Development of a Bowel Management Scoring Tool in Pediatric Patients with Constipation

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Objective To develop a reliable and valid scoring tool, the Pediatric Bowel Management Scoring Tool (PBMST), to better guide management of constipation in pediatric patients.

Study design The project comprised 2 stages, development of the questionnaire and construction of the bowel management score. Two questionnaires were created, one for children aged 8-18 years to self-report and one parent proxy-report for children aged 4-8 years. Questions regarding physical symptoms (n = 6), emotional aspects (n = 2), social activities/school (n = 1), and treatment (n = 1) were included. Patients (or parents of patients) with symptoms of constipation completed the questionnaire. The reproducibility of each question was computed using the Cohen weighted kappa coefficient (κ). A bowel management score was developed using logistic regression analysis, assessing the associations between the questions and impact on self-reported quality of life (QoL). Questions with adequate reproducibility and significantly associated with QoL were incorporated into the score.

Results The questionnaire was completed by 385 patients. Six questions met the inclusion criteria and were incorporated into the score: stool shape (range, 0-3 points), anorectal pain (0-4 points), abdominal pain (0-3 points), frequency of fecal incontinence (0-3 points), assistance of caregivers (0-3 points), and interference with social activities (0-6 points). Differences in bowel management scores among patients reporting no, little, some, or major impact on QoL were statistically significant ($P < .001$).

Conclusions The newly developed and validated PBMST is a reliable tool for evaluating bowel management strategies in children with constipation. *(J Pediatr 2022;244:107-14)*.

Constipation, a common problem in childhood, is characterized by infrequent evacuation of hard and painful stools, often accompanied by fecal incontinence and/or abdominal pain. The prevalence of constipation in children ranges from 0.5% to 32.2%.[1] In more than 95% of children presenting with symptoms of constipation, no underlying cause can be found.[2] These children are diagnosed with functional constipation as defined by the Rome IV criteria.[3,4] Although the majority of children with constipation are diagnosed with functional constiptation, exclusion of organic causes remains important. Organic etiologies include intestinal, anorectal, metabolic, neuropathic, and endocrine conditions. Anorectal malformations, Hirschsprung disease, and spinal cord defects are among the most common organic causes and should be excluded in the first year of life. In adolescents, eating disorders are sometimes associated with constipation.[5]

Pediatric patients with constipation represent a complex group in whom management can be challenging. Currently, the first step in treating constipation in children consists of nonpharmacologic interventions, such as education and toilet training, and pharmacologic treatment with oral and/or rectal laxatives.[6] In children who do not respond to conventional treatment, management can be applied in a stepwise pyramid of care, with transanal irrigation being the next step.[7] In rare cases, surgical interventions, such as the antegrade continence enema procedure, ostomy, or sacral nerve modulation, are necessary.[7] Evaluation of the effectiveness of applied treatment strategies at 2 weeks after the initiation of an intervention is advised.[3] In daily practice, this evaluation is based on expert opinion, for which the

COS	Core outcome set
MBSFS	Modified Bristol Stool Form Scale
PBMST	Pediatric Bowel Management Scoring Tool
QoL	Quality of life

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use of a symptom diary to record stool and fecal incontinence frequency for several consecutive days can be helpful. In the adult population, validated scoring systems exist to evaluate the management of constipation.[8,9] The aim of the present study was to develop a tool, the Pediatric Bowel Management Scoring Tool (PBMST), to better guide the management of childhood constipation.

Methods

A mixed-method study was conducted to develop the PBMST, consisting of semistructured interviews and a quantitative questionnaire study. The study comprised 2 stages: development of the questionnaire and construction of the score. The final PBMST included cutoffs for the score corresponding to fair, moderate, poor, and very poor bowel management. The study involved an international collaboration of experts including 2 pediatric urologists, 1 pediatric neurourologist, 2 pediatric gastroenterologists, and 1 pediatric surgeon specializing in pediatric gastroenterology. Pediatric patients with symptoms of constipation due to organic causes (eg, anorectal malformations or Hirschsprung disease) and functional constipation (according to the Rome IV criteria) were invited to participate in the study.

Two PBMST versions were created: a self-report questionnaire for children aged 8-18 year and a proxy-report questionnaire for parents of children aged 4-8 years. Therefore, every step in the development process of the tool was performed in duplicate. Data collection took place between July 2019 and September 2020 at Emma Children's Hospital (Amsterdam), Bambino Gesù Pediatric Hospital (Rome), Frankfurt University Hospital, and Arnold Palmer Hospital for Children (Orlando, Florida).

Stage 1: Development of the Questionnaire

Two 10-item questionnaires (parental proxy-report version and child self-report version) were developed.

Phase 1: Question Generation. Questions to assess fecal incontinence or constipation were generated based on a review of existing questionnaires[10-17] and on our clinical experience and knowledge. Duplicate questions were removed. A total of 48 questions were generated. During the first expert panel meeting, questions were sorted by domain, including bowel dysfunction (n = 17), physical symptoms (n = 13), behavior/coping/emotional aspects (n = 3), social activities/school (n = 4), and bowel management (n = 11).

Phase 2: Draft Version of the Tool (Question Reduction and Phrasing). The expert panelists were asked to vote for the most important/clinically relevant question for each domain. Questions that received a majority (>50%) of votes were considered suitable for the draft version of the tool. In the event of an equal number of votes, consensus was reached through group discussion. The draft version of the tool consisted of 12 questions. Response items were added or adjusted using a Likert-type or dichotomous scale. Problems of phrasing were identified using the Question Appraisal System-99.[18] To enable international collaboration, the questionnaires were translated forward from English into Dutch, German, Spanish, and Italian, and then backward.[19] No further modifications were needed after the backward translation.

Phase 3: Pilot Testing. Thirteen parents and children completed the draft version of the questionnaire. Cognitive interviews were performed after completion of the questionnaire to ensure that the children and parents understood the content, that they all interpreted the questions similarly, and to identify any missing items. During the second expert meeting, the results were discussed and used to revise the questionnaire. Two questions were excluded because of comparable content. The final questionnaire consisted of 10 items and included questions regarding bowel dysfunction and physical symptoms (n = 6), behavior/coping/emotional aspects (n = 2), social activities/school (n = 1), and bowel management treatment (n = 1). The questionnaires are provided in the **Appendix 1** and **2** (available at www.jpeds.com).

Phase 4: Reproducibility (Intrarater Reliability). Patients or parents of patients aged 4-8 years with symptoms of constipation who visited the outpatient clinic during the study period were invited to complete the questionnaire (**Appendix 1** and **2**). To evaluate the intrarater reliability of the questionnaire, an identical questionnaire was sent to the original respondents (parents and children) at 2 weeks after they completed the first questionnaire. The patient's condition was not expected to change significantly during this 2-week period.

Sample Size Calculation. Because no gold standard exists regarding the sample size needed to perform reliability testing, we intended to include 40 patients based on previously performed studies.[11,17]

Analyses. Statistical analyses were performed using R Studio version 3.6.1.[20] The Cohen weighted kappa coefficient (κ) was used to compute intrarater reliability. κ values were computed to measure the level of agreement between the answers to the first and second questionnaires. κ values ranged between 0 (if no correlation is found) and 1 (if all answers are equal); reproducibility was considered fair at 0.41-0.60, good at 0.61-0.80, and very good at >0.81.[21] Questions with a κ value of 0-0.40 were not used in the study.

Stage 2: Construction of the PBMST

The aim of stage 2 was to construct a scoring system for the questionnaire. The methodology for this was derived

from previously published scoring questionnaires.[17,22] Also in this stage of the study, patients and parents of patients aged 4-8 years with symptoms of constipation who visited the outpatient clinic during the study period were invited to complete the questionnaire (**Appendix 1** and **2**). At the time of questionnaire completion, information on patient status was recorded, and the patients were assigned to 1 of 3 groups: group A (new patient, treatment not yet initiated); group B (established patient on treatment, not optimized as judged by their specialist); or group C (established patient on treatment, doing well as judged by their specialist).

Construction of the Score. The PBMST score was computed based on associations between the questions and self-reported impact on quality of life (QoL; question 10). Patients were divided into 2 groups based on the assessment of self-reported impact on QoL: group 1 (no or little impact) and group 2 (some or major impact). Logistic regression analyses were performed with the degree of impact on QoL as the dependent variable and all other items as independent variables. The Modified Bristol Stool Form Scale (MBSFS) question (question 2; 5 points) was recoded into 3 categories before inclusion in the logistic regression analyses (category 1, MBSFS 3 and 4; category 2, MBSFS 2; and category 3, MBSFS 1 and 5). Questions not significantly associated with an impact on QoL were excluded from the multivariable model and not incorporated into the scoring system. For questions significantly associated with an impact on QoL, OR and 95% CI were computed. Each question was given a value in the score based on the OR. To increase distinctiveness, the OR was multiplied by 2 before rounding to whole numbers; for example, an OR of 3.8 would result in 8 points in the score ($3.8 \times 2 = 7.6$, rounding to whole numbers) for that question. To determine the weight of each answer option for the question, a new logistic regression analysis was performed with the normal answer (eg, "never experienced pain") as the reference value.

Sample Size Calculation. To calculate the sample size needed for this stage of the study (construction of the score), we used $N = 10\ k/P$,[23] with k as the number of independent variables (in this study, the number of questions) and P as the reported impact of constipation on QoL, which is 52% for patients of all ages.[24] This resulted in a total of at least 173 patients needed to construct a scoring system for the questionnaire.

Analyses. Mean and SD values of the PBMST score were calculated for each group: group 1 (no impact on QoL), group 2 (little impact on QoL), group 3 (some impact on QoL), and group 4 (major impact on QoL). In addition, mean and SD of the bowel management score were calculated and tested for groups based on patient status: group A (new patient, treatment not yet initiated), group B (established patient on treatment, not optimized), and group C (established patient on treatment, doing well). Overall score differences were tested using the Kruskal–Wallis test. A 2-sided t test was used to test for differences between each group of increasing impact on QoL. The mean bowel management score of each QoL group were used to determine cutoffs in the score corresponding to fair bowel management, moderate bowel management, poor bowel management, and very poor bowel management. All statistical analyses were performed using SPSS for Windows, version 26.0 (IBM). The significance level was set at $P < .05$ for all statistical analyses.

Construct Validity of the PBMST

Owing to the lack of a gold standard for evaluating bowel management strategies in children with constipation, the Spearman rank correlation (r_s) was used to determine construct validity. To test the construct validity of the scoring system, 38 patients (children or parents on a child's behalf) underwent a health history assessment via telephone conducted by a research assistant. The telephone assessment was performed as soon as possible after questionnaire completion. Afterward, the interviewer completed an identical questionnaire based on their assessment, without knowing the results of the patient/parent-completed questionnaire. Scores were calculated, and construct validity was evaluated using Spearman rank correlation.

Table III. Patient characteristics, stage 2 (N = 385)

Characteristics	Values
Sex, n (%)	
Male	184 (48)
Female	201 (52)
Age, y, mean (SD)	9.2 (4.2)
Pathology, n (%)	
Functional constipation	283 (74)
Hirschsprung disease	18 (5)
Anorectal malformation	28 (7)
Neurogenic bowel/spina bifida	48 (12)
Other*	6 (2)
Missing	2 (1)
Country, n (%)	
United States	211 (55)
The Netherlands	101 (26)
Germany	43 (11)
Italy	30 (8)
Patient status, n (%)	
New patient	74 (19)
Established patient, not optimized	120 (31)
Established patient, doing well	142 (37)
Missing	49 (13)

*Other diagnoses include rectal prolapse, prune belly syndrome, and ganglioneuromatosis (MEN2B syndrome).

Ethics and Dissemination

The study was approved by the Medical Ethics Committee of the Amsterdam University Medical Center (MEC AMC 018) as well as the Medical Ethics Committees of all other participating hospitals.

Results

Stage 1: Development of the Questionnaire

Patient Characteristics. Questionnaires were completed for 51 patients; characteristics of these patients are summarized in Table I (available at www.jpeds.com).

Reproducibility (Intrarater Reliability). The results of the intrarater reliability of the questions are presented in Table II (available at www.jpeds.com). For all questions, reproducibility was fair to very good. There were no questions with a value between 0 and 0.40; therefore, all questions were used in the study.

Stage 2: Construction of the PBMST

Patient Characteristics. This stage of the study included 385 patients in the analyses. Table III presents the baseline characteristics of these patients.

Score Construction. Results of logistic regression analyses are presented in Table IV, and results of additional logistic regression analyses to determine the weight of each answer option are provided in Table V. These results show that the OR for the impact of daily fecal incontinence on QoL was smaller than that for several times a week fecal incontinence. The maximum number of points given to fecal incontinence was 3 (Table IV); however, we also chose to attribute 3 points for daily fecal incontinence (Table V).

Interpretation of the Score. The median bowel management score of the total cohort was 7.2 (range, 0-19), and 90% of the patients had a bowel management score between 3 and 12. For patients in group 1 (no impact on QoL), group 2 (little impact on QoL), group 3 (some impact on QoL), and group 4 (major impact on QoL), mean (SD) bowel management scores were 4.4 (2.3), 5.7 (2.6), 8.3 (3.1), and 11.4 (4.1), respectively. Overall bowel management scores differed significantly among the 4 groups: $\chi^2(3) = 142.31$ ($P = .000$). When each group was compared with the next group of increasing impact on QoL (ie, group 1 vs group 2, group 2 vs group 3, group 3 vs group 4), the differences were all highly significant ($P \leq .001$). Accordingly, we determined that a bowel management score of 0-5 corresponded to fair bowel management, a score of 6-7 corresponded to moderate bowel management, a score of 8-10 corresponded to poor bowel management, and a score ≥11 corresponded to very poor bowel management. Based on this, the bowel management strategy was fair in 40% of the patients, moderate in 22%, poor in 20%, and very poor in 18%. A cross-table of bowel management score and QoL is provided in Table VI (available at www.jpeds.com). For groups based on patient status, the mean (SD) bowel management scores were 8.6 (4.4) for new patients not yet treated, 8.0 (3.6) for established patients on treatment not optimized, and 5.4 (2.7) for established patients on treatment doing well. Bowel management scores also differed significantly

Table IV. Associations between questions and impact on QoL

Question	OR (95% CI)	Points in score
1. Stool frequency	NS	
2. Stool shape	1.5 (1.0-2.2)	3
3. Anorectal pain	1.8 (1.1-2.8)	4
4. Abdominal pain	1.7 (1.3-2.1)	3
5. Fecal incontinence	1.3 (1.1-1.6)	3
6. Urine incontinence	NS	
7. Medication	NS	
8. Support from parents or caregivers	1.6 (1.1-2.3)	3
9. School/social interference	2.9 (2.0-4.2)	6
Total points		*22*

NS, not significant and thus not incorporated in the scoring system.

Table V. Weight of the score per answer option

Question	OR	95% CI	Points in score
2. Stool shape			
MSBSFS 3/MSBSFS 4	1		0
MSBSFS 2	1.7	1.0-2.8	1
MSBSFS 1/MSBSFS 5	5.3	2.8-10.1	3
3. Anorectal pain			
Never	1		0
Sometimes	2.1	1.3-3.3	1
Always	27.4	9.3-80.6	4
4. Abdominal pain			
Never	1		0
Once a month or less	NS		0
Once a week or less	2.7	1.4-5.2	1
Several times a week	6.2	3.2-12.0	2
Daily	11.0	4.7-26.0	3
5. Fecal incontinence			
Never	1		0
Once a month or less	NS		0
Once a week or less	2.7	1.4-5.2	1
Several times a week	7.6	3.9-15.2	3
Daily	4.4	2.3-8.4	3
8. Support from parents or caregivers			
No, independent	1		0
Yes, partially dependent	NS		0
Yes, completely dependent	3.5	2.0-6.0	3
9. School/social interference			
Never	1		0
Rarely	3.0	1.7-5.4	1
Usually	16.5	8.4-32.4	2
Always	120.1	15.4-935.0	6
Total maximum points			*22*

MSBSFS, Modified Bristol Stool Form Scale.

between new and not optimized patients (groups A and B) versus patients in group C: $\chi^2(2) = 51.150$ ($P = .000$). The complete version of the PBMST is shown in the **Appendix 3** and **4** (available at www.jpeds.com).

Construct Validity of the PBMST

A Spearmans rank-order correlation was run to determine the relationship between the scores based on the research assistant's assessment of each patient and the patient's scores. The results showed a significant positive correlation between the 2 scores: r_s (38) = .525 ($P = .001$).

Discussion

Pediatric patients with constipation represent a complex group in whom management can be challenging. Despite the different treatment options available (ie, cognitive behavior therapy, laxatives, transanal irrigation, and surgical interventions), there currently are no available tools for evaluating bowel management strategies. In daily practice, treatment evaluation is based on expert opinion and can be better monitored with the use of a diary to record stool and fecal incontinence frequency for several consecutive days. To our knowledge, this is the first study to develop a scoring system for reliably evaluating bowel management strategies in different patient populations with both functional and organic causes (eg, Hirschsprung disease, anorectal malformation, spina bifida) of constipation. Our PBMST was developed and validated for children aged 4-18 years by an international team of experts in the field. This study shows that use of the PBMST can better guide management of childhood constipation, with its fair reproducibility indicating that it is stable over a specified time period. Indeed, consistent use of the PBMST can objectify the patient's clinical condition over a longer period. Consequently, the score provides feedback regarding the effect of the applied bowel management strategy for each individual patient. In our cohort, the mean bowel management score of established patients doing well generated scores corresponding to fair management, whereas the mean bowel management score of patients not doing well and new patients who had not yet started treatment generated scores corresponding to poor management. These outcomes confirm the applicability of the PBMST in clinical practice.

Most existing questionnaires for assessing constipation and/or fecal incontinence use a linear scoring system per question, with the number of points in the score in consecutive order per answer option[10-16]; for example, in the Neurogenic Bowel Dysfunction Score for children developed by Kelly et al, the answer options are not necessarily distributed linearly.[12] Therefore, we performed additional analyses to determine the appropriate weight for each answer option. When performing logistic regression analyses, it is important to define the dependent variable. We decided to define self-reported impact of symptoms of constipation on QoL as our dependent variable. However, because a validated single question to assess QoL is lacking, we created this question in line with the symptom score development study of Krogh et al.[17] Currently validated and widely used instruments to assess the impact of pediatric diseases and treatments on QoL include the KIDSCREEN-52 questionnaire and Pediatric Quality of Life Inventory (PedsQL).[25,26] These instruments include multiple questions on several dimensions related to QoL, such as moods and emotions, self-perception, psychological well-being, social acceptance (bullying), and financial resources. The use of such instruments makes it possible to thoroughly assess which aspects of QoL are affected. In our study, such assessments were limited, because we included only 1 question to assess QoL; thus, it was not possible to assess which aspects of QoL were affected.

Traditionally, self-reporting instruments of subjective measures such as QoL have been aimed at patients aged >8 years.[27,28] For patients aged <8 years, proxy reports have been widely used to gain information.[29] In line with recommendations for child self-reports and parent proxy reports, this study validated 2 versions of the PBMST. However, well-known differences exist between parent proxy reports and child self-reports.[30] It could be hypothesized that the results of logistic regression analyses, and subsequently the selection of the questions incorporated in our scores, would have been different when creating 2 versions of the PBMST (patient BMST vs parent proxy BMST). Post hoc analysis showed that 2 questions on the parent proxy-reported questionnaire that were significantly associated with the patient self-reported impact on QoL were not incorporated into the final version of the PBMST: "how often does your child wet more than a few drops of urine into their underwear or clothing during the day?" and "how often does your child take medication to treat their bowel problems?" We assume that the younger the patient, the more assistance from parents or caregivers is needed to take medication and change underwear and clothing. Indeed, in our study, 73% of the patients aged <8 years needed some form of assistance from parents or caregivers. Not surprisingly, the question "does your child need help from you or caregivers to carry out bowel treatment?" was incorporated into the final version of the PBMST. Post hoc analysis of the patient self-reported questionnaire revealed that all questions that were significantly associated with the self-reported impact on QoL were incorporated into the final version of the PBMST. Notably, cutoffs of bowel management scores corresponding to fair, moderate, poor, and very poor bowel management could be different for the patient self-report and the parent proxy-report versions of the PBMST. We chose not to create 2 different scores to avoid confusion and reduce misinterpretation. The aim was to create a PBMST that is easy to use in clinical practice. The PBMST enables healthcare

professionals, as well as parents or caregivers, to objectify the effect of the applied bowel management strategies. Outcomes can be used to determine that adjustment of management strategy is preferable to provide a tailored approach for each patient.

Up to 29% of pediatric patients with functional constipation experience daytime urine incontinence at least once weekly.[31] In our cohort, the number of patients who experienced daytime urine incontinence at least once weekly was even higher (37%), possibly due to the inclusion of some patients with organic causes (eg, Hirschsprung disease, anorectal malformation, spinal cord injury). Because daytime urine incontinence was not significantly associated with QoL, it was not incorporated in the score. A possible explanation could be that the degree of urine incontinence (and consequently the need to change and wash clothes) was limited and thus did not impact QoL. The question "how often does your child wet more than a few drops of urine into their underwear or clothing during the day?" assesses only the frequency of urine incontinence. Future trials are warranted to further examine the association between constipation and the degree of urine incontinence and its impact on QoL.

Kuizenga-Wessel et al developed a core outcome set (COS) for clinical trials in childhood constipation.[32] The major advantages of using a COS in pediatric trials are decreased study heterogeneity and improved comparability of studies. The 6 questions included in the newly developed and validated PBMST encompass 5 out of 8 outcomes from the COS. Three outcomes from the COS are not covered in the PBMST: QoL of parents, child's defecation frequency, and side effects of treatment. QoL is not included in the PBSMT as a question, but the outcome of patient QoL was used in the development process. Regarding the outcome of defecation frequency, Kuizenga-Wessel et al reported that health care professionals scored this as the most important treatment outcome, whereas parents and patients less forequently identified this as an important outcome. Because our study included only questions significantly associated with impact on QoL as reported by parents and patients, it is not surprising that the defecation frequency question is not included in the PBMST. In addition, Kuizenga-Wessel et al included side effects of treatment in their COS. Although this is not included in the PBMST, we agree that side effects of treatments always should be assessed to evaluate applied treatments. Finally, and in accordance with Kuizenga-Wessel et al, the question regarding school absenteeism and social interference was found to be the question most strongly associated with QoL and thus was incorporated into the final PBMST.

This study has several strengths. First, it was an international collaboration and children were included from 4 different countries and from both secondary and tertiary care centers in both rural and urban areas, increasing the generalizability of our results. Furthermore, both functional and organic causes of constipation were included, also increasing the generalizability of our results. To enable the international collaboration, the questionnaire was professionally translated into 5 languages—Dutch, English, German, Spanish, and Italian—making the PBMST available for a high percenntage of healthcare professionals worldwide.

This study also has some limitations. First, to compute the reproducibility of the PBMST, an identical questionnaire was sent to the original respondents (parents and children) within a 2-week period in which it was expected that the patient's condition would remain unchanged; however, it can be hypothesized that small changes in a patient's condition within the 2 weeks could have influenced the analyses. Nevertheless, as our results show, reproducibility was fair to very good for all questions, indicating a good level of agreement between the answers before and after the 2-week period. Therefore, we believe that the effect of possible changes in patient condition on the development process of the scoring system is negligible. Second, a score will always be limited by the questions on which it is based. In the end, 6 questions were incorporated into the PBMST. Surprisingly, the question on bowel movement frequency was not included in the final score. A bowel movement frequency <2 times per week informs about the presence and possible severity of constipation and is one of the important pediatric Rome IV criteria for functional constipation.[33] In our study, the question was not significantly associated with QoL and thus was not incorporated into the PBMST; however, the purpose of the PBMST is to help patients, parents, and health care professionals to evaluate bowel management strategies, and the tool was not developed for diagnostic purposes. Moreover, 5 different experts in the field, as well as parents and patients, were closely involved in the development of the questionnaire, ensuring that important items for properly evaluating treatment were covered. Third, it could be argued that objective findings, such as abdominal examination to detect a palpable fecal mass and the presence of abdominal distension, should be incorporated in the score as well.[34] Again, we chose not to do so because we wanted a score that was easy to use in clinical practice for both health care professionals and parents or caregivers without the need to perform physical examination. Finally, this study validated a parental proxy-report version of the PBMST for children aged 4-8 years; applicability of the tool for younger children should be carefully evaluated.

In conclusion, this study developed a reliable and valid bowel management scoring tool – the PBMST – for pediatric patients aged 4-18 years with both functional and organic causes of constipation. This tool will allow

interested parties to determine the effect of different bowel management strategies for individual patients by monitoring their change in scores over time. The PBMST is available in different languages and provides a standardized instrument which is easy to use in clinical practice for both healthcare professionals and parents or caregivers. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Fatal Genetic Newborn Lung Disease

Mazyck EM, Bonner JT, Herd HM, Symbas PN. Childhood pulmonary alveolar proteinosis. J Pediatr 1972;80:839-42.

Mazyck et al described an infant with pulmonary alveolar proteinosis (PAP). At the age of 4.5 months, she was admitted to the unit due to vomiting and poor weight gain. Following an open lung biopsy, the diagnosis of PAP was made, and treatment with multiple lung lavages resulted in temporary improvements. However, the infant died at the age of 15-16 months.

PAP is a rare lung disease classified as congenital, secondary, or acquired.[1] In 1988, I treated a 3-week-old newborn infant born at term with severe respiratory distress. Lung tissue was examined by histology, immunohistochemistry, and electron microscopy, indicating PAP. Lung lavage was carried out without improvement, and the boy died within a few weeks. Nineteen years later, the genes encoding surfactant proteins (SP)—B, C, and D, and ABCA3 (ATP-binding cassette transporter A3)—were sequenced from the parents. An *ABCA3* mutation was identified on 1 allele in each parent. Thus, the diagnosis of ABCA3 deficiency was established by analyzing DNA material from the parents.[2]

Accumulation of proteinaceous material that fills distal air spaces may be a common finding in PAP and other surfactant dysfunction disorders, classified by Nogee as interstitial lung disease.[3] Four genes expressing SP A and B, ABCA3, and NKX2 have been identified in which mutations result in lung disease with PAP like phenotype. *NKX2* is a transcription factor important for expression of SP-B, SP-C, ABCA3, and SP-A. Mutations in several different genes, as *CSF2RA and CSF2RB* encoding the receptor for GM-CSF on alveolar macrophages, may result in a syndrome of PAP in children and adults. During the last 50 years, the understanding of PAP and overlapping conditions has exploded.

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Table I. Patient characteristics, stage 1 (N = 51)

Characteristics	Age 4-8 y (N = 21)	Age 8-18 y (N = 30)
Sex, (%)		
Male	10 (48)	11 (37)
Female	11 (52)	19 (63)
Age, y, mean (SD)	5.5 (1.4)	12.0 (2.7)
Pathology, n (%)		
Functional constipation	16 (76)	27 (90)
Hirschsprung disease	4 (19)	2 (7)
Anorectal malformation	1 (5)	1 (3)
Bowel movements per week, median (IQR)	6.5 (5-10)	4.5 (3-7)

Table II. Reproducibility (intrarater reliability)

Variables	Age 4-8 y (N = 21), κ (95% CI)	Age 8-18 y (N = 30), κ (95% CI)
Stool frequency	—*	—*
Stool shape	0.46 (0.03-0.89)	0.73 (0.45-1.00)
Anorectal pain	0.81 (0.56-1.00)	0.58 (0.34-0.82)
Abdominal pain	0.79 (0.63-0.94)	0.74 (0.56-0.92)
Fecal incontinence	0.78 (0.62-0.94)	0.85 (0.73-0.96)
Urine incontinence	0.62 (0.28-0.95)	0.78 (0.57-0.99)
Medication	0.86 (0.60-1.00)	0.71 (0.47-0.95)
Support from parents or caregivers	0.74 (0.50-0.99)	0.53 (0.26-0.79)
School/social interference	0.54 (0.14-0.93)	0.66 (0.47-0.84)
QoL	0.72 (0.53-0.91)	0.55 (0.24-0.87)

*κ values could not be computed because number of rows did not equal the number of columns.

Table VI. Bowel management score versus impact on QoL

Impact on QoL	Fair bowel management (0-5), % (n)	Moderate bowel management (6-7), % (n)	Poor bowel management (8-10), % (n)	Very poor bowel management (≥11), % (n)	Total, n
None	35 (53)	13 (11)	6 (5)	1 (1)	70
Little	48 (74)	41 (34)	27 (21)	10 (7)	136
Some	15 (23)	34 (28)	48 (37)	38 (27)	115
Major	2 (3)	12 (10)	19 (15)	51 (36)	64
Total	40 (153)	22 (83)	20 (78)	18 (71)	385