars show the numbers of patients due for follow-up evaluation each year. Numbers in the second row show the numbers of patients reached for follow-up evaluation each year.



**FIGURE 2**

Clinical outcomes of patients according to biological age, divided into the 4 defined outcome categories. Numbers in the upper row above the bars show the numbers of patients who reached each age at any time during the follow-up period. Numbers in the second row show the numbers of patients reached for follow-up evaluation at each age.

tivariate GEE model for analysis. Clinical outcomes were found to be significantly correlated with 3 baseline characteristics, namely, delay (odds ratio [OR]: 1.24 [95% CI: 1.10–1.40];  $P = .001$ ), age at onset (OR: 1.15 [95% CI: 1.02–1.30];  $P = .04$ ), and defecation frequency (OR: 0.92 [95% CI: 0.84–1.00];  $P = .03$ ). Gender and fecal incontinence frequency were not correlated with clinical outcomes. For better illustration of the absolute impact of these findings, we introduce the fol-

lowing patient groups. A typical patient from our study is a male patient who experienced onset of symptoms at the age of 3 years and presented for the first time at our outpatient clinic with a delay of 5 years, reporting a defecation frequency of twice per week and 10 episodes of fecal incontinence per week. The estimated risk for a poor clinical outcome for this patient would be 16%. For such a patient, if the delay between onset and the first visit to our outpatient clinic was 1 year, then the esti-

mated risk for a poor clinical outcome at adult age (16–18 years) would decrease to 7%. If the delay was 9 years instead of 1 year, then the estimated risk would increase to 31%. The influence of age at onset of constipation also can be illustrated by using our typical patient and varying the age at onset. The estimated risk of a poor clinical outcome at adult age would be ~11% for such a patient if complaints of constipation started at birth, compared with 24% with onset of com-

plaints at age 7. Finally, a low defecation frequency (ie, once per week) at first presentation corresponded to an estimated risk of a poor clinical outcome at adult age of 17%, and this risk decreased to 11% for patients presenting with defecation frequency of 7 times per week.

### Relapses in Adulthood

After achievement of good clinical outcomes at adult age, relapses occurred significantly more frequently among women than among men (Fig 3). Within 1 year after clinical success, relapse rates were similar for women and men (5% and 4%, respectively). Thereafter, the cumulative relapse frequency increased to 28% after 5 years and 40% after 7 years for women, compared with 12% and 20%, respectively, for men ( $P = .01$ ).

### DISCUSSION

Our long-term follow-up study revealed that, for ~25% of children with functional constipation, symptoms persisted into adulthood. Poor clinical outcomes at adult age were associated with older age at onset, longer delay between onset and first presentation to our pediatric gastro-

intestinal outpatient clinic, and lower defecation frequency at first presentation. Lastly, relapses at adult age were more common among women than men.

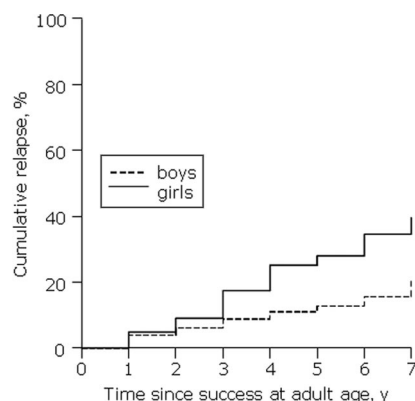
In line with our earlier observations,<sup>12</sup> the rate of good clinical outcomes in this study population showed a steady increase with longer follow-up periods. Laxative use in the subgroup of children with poor clinical outcomes was limited. As early as a follow-up time of 6 months, two-thirds of children with poor clinical outcomes no longer used laxatives; at 10 years, only 4% of patients were still using laxatives. This poor compliance is most likely explained by the fact that these patients were tired of taking laxatives for long periods without good results. Furthermore, many parents are reluctant to give their children laxatives for longer periods of time. To date, however, there is no strong evidence that long-term laxative use leads to tolerance or causes mucosal or neurologic colonic damage.<sup>19</sup>

Conversely, our follow-up results seemed to indicate that some children with poor clinical outcomes achieved success over the years without the use of laxatives. Clinical outcomes according to follow-up duration seemed to be related to outcomes according to biological age, because success rates showed a similar steady increase with biological age. In line with long-term follow-up findings for children with functional nonretentive fecal incontinence,<sup>20</sup> a steady increase in achievement of good outcomes during puberty was seen. During puberty, young adolescents learn to take more responsibility for their own actions in general. In relation to their defecation problems in particular, they may take better responsibility for regular toileting and no longer withholding their urge to defecate. Peer pressure and social

embarrassment may contribute to this as well.

However, the fact that one-fourth of children with functional constipation reported symptoms persisting into young adulthood refutes the general belief that all children outgrow constipation over the years. In this respect, extension of follow-up monitoring for our cohort confirms our previously reported clinical results.<sup>12</sup> To date, comparisons with other follow-up studies are still hampered by differences in applied definitions of constipation,<sup>6,8,15,21</sup> small numbers of patients,<sup>7-9,15,22,23</sup> low follow-up rates,<sup>6-9,21,22</sup> or the use of retrospective or cross-sectional, rather than longitudinal, study designs.<sup>15,21,24</sup>

Poor clinical outcomes at adult age were correlated with 3 clinical characteristics, namely, older age at onset, longer delay between onset of symptoms and the first visit to our outpatient clinic, and low defecation frequency at baseline. This seems to be in contrast to previous findings for this cohort, which indicated that higher fecal incontinence frequency and onset of constipation before the age of 1 year resulted in lower success rates.<sup>12</sup> The following explanations can be given for the different results within the same cohort. The study by van Ginkel et al<sup>12</sup> aimed to analyze prognostic factors for first clinical success, whereas the current study analyzed clinical factors associated with clinical outcomes at adult age. Because the large majority of children achieved good clinical outcomes within the first 2 years of follow-up monitoring, the prognostic factors for first clinical success described by van Ginkel et al<sup>12</sup> can be considered indicators for short-term outcomes. Furthermore, van Ginkel et al<sup>12</sup> defined good clinical outcomes as only those in clinical outcome category 1 (clinical success and no laxative use). It is our current opinion that all pa-



**FIGURE 3** Cumulative proportions of patients who experienced relapses after good clinical outcomes at adult age, showing a significant greater rate of relapse for women, compared with men ( $P = .01$ ).

tients who reached adult age and no longer reported symptoms of constipation should be considered to have achieved good clinical outcomes, regardless of the use of laxatives. Therefore, in the current study, we defined both category 1 and 2 outcomes as good clinical outcomes at adult age and compared those groups with categories 3 and 4.

van Ginkel et al<sup>12</sup> reported that late onset was positively associated with first success, but the current study showed that such patients have a higher risk of experiencing constipation in adulthood. This finding indicates that this group is more likely to experience relapse after initial success. The onset of constipation during adolescence may be an early expression in the continuum of functional gastrointestinal disorders, such as adult constipation or constipation-predominant IBS. In a small retrospective study by Khan et al,<sup>15</sup> childhood constipation seemed to be a predictor of IBS in adulthood. Furthermore, our study showed that relapses at adult age occurred more often among women than men. Although we cannot fully explain this finding, it seems in line with adult studies that reported a predominance of functional gastrointestinal disorders in women, compared with men.<sup>25–28</sup> Whether women in our cohort experienced true relapse of their childhood constipation or developed a new functional gastrointestinal disorder needs to be studied further.

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Longer delays between symptom onset and the first visit to our outpatient clinic were associated with poor clinical outcomes at adult age. Conversely, we hypothesize that, with earlier referral to a specialized pediatric gastrointestinal outpatient clinic, children may receive adequate, intensive treatment sooner. A previous study showed that infants with constipation symptoms for <3 months before presentation achieved higher success rates than did those with longer symptom duration.<sup>29</sup> However, in contrast to relatively short delays in the study by van den Berg et al,<sup>29</sup> the median delay for our patient cohort was 5 years, which indicates that other factors might have biased results for the group of children with longer delays. The parents' role in managing their child's defecation problem might be a potential delaying factor, as well as contributing to poor clinical outcomes. Inadequate parenting style with respect to setting limits for the child in general and with respect to toileting behaviors specifically is thought to play an important role in both the development and the persistence of constipation.<sup>30</sup> Parents' inability to set limits also may complicate adequate treatment. Additional studies are needed to support these presumptions.

Lastly, a low defecation frequency was associated with poor clinical outcomes. This is in contrast to several studies that found no association between defecation frequency and clinical outcomes.<sup>7,8,29,31,32</sup> For children with intractable constipation, however, low

defecation frequency might reflect primary colonic dysmotility attributable to neuromuscular abnormalities or might result from an acquired motility disorder after years of severe functional constipation.<sup>33–39</sup>

Some limitations of this study need to be addressed. Our population consisted of children who were referred to a tertiary care center for treatment of chronic constipation. Therefore, our results cannot be generalized directly to children seen in primary care centers or general pediatric settings. Furthermore, to determine clinical outcomes at adult age, we still used our pediatric definition of constipation. In future follow-up studies of our patient cohort, it would be interesting to determine clinical outcomes at adult age by using the definition of functional constipation for adults, as well as definitions of other functional gastrointestinal disorders, to investigate whether childhood constipation is an early expression in the continuum of functional gastrointestinal disorders.

## CONCLUSIONS

One-fourth of children with functional constipation continued to experience symptoms at adult age. Older age at onset, longer delay between onset of symptoms and referral to a specialized pediatric gastrointestinal clinic, and lower defecation frequency at intake were related to poor clinical outcomes at adult age. Referral to a specialized clinic should be considered at an early stage for children who are unresponsive to first-line treatment.

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