Part II

Prognosis of functional constipation
Functional constipation in children: A systematic review on prognosis and predictive factors

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ABSTRACT

Background
Knowledge on prognosis and factors influencing the clinical course of functional constipation in children is important to enable general practitioners and paediatricians to give accurate patient information, to weigh treatment strategies and identify children with high-risk for unfavourable outcome.

Objective
To investigate and summarize the quantity and quality of current evidence on prognosis of childhood constipation with and without treatment and its predictive factors.

Methods
An extensive literature search in Medline and Embase was performed to identify prospective follow-up studies evaluating the prognosis or prognostic determinants of functional constipation. Methodological quality was assessed using a standardized list. Results on prognosis of constipation were statistically pooled, and the influence of prognostic factors was summarized in a best evidence synthesis.

Results
The search strategy resulted in a total of 2386 abstracts. Only 19 publications met our inclusion criteria, of which 23% scored high methodological quality. Included studies showed large heterogeneity in study populations and outcome measures. With disregard of these differences, 58.9±20.2% of all children followed for 6-12 months was recovered and off laxatives. Six studies showed that at the end of follow-up, 13.9±6.6% of recovered children were still using laxatives. There is substantial evidence that defecation frequency and a positive family history are not associated with recovery of constipation.

Conclusion
The few studies published on prognosis of childhood functional constipation and predictive factors showed large heterogeneity and poor methodological quality. Overall, 58.9% of children are found to recover after 6-12 months. Recovery rate showed no relation with defecation frequency or positive family history. Based on the current literature, we are unable to identify a group of children with high-risk for poor prognosis.
BACKGROUND

In childhood, functional constipation is a common complaint. In the general population prevalence is reported to vary from 0.7 to 29.6% \(^1\). This large variation may be due to lack of a generally used definition to classify constipation. Consensus is hampered by the fact that clinical presentation is divers and pathophysiology is multifactorial. Even though several internationally accepted guidelines such as NASPGHAN\(^2\), PACCT\(^3\) and recently Rome III\(^4\) have been developed to provide criteria for constipation, none of them have been worldwide implemented in research or clinical practice yet.

There are different concepts on the clinical course of constipation in children. Some authors suggest that constipation is a constitutional condition which gradually disappears \(^5\). Others find that despite intensive therapy 30-50% percent of the children persist to have severe symptoms after 5 years of follow-up \(^6\),\(^7\).

Knowledge on factors influencing the clinical course of functional constipation in children is important to enable general practitioners and paediatricians to give accurate patient information, to weigh treatment strategies and identify children with high-risk for unfavourable outcome. However, no overview of these prognostic factors exists in current literature. Therefore our aim was to investigate and summarize the quantity and quality of the current evidence on the course of constipation in children with and without treatment, and determinants that predict this course.

METHODS

Search strategy

The Medline database was searched from 1965 to March 2008, and EMBASE from 1980 to April 2007. The keywords (medical subheadings (MeSH) and text words) used to describe constipation were: “constipation”, “obstipation”, “coprostasis”, “encopresis”, and “soiling”. The study population was identified by the words: “child”, “infant” and “adolescent”. For Medline the following query was added: (incidence[MeSH] OR follow-up studies[MeSH] OR prognosis OR predict*[Text Word] OR course*[Text Word] OR Epidemiologic Studies). For EMBASE we combined the search with the strategy for detecting prognostic studies recommended by Wilczynski et al. \(^8\). In addition, reference lists of review articles and included studies were searched. No language restriction was applied.
Two reviewers independently screened all abstracts of identified published articles for eligibility. For this purpose, four inclusion criteria were used: 1) study population consisted of children between 0 to 18 years of age; 2) a prospective observational study design; 3) one of the aims of the study was to evaluate the prognosis of functional constipation expressed as duration or recurrence of functional constipation and determinants that influence prognosis; 4) follow-up was at least 8 weeks.

Excluded were papers concerning children with mental handicaps or psychiatric diseases (i.e. eating disorders), as well as studies investigating children with organic causes of constipation and children with functional non-retentive faecal incontinence.

All potentially relevant studies, as well as the studies of which the abstracts didn’t provide sufficient information for in- or exclusion, were retrieved as full papers.

Any disagreements regarding the inclusion of articles were resolved through consensus when possible or by arbitration of a third person.

Quality assessment

To assess methodological quality of the included studies we developed a standardized list (Table 1). We modified an established criteria list used in systematic reviews of prognostic studies 9-12. Two reviewers independently rated the methodological quality with the 15 items of the quality score list. Each of the items had an answer option of ‘yes’/’no’/’unclear’ (i.e. insufficient information). A score of 1 point was given only to a criterion that is assessed with ‘yes’. Equal weights were applied to all items, resulting in a maximum score of 15 points. Disagreements were resolved through consensus or by arbitration of a third person.

Data extraction

Two reviewers independently performed a structured data extraction from the original reports. Extracted information included (if available) items referring to setting, participants (diagnosis, age, gender, withdrawal/dropouts), interventions and outcome measures. Disagreements were resolved by consensus or by arbitration of a third person.

Data analysis

Inter-assessor reliability on methodological quality was calculated using kappa-scores 13. Our primary outcome was recovery of constipation as defined
by the authors of the papers. Large clinical diversity among included studies with regard to participants, disease definitions and definition of outcomes existed. Furthermore, different statistical approaches and adjustments for different variables were used. Nevertheless results on prognosis of constipation were pooled using stratification to overcome large differences in duration of follow-up, study quality and setting. We refrained from statistically pooling of results with regard to prognostic factors \(^{11}\), but carried out a best evidence synthesis for associations with recovery from constipation. Using the methodological quality list, quality scores were calculated as a percentage of the maximum score. High quality is defined as a score of 60% or more of the maximum score (i.e. a score of \( \geq 9 \) points).

In the best evidence synthesis, evidence was divided in the following levels: 1) Strong: consistent findings (\( \geq 75\% \) of the studies report consistent findings) in at least 2 high quality studies; 2) Moderate: consistent findings in one high

### Table 1. Methodological quality list

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<th>Study population</th>
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<td>1. Inception cohort</td>
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<td>2. Description of study population at least mentioned are: setting; age; duration of constipation; severity of constipation (described as defecation frequency or presence of faecal incontinence)</td>
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<td>3. Description of in- and exclusion criteria</td>
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<td>Follow up</td>
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<td>5. Prospective data collection</td>
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<td>6. Follow up of at least 12 months</td>
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<td>7. Loss to follow up &lt;20 %</td>
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<td>8. Information about loss to follow up</td>
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<td>Outcome</td>
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<td>9. Standardized measurement of outcome (baseline and FU identically measured)</td>
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<td>10. Independent measurement of outcome (blinded for prognostic factors)</td>
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<td>Prognostic factors</td>
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<td>11. Presentation of prognostic factors at baseline. (At least mentioned are age, gender, duration of constipation and severity of constipation).</td>
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<td>12. Standardized measurement of prognostic factors (baseline and FU identically measured and presented)</td>
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<td>13. Independent measurement of prognostic factors (blinded for outcome)</td>
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<td>Analysis</td>
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<td>14. Measure of association and measures of variance given</td>
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<td>15. Multivariate analysis used</td>
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quality cohort and at least 2 low quality studies; 3) Limited: findings of one high quality cohort or consistent findings in at least 3 low quality studies; 4) Conflicting: inconsistent findings (<75% of the studies report consistent findings); 5) Insufficient: no high quality studies and less than 3 low quality studies available 14,15. The level of evidence was based on the results in high quality studies only in case ≥2 high quality studies were available. Only statistically significant associations are considered as associated prognostic factors in this synthesis.

RESULTS

Included studies

The search strategy resulted in a total of 2386 abstracts. After eligibility screening 19 publications were judged potentially relevant 5-7, 16-31. After reading the full text articles, 6 studies were excluded 5,19-21,28,29, because the study design was not a prospective observational study, but based on a retrospective chart review 5,20,21,28,29 or a cross-sectional survey 19. Only three studies were not published in English, but in Polish 16 and Spanish 27,31. These papers were translated. Full characteristics of the included studies are described in Table 2 (see Appendix).

Setting Of the 13 included studies, six were conducted in a general paediatric department 18,22-26, six in a paediatric gastroenterology department 7,16,17,27,30,31 and in one paper 6 no setting was stated. None of the included studies were conducted in a primary care centre.

Outcome measures All studies described a composed definition of recovery, resolvement or successful treatment of constipation as positive outcome, except for two studies 18,26 that did not specify their outcome. Definitions of outcome measures varied strongly, nevertheless all studies took into account defecation frequency: in one study, having more than four bowel movements per week was a requirement for success 6, all other studies applied the criterion of at least three bowel movements per week. Frequency of fecal incontinence was included in the success definitions of eight studies: in five studies 7,22,23,25,31 the success definition required less than two episodes per month, one study 17 allowed one episode per two weeks, and in two studies 16,24 children were not allowed to have any fecal incontinence. No abdominal pain or no pain with defecation was included in the success definition of three studies 25,30,31. All studies but four 16,24,27,31 took laxative use into account in their definition of success, and six studies 7,16-18,25,30 presented recovery rates of children off laxatives and children still using laxatives.
**Study population** In total 1680 children participated in the included studies. Age was reported in mean\(^{16,18,22-27}\) (mean 71.7±38.0 months) or median\(^{6,7,17,30,31}\) (range 3.5 to 100.8 months). Distribution of gender of all randomised children was reported in all studies but two\(^{18,23}\): 50.9% of participants were boys (M/F 782/752). Duration of constipation before start of the study was reported in 11 papers (expressed in mean or median duration before start of the study\(^{7,16,18,30}\), mean or median age of onset\(^{17,24,26,27}\), or defined in the inclusion criteria\(^{6,22,31}\)). Two studies did not report duration\(^{23,25}\). Numbers on severity of constipation at baseline (e.g. defecation frequency, frequency of faecal incontinence episodes, presence of abdominal pain) were not presented in 3 studies\(^{18,25,26}\). All other included studies used symptoms of constipation to express severity of constipation.

**Follow-up time** Most papers expressed follow-up time in mean number of months (mean: 2.75±24.79 months). Two studies presented follow-up time in median number of months\(^{7,30}\), and one study presented a range\(^{22}\).

**Methodological quality**

The three reviewers (MP, MBo and MYB) initially agreed on 85.6% of the items of the methodological quality list. Inter-observer reliability of methodological quality assessment (0.71) was high. Overall methodological quality score of all included studies ranged from 4 to 10 out of maximal 15 points, with a mean score of 6.9. Only 23% (n=3) \(^{7,17,30}\) of the included studies were considered of high quality. Most prevalent shortcomings of the studies were the following: outcome measurement not independent of prognostic factors (100%, n=13); unstandardized or dependent measurement of prognostic factors (84.6%, n=11 and 92.3%, n=12, respectively); no presentation of association measures and measures of variance, or no multivariate analysis performed (both 76.9%, n=10).

**Prognosis**

Of all children followed for 6 to 12 months\(^{7,16,17,22-27,30,31}\), 58.9±20.2% (mean±SD) was recovered and off laxatives at the time of follow-up. Children followed for one to two years\(^{7,16,18}\) or for five years\(^{6,25}\) showed a recovery rate of 58.0±14.1% and 56.0±11.3%, respectively. A total of 70.8±16.8% of the children included in a paediatric gastroenterology department (n=934) were recovered and off laxatives at time of follow-up (mean follow-up: 21.0±19.9 months) \(^{7,16,17,27,30,31}\). Studies performed in general paediatric departments\(^{18,22-26}\) (n=647) showed a significantly lower recovery rate of 54.1±15.6% \((p<0.01)\)(mean follow-up: 13.0±2.5 months, \(p<0.01\)).
Studies of high methodological quality\textsuperscript{7,17,30} (n=634) showed a recovery rate of 60.6±3.2\%, compared to 61.6±20.1\% (p=0.12) in low quality studies\textsuperscript{6,16,18,22-27,31} (n=1046). In addition, six studies\textsuperscript{7,16-18,25,30} (n=992) showed that at end of follow-up, 13.9±6.6\% children recovered from constipation were still using laxatives.

Prognostic factors

In the present review a total of 22 prognostic factors were analysed in 61 associations with recovery. In 42 evaluations no significant association was found, in 19 evaluations a statistically significant association was reported. The mean sample size of studies that reported ‘no association’ was not significantly different from the mean sample size of studies that reported a significant association (mean sample size 140.57±104.36 versus 142.16±115.52, p=0.95). All results of the best evidence syntheses on the prognostic factors are presented in Table 3 (see Appendix).

Demographics

\textit{Gender} Six studies reported on the association between gender and recovery from constipation. Two studies of high methodological quality\textsuperscript{7,30} found no statistically significant association, and one high quality study\textsuperscript{17} found that male gender was negatively associated with recovery. In addition three studies of low methodological quality\textsuperscript{6,23,24} found no significant association. In conclusion, there is conflicting evidence that gender influences recovery rate.

\textit{Age at intake} Based on four low quality studies reporting no significant association between age and recovery, limited evidence for no association was found\textsuperscript{6,22-24}.

Medical history

\textit{Age of onset/duration} One high quality\textsuperscript{30} and three low quality studies\textsuperscript{22-24} concluded that age of onset of constipation and recovery are not statistically significantly associated. In contrast, a high quality study\textsuperscript{7} showed that onset between one to four years of age is not significantly associated with recovery, but onset at the age of four years or older gives a higher recovery rate than onset before the age of one year. A low quality study\textsuperscript{6} supports the finding that an older age at onset was associated with a higher recovery rate. Based on these six papers, we conclude that evidence is conflicting.

\textit{Family history} Two high quality studies\textsuperscript{7,30} found no significant association between a positive family history for childhood constipation and recovery. In
contrast, one low quality study\textsuperscript{6} found a negative association. Based on these three studies, we found strong evidence for no association.

Clinical symptoms

Defecation frequency at intake Two high quality studies\textsuperscript{17,30} found no statistically significant association between defecation frequency and recovery. We found three low quality studies\textsuperscript{6,23,24} that support this finding. In conclusion, these studies provide strong evidence that there is no association between defecation frequency and recovery.

Presence of faecal incontinence at intake Two low quality studies report on the association between the presence of faecal incontinence and recovery from constipation. One of them\textsuperscript{25} found a positive association, the other\textsuperscript{6} found no significant association. Therefore, evidence on this association is insufficient.

Frequency of faecal incontinence We included one high quality\textsuperscript{17} and one low quality\textsuperscript{22} study that found no significant association between the frequency of episodes of faecal incontinence and recovery. In contrast, another high quality\textsuperscript{7} and low quality\textsuperscript{23} study showed that in recovered children the frequency of episodes of faecal incontinence was significantly lower at baseline than in children that did not recover during follow-up (negative association). Overall, this provides conflicting evidence.

Abdominal pain We found three low quality studies reporting on history of abdominal pain or abdominal pain at presentation\textsuperscript{6,22,23}. All three show the same results, together providing limited evidence for no association between abdominal pain and recovery from constipation.

Urinary tract infection Two low quality studies\textsuperscript{23,24} both found no significant association between previous urinary tract infections and recovery from constipation. Evidence on this association is insufficient.

Physical examination

Palpable rectal or abdominal mass Two high quality studies\textsuperscript{7,17} evaluated the relation between absence of a rectal or abdominal mass on physical examination and recovery of constipation. One study\textsuperscript{7} found no statistically significant association, whereas the second study\textsuperscript{17} found absence of a palpable abdominal mass to be positively associated but absence of palpable rectal mass not significantly associated with recovery. These findings provided conflicting evidence for an association. In addition, one low quality study found no significant association between absence of an abdominal or rectal mass and recovery\textsuperscript{24}, one low quality study found a negative association\textsuperscript{23},
and one low quality study\textsuperscript{22} investigated the association between presence of an abdominal mass and treatment failure, and found a negative association.

**Additional examination**

*Balloon defecation* On the association between the ability to defecate a rectal balloon and recovery, two low quality studies\textsuperscript{22,25} report a positive association, which provides insufficient evidence. Another low quality study\textsuperscript{23} that reported on the association between the disability to defecate a rectal balloon and treatment failure, found a positive association as well.

*Relaxation of external anal sphincter* One low quality study\textsuperscript{22} found a positive association between the ability to relax the external sphincter and recovery. Another low quality study\textsuperscript{23} investigated the association between an abnormal contraction of the external sphincter and treatment failure, and also found a positive association. This provides insufficient evidence.

*Colonic Transit Time/Total Gastrointestinal Transit Time (CTT/TGTT)* We found two studies reporting on the association between CTT or TGTT and recovery. One high quality study\textsuperscript{17} found a negative association, and a low quality study\textsuperscript{6} found no significant association. In conclusion, we found limited evidence that children with a longer transit time have a lower recovery rate.

In addition, there are several prognostic factors that are investigated in one single high quality study. We found limited evidence that premature birth\textsuperscript{30}, delayed passage of meconium\textsuperscript{30} and production of large stools\textsuperscript{17} are not associated with recovery. There also is limited evidence that children with duration of symptoms of less than 3 months before presentation and children with treatment duration of less than 2 months have a higher recovery rate than children with longer treatment or symptom duration\textsuperscript{30}.

**DISCUSSION**

To our knowledge, no previous reviews on prognosis or prognostic factors of childhood constipation have been performed. In the present systematic review, only 13 papers concerning the course of childhood constipation and its determinants could be included. The majority of these studies showed poor methodological quality. Furthermore, studies were heterogeneous, encompassing different definitions, populations, outcome measures and follow-up periods. With disregard of these differences, the prognosis of constipation in children was found to be fairly good with an overall 6-12 month
recovery rate of 58.9±20.2%. Children included in a specialist setting show a higher recovery rate (70.8±16.8%) than children included in general paediatric departments (54.1±15.6%).

Based on the current literature, there is substantial evidence that defecation frequency and a positive family history are not associated with recovery of constipation. With limited level of evidence, a short duration of symptoms and treatment before presentation results in better prognosis, while studies evaluating other factors in the medical history showed no relation or were insufficient to draw firm conclusions. Conflicting evidence exists on the prognostic value of gender, age of onset and fecal incontinence. Furthermore, there is insufficient evidence available to determine the role on prognosis for one third of the prognostic factors described in literature.

Limitations

A potential shortcoming of this systematic review is the literature search. To minimize the risk of missing relevant publications as much as possible, we performed an extensive and sensitive literature search without language restrictions.

Various outcome measures have been used in the included studies. A definition of recovery, resolvement or success was described by every author except two, but no uniformity among these definitions existed. Of all symptoms that may occur with constipation, only defecation frequency was consistently included in the recovery definitions, but not all studies applied the same limiting value.

As presentation of outcome and prognostic factors varied large between the studies, it was impossible to perform a true meta-analysis on prognostic factors. Therefore we used a best evidence synthesis to be able to present a summary of these factors. We assessed methodological quality of the included studies for the best evidence synthesis using a standardized list. Due to misclassification of items, bias might occur. However, of the 13 included studies, only 3 scored a high quality. Because of low quality scores of most studies, misclassification of one item would not change the classification into a high methodological quality. Therefore we assume that the effect of a possible bias on the results is minimal.

In the best evidence synthesis, we only considered statistically significant associations as associated prognostic factors. We included several studies with a small sample size (implying low statistical power), of which misclassification could have occurred because their results did not reach statistical significance. Statistically pooling of data would have been a solution to this problem, but
was not possible because of the large clinical heterogeneity. However, we found that small sample size did not influence the results of our best evidence synthesis.

Prognosis

Despite differences between the studies included, we statistically pooled data to summarize results on prognosis of constipation. Although overall 6-12 month recovery rate of constipation in children was found to be 58.9%, a large variation (range 36.0%\textsuperscript{22} to 98.4%\textsuperscript{27}) among included studies was found. Interpretation of these pooled recovery rates is biased because studies were heterogeneous with regard to study populations and definitions of constipation and outcome measures used.

The finding that prognosis is more favourable for children in specialized centres than for children in general paediatric departments is somewhat surprising. Previous research showed that prognosis is better the earlier treatment starts after onset of constipation\textsuperscript{1}. Since children usually first present to their general practitioner or paediatrician before being referred to a more specialized centre, one would expect better prognosis in first and second line settings. Furthermore, children with constipation referred to a tertiary centre are most likely children with a more severe form of constipation unresponsive to conventional treatment. On the other hand, children seen in specialist settings may receive more advanced or more aggressive treatment than children in general paediatric settings. Because of the large diversity between the studies, it was impossible to make a valid comparison in study population or treatment regimens applied.

Prognostic factors

Current literature shows strong evidence that a positive family history is not associated with recovery of constipation. Strong evidence also exists that defecation frequency is not of influence on prognosis of constipation. This finding supports the idea that functional constipation is a disease entity which comprises more aspects than defecation frequency only, as is described recently in the Rome III criteria\textsuperscript{4}.

The present review does not provide insight on the prognostic value of fecal incontinence. A negative influence would be expected based on experience, but at the moment evidence is conflicting due to a lack of studies evaluating its role.
Future research

The results of our review show that further research by means of large follow-up studies on prognosis of childhood constipation and factors of influence on prognosis is necessary. We recommend using a clear definition for both the diagnosis of constipation as for recovery of constipation. This definition preferably is a worldwide used uniform definition, taking into account all aspects of constipation, such as the recently developed Rome III criteria. It is important to investigate prognosis not only in children seen in specialized settings, but also in a more general population to gain insight in possible differences between these settings. In addition, more detailed registration of symptom severity and treatment regimens applied is needed.

CONCLUSION

The few studies published on prognosis of childhood functional constipation and its predictive factors showed large clinical diversity and poor methodological quality. Overall 6 to 12 month recovery rate of constipation in children was found to be 58.9%, but large variation ranging from 36.0% to 98.4% among the included studies was found. Children included in a specialist setting show a higher recovery rate than children included in general paediatric departments. Recovery rate showed no relation with defecation frequency or positive family history. Based on the current literature, we are not able to identify a group of children at risk for poor outcome.
REFERENCES


