UC Davis UC Davis Previously Published Works

Title

Derivation of the Pediatric Acute Gastroenteritis Risk Score to Predict Moderate-to-Severe Acute Gastroenteritis

Permalink https://escholarship.org/uc/item/4kc2h00c

Journal Journal of Pediatric Gastroenterology and Nutrition, 74(4)

ISSN 0277-2116

Authors

Levine, Adam C O'Connell, Karen J Schnadower, David <u>et al.</u>

Publication Date

2022-04-01

DOI

10.1097/mpg.000000000003395

Peer reviewed



HHS Public Access

Author manuscript *J Pediatr Gastroenterol Nutr*. Author manuscript; available in PMC 2022 June 17.

Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2022 April 01; 74(4): 446-453. doi:10.1097/MPG.00000000003395.

Derivation of the Pediatric Acute Gastroenteritis Risk Score to Predict Moderate-to-Severe Acute Gastroenteritis

Adam C. Levine^{*}, Karen J. O'Connell[†],

David Schnadower[‡],

T. John M. VanBuren[§], Prashant Mahajan^{II,¶,#},

Katrina F. Hurley^{**},

Phillip Tarr^{††},

Cody S. Olsen^{‡‡},

Naveen Poonai^{§§,III},

Suzanne Schuh^{¶¶},

Elizabeth C. Powell##,

Ken J. Farion***, †††,

Robert E. Sapien^{‡‡‡},

Cindy G. Roskind^{§§§},

Alexander J. Rogers#,

Seema Bhatt

Serge Gouin^{¶¶¶},

Cheryl Vance###,

Stephen B. Freedman****, ††††

Pediatric Emergency Research Canada (PERC) the Pediatric Emergency Care Applied Research Network (PECARN)

^{*}Department of Emergency Medicine, Rhode Island Hospital/Hasbro Children's Hospital and Brown University, Providence, RI

[†]Division of Emergency Medicine, Children's National Hospital, Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, DC

[‡]Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

§Department of Pediatrics, University of Utah, Salt Lake City, UT

Address correspondence and reprint requests to Adam C. Levine, MD, MPH, Department of Emergency Medicine, Rhode Island Hospital/Hasbro Children's Hospital and Brown University, 55 Claverick Street, 2nd Floor, Providence, RI 02903 (adam_levine@brown.edu).

URL and Trial Identification Number: https://clinicaltrials.gov/ct2/show/NCT01773967.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpgn.org).

An infographic is available for this article at: http://links.lww.com/MPG/C670.

Division of Emergency Medicine, Department of Pediatrics, Children's Hospital of Michigan

[¶]Wayne State University, Detroit

[#]Departments of Emergency Medicine and Pediatrics, University of Michigan, Ann Arbor, MI

**Department of Emergency Medicine, IWK Health, Halifax, Nova Scotia, Canada

⁺⁺Division of Gastroenterology, Hepatology, & Nutrition, Department of Pediatrics, Washington University in St. Louis School of Medicine, St. Louis, MO

^{‡‡}Department of Pediatrics, University of Utah, Salt Lake City, UT

^{§§}Departments of Pediatrics, Internal Medicine, Epidemiology & Biostatistics, Schulich School of Medicine and Dentistry

Children's Health Research Institute, London Health Sciences Centre, London

[¶]Division of Pediatric Emergency Medicine, The Hospital for Sick Children, SickKids Research Institute, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

^{##}Division of Emergency Medicine, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL

*** Departments of Pediatrics and Emergency Medicine, University of Ottawa

⁺⁺⁺Pediatric Emergency Department, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

^{‡‡‡}Department of Emergency Medicine, University of New Mexico, Albuquerque, NM

^{§§§}Department of Emergency Medicine, Columbia University Vagelos College of Physicians & Surgeons, New York, NY

^{IIII}Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH

^{¶¶}Departments of Pediatric Emergency Medicine & Pediatrics, Université de Montréal, Montréal, Quebec, Canada

^{###}Departments of Pediatrics and Emergency Medicine, University of California, Davis, School of Medicine, Sacramento, CA

****Divisions of Pediatric Emergency Medicine and Gastroenterology, Alberta, Children's Hospital, Alberta, Canada

⁺⁺⁺⁺Sections of Pediatric Emergency Medicine and Gastroenterology, Departments of Pediatrics and Emergency Medicine, Alberta Children's Hospital, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, AB

Abstract

Objectives: Although most acute gastroenteritis (AGE) episodes in children rapidly self-resolve, some children go on to experience more significant and prolonged illness. We sought to develop a prognostic score to identify children at risk of experiencing moderate-to-severe disease after an index emergency department (ED) visit.

Methods: Data were collected from a cohort of children 3 to 48 months of age diagnosed with AGE in 16 North American pediatric EDs. Moderate-to-severe AGE was defined as a Modified Vesikari Scale (MVS) score 9 during the 14-day post-ED visit. A clinical prognostic model was derived using multivariable logistic regression and converted into a simple risk score. The model's accuracy was assessed for moderate-to-severe AGE and several secondary outcomes.

Results: After their index ED visit, 19% (336/1770) of participants developed moderate-tosevere AGE. Patient age, number of vomiting episodes, dehydration status, prior ED visits, and intravenous rehydration were associated with MVS 9 in multivariable regression. Calibration of the prognostic model was strong with a P value of 0.77 by the Hosmer-Lemenshow goodness-offit test, and discrimination was moderate with an area under the receiver operator characteristic curve of 0.68 (95% confidence interval [CI] 0.65–0.72). Similarly, the model was shown to have good calibration when fit to the secondary outcomes of subsequent ED revisit, intravenous rehydration, or hospitalization within 72 hours after the index visit.

Conclusions: After external validation, this new risk score may provide clinicians with accurate prognostic insight into the likely disease course of children with AGE, informing disposition decisions, anticipatory guidance, and follow-up care.

Keywords

children; diarrhea; emergency department; prognosis

Despite recent progress and advancement in clinical management, acute gastroenteritis (AGE) in the United States still contributes to over 1.7 million pediatric emergency department (ED) visits and 70,000 hospitalizations annually, with an average hospital stay of 2.1 days (1). The direct costs of AGE because of norovirus alone across all ages are estimated to be \$106 million annually in the United States (2).

The vast majority of pediatric AGE cases, including those presenting to the ED, will follow a benign course (3). Some children will, however, experience moderate-to-severe symptoms after they are discharged, resulting in significant school and work absenteeism, revisits, and hospitalizations (4,5). Prior research has found that 4.3% of children discharged from the ED with AGE will return within 72 hours, and up to 18% within 7 days (6,7). Among young children and their caregivers, AGE is closely linked to missing days of school/daycare and work (8–10). Both direct and indirect costs of pediatric AGE increase for patients with moderate-to-severe symptoms requiring ED revisits, intravenous rehydration, or hospitalization. Although parents are estimated to miss 1 workday for each AGE-related outpatient visit without intravenous rehydration, this increases to 2 workdays for outpatient visits with intravenous rehydration and 3 for pediatric hospitalizations because of AGE (1). Clinicians, however, currently have limited ability to predict the likelihood that their patient may follow this more severe, prolonged, and costly disease course.

The primary aim of this study is to produce and internally validate the first pragmatic risk score for predicting the onset or continuation of moderate-to-severe AGE following an ED visit. Such a score could aid clinicians in providing appropriate anticipatory guidance to parents of young children regarding the expected course of their child's illness, as well

as inform planned follow-up decisions. Secondary outcomes evaluate the ability of the score to identify children at risk for a subsequent ED visit, intravenous rehydration, and hospitalization after the index visit.

METHODS

Study Design

We conducted an a priori planned secondary analysis of data gathered through the 2 randomized, double-blind multi-center clinical trials of probiotic efficacy in children with AGE (11–14). We used standard methods from the literature, including guidelines provided by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement, to conduct our secondary analysis of these 2 datasets (15). These trials had comparable designs and occurred in 6 Canadian and 10 United States-based pediatric EDs via Pediatric Emergency Research Canada (PERC) and Pediatric Emergency Care Applied Research Network (PECARN), respectively. Institutional review board (IRB) approval for this a prior planned secondary analysis was obtained at all study locations for both the PERC and PECARN trials. Financial compensation for completing follow-up procedures was approved through the original IRBs. This secondary analysis was conducted through data use agreements between all sites and in alignment with the original IRB protocols.

Sample Population

Both trial populations included children between 3 and 48 months old who were diagnosed with AGE by an ED provider, regardless of disposition. All participants had a minimum of 3 or more episodes of watery stools in a 24-hour period. Participants in the PERC trial had a maximal symptom duration of 72 hours before enrollment; in the PECARN trial the maximal duration was 7 days. Children were excluded if they had a chronic gastrointestinal disorder, pancreatitis, bilious emesis, hematochezia, or a known allergy to the interventional or placebo agents. Children were deemed ineligible if they or their caregivers had risk factors for bacteremia or if there were language barriers precluding a complete understanding of the trials or study procedures.

Data Collection

The Clinical Dehydration Scale (CDS) was used to evaluate patient dehydration status during their index ED visit (16,17). All participants then completed a daily online or telephone survey for 5 days afterwards. These surveys touched on the frequency and duration of diarrhea, and whenever relevant, vomiting, missed daycare days, work hours missed by caregivers, and household transmission after the index visit. If symptoms persisted beyond 5 days, data collection continued until symptoms resolved, with final follow-up collected at 14 days. Children were deemed lost to follow-up if no daily surveys were collected; such children were excluded from this analysis.

Outcome Measures

The primary outcome of interest is the development or continuation of moderate-to-severe AGE following the index ED visit, defined by a Modified Vesikari Scale (MVS) score

of 9 or higher during the 14-day follow-up period. The MVS score was selected as it has been validated for pediatric use in both Canadian and United States-based pediatric EDs to quantify AGE severity following discharge (Table 1, Supplemental Digital Content, http://links.lww.com/MPG/C664) (18–20). Postenrollment MVS scores were based on data gathered between randomization and day 14, which were not available to clinicians during the patient's index ED visit. Symptoms were attributed to the index AGE episode until the caregiver reported a 24-hour period with no evidence of diarrhea, vomiting, and fever. Secondary outcomes included ED revisit(s), intravenous rehydration, and hospitalization for AGE-related symptoms within 72 hours after discharge from the index ED visit.

Statistical Analysis

Patient baseline characteristics are summarized by MVS outcome (MVS <9 vs MVS 9) using medians and interquartile ranges (IQR) for continuous characteristics and frequencies and percentages for categorical characteristics. For patients with incomplete daily surveys, the analysis used chained regression equations to create 10 multiple imputed datasets, which were combined using standard methods across multiple imputations (21,22). Imputation was implemented in IVEware software (University of Michigan, Ann Arbor, MI). Logistic regression models were used to calculate unadjusted odds-ratios and 95% confidence intervals (CIs) of MVS 9 for demographic and clinical characteristics. Logistic regression models tested for associations between patient characteristics and secondary outcomes.

A clinical prognostic model for MVS 9 was derived using logistic regression methods. First, continuous variables were assigned to categories. Those that are components of MVS were assigned categories aligned with the MVS scoring algorithm categories. Other continuous variables were categorized by study investigators into clinically relevant categories. Combinations of predictors with over 2 categories were created by fitting logistic regression models to MVS 9 and testing for effect differences between adjacent categories. Adjacent categories with no significantly different effect (i.e. P < 0.05) were combined to produce the candidate predictors and categories for the clinical prognostic model.

In order to identify a parsimonious set of predictors of MVS 9, logistic regression models with least absolute shrinkage and selection operator, or Lasso logistic regression, was applied to the 10 imputed datasets, and results were combined using standard methods (22,23). Lasso regression deflates the estimates for less important predictors and identifies a subset of more important predictors. The reference values were chosen such that all log-odds estimates were positive or negligible. Log odds ratio estimates from that model were plotted, grouped, and assigned scores such that predictors with similar log odds ratios received similar scores. Component scores based on each predictor contribute an integer between 0 and 3 to the final score, where the integer was based on the relative size of the log odds ratio. Predictors with component scores < 1 were dropped. The final risk severity score for MVS 9 is the sum of the component scores.

Each enrolled subject received a risk severity score termed the Pediatric Acute Gastroenteritis Risk (PAGER) score. Using their computed scores, we calculated Receiver-Operating Curves (ROC) for predicting MVS 9 and the area under the curve (AUC). The logistic regression derived probabilities using the individual's PAGER score as the

primary continuous predictor, which are referred to as the model-predicted probabilities. We used 1000 bootstrap samples of the full dataset to estimate the AUC and its standard error. A comparison between the model-predicted probability of MVS 9 and the observed proportions for each risk score level assessed the model's calibration, and a Hosmer-Lemeshow goodness-of-fit chi-square test was used to evaluate the model fit (24).

To examine how well the PAGER score for MVS 9 predicted other outcomes, including return ED visits, subsequent intravenous fluids, and subsequent hospitalizations, logistic regressions with the continuous PAGER score was applied to these secondary outcomes. For each, we used the AUC and goodness-of-fit to evaluate discrimination and model fit. As a sensitivity analysis, we estimated the AUC and goodness of fit of the derived model when applied to the dataset after excluding PECARN patients presenting more than 72 hours after symptoms began. Data were analyzed using SAS/STAT® software (version 9.4, Cary, NC).

RESULTS

Baseline Characteristics of Training Dataset

For the 2 studies, 1857 total children were recruited. After excluding 87 children lost to follow-up, the final study cohort (N = 1770) consisted of 827 PERC (46.7%) and 943 PECARN (53.3%) participants (Fig. 1). The cohort had a median age of 1.3 (0.8–2.2) years, and 55.1% (976/1770) of participants were boys (Table 1). At the index ED visit, 60.2% (1065/1770) of the cohort had no dehydration, whereas 37.3% (660/1770) and 2.2% (39/1770) had mild-moderate and severe dehydration, respectively (17,18). At the index visit, 13.2% (233/1770) received intravenous rehydration, 34.5% (610/1770) ondansetron, and 3.2% (57/1770) antibiotics.

Overall, data was missing for the primary outcome of MVS in about 16% of patients, whereas about 5% of patients across the 2 study cohorts were missing data on secondary outcomes of ED revisits or subsequent hospitalizations (Table 6, Supplemental Digital Content, http://links.lww.com/MPG/C669). Multiple imputation was used, as described in the methods above, to allow analysis of included subjects.

Primary Outcomes

Of the 1770 cohort participants, 336 (19%) developed moderate-to-severe AGE during the 14 days after their index ED visit, defined by a MVS score 9. In bivariate analysis, this primary outcome was statistically associated with several different factors. For example, development of moderate-to-severe AGE was inversely associated with diarrhea duration [OR: 0.88 (95% CI: 0.80–0.97 per 24 hours)]. Using <12 months as the reference group, the odds of experiencing the primary outcome declined with each increasing year of age: 0.66 (95% CI: 0.50–0.88) for 12–24months; 0.54 (95% CI: 0.37–0.77) for 24–36 months; and 0.46 (95% CI: 0.29–0.73) for 36 to 48 months. Moderate-to-severe AGE was positively associated with the number of diarrheal episodes in the 24 hours preceding the ED visit [OR: 1.21 (95% CI: 1.07–1.36) per 5 episodes], the presence of vomiting [OR: 2.56 (95% CI: 1.79–3.65)], the number of vomiting episodes in the 24 hours preceding the ED visit [OR: 1.64 (95% CI: 1.44–1.85)], increasing dehydration severity [4.35 (95% CI: 2.18–8.70

for severe relative to none)], prior ED visits for the same episode of AGE [2.04 (95% CI: 1.34–3.10)], and prior intravenous fluid administration [2.29 (95% CI: 1.67–3.13)]. We next used Lasso logistic regression, as described in the methods above, to select a parsimonious set of predictors for the development of moderate AGE with a MVS score 9.

The variables in the final parsimonious model included age, the number of vomiting episodes in the 24 hours preceding the ED visit, Clinical Dehydration Scale assessment, intravenous fluid administration during the index visit, and prior ED visits for this same episode of AGE. Regression coefficients for each variable in the final model were converted into points and totaled to provide a PAGER score for bedside use to predict 14-day outcomes in children with AGE (Table 2). PAGER scores range from 0 to 10 points, expressed in discrete integer values, and linearly correspond to the risk of developing moderate-to-severe AGE (MVS 9) after the index visit. Three cutoff points were selected based on expert clinician opinion to stratify the risk estimate, with low risk designated 4 points or less, medium risk 5 to 7 points, and high risk 8 points or more (Table 3).

The AUC for the PAGER score predicting moderate-to-severe AGE during the 14 days following the index ED visit in the full study cohort was 0.68 (95% CI: 0.65–0.72) with the ROC curve shown (Fig. 2, Supplemental Digital Content, http://links.lww.com/MPG/C665). An internal validation using 1000 bootstrapped samples of the model confirmed a similar AUC of 0.68 (95% CI: 0.65–0.72), suggesting minimal optimism of the primary model. In addition to assessing the model's discrimination, we also assessed its calibration as described in the methods above (24). The calibration plot of observed frequency correlated well with the model-predicted probability of developing moderate-to-severe AGE, and the Hosmer-Lemenshow goodness-of-fit test had a *P* value of 0.77, suggesting good calibration (Fig. 3, Supplemental Digital Content, http://links.lww.com/MPG/C666).

An additional sensitivity analysis was conducted using a subset of the sample to account for differences in the symptom duration characteristics of the PECARN versus PERC datasets. This analysis sample excluded PECARN patients that reported experiencing a symptomatic period longer than 72 hours before presentation. When the model was applied to predict MVS 9 only among this subset of patients, the AUC [0.69 (95% CI: 0.65-0.72)] and Hosmer-Lemenshow goodness-of-fit test (*P* value: 0.43) were consistent with those of the whole sample.

Secondary Outcomes

Overall, 6.7% (119/1770) of study participants had an ED revisit, 2.5% (45/1770) received intravenous fluids during a subsequent visit, and 1.6% (29/1770) were hospitalized within 72 hours of the index ED visit. Predictors of these outcomes in bivariate analysis included the number of vomiting episodes in the 24 hours preceding the index ED visit, increasing dehydration severity assessed using the Clinical Dehydration Scale score, and intravenous fluids administered at the index ED visit (Table 4, Supplemental Digital Content, http://links.lww.com/MPG/C667).

The AUCs of the PAGER score for predicting ED revisits (0.61; 95% CI: 0.55–0.66), intravenous rehydration (0.69; 95% CI: 0.61–0.77), and subsequent hospitalizations (0.69;

95% CI: 0.58–0.81) within 72 hours of the index ED visit were similar to that for predicting the primary outcome of moderate-to-severe AGE (Table 5, Supplemental Digital Content, http://links.lww.com/MPG/C668). The Hosmer-Lemeshow goodness-of-fit test *P* values for the PAGER score were 0.57 for ED revisits, 0.73 for intravenous rehydration, and 0.88 for hospitalization, suggesting good calibration for these secondary outcomes.

DISCUSSION

Using data from 2 large, high-quality RCTs, we have developed the PAGER score using demographic and clinical characteristics captured at the index ED visit to predict the development of moderate-to-severe AGE in young children following the index visit. In addition to predicting the primary outcome of moderate-to-severe AGE, the PAGER score can also be used to predict other important outcomes up to 72 hours following the index ED visit, including ED revisits, subsequent intravenous fluid administration, and hospitalization.

In our derivation cohort, the discrimination of the PAGER score was found to be moderate with an AUC of 0.68. Although high discrimination is most important for a diagnostic tool designed to help make specific clinical decisions in the moment, the PAGER score is not intended for such a purpose (24). Rather, the score is intended to be used by clinicians as a prognostic tool to inform anticipatory guidance for parents of young children with AGE, which can help prepare them for a more severe disease course and the need to miss school and work (25). Used in this manner, calibration may be a better measure of the tool's accuracy (24). As measured by the Hosmer-Lemenshow goodness-of-fit test, the PAGER score had good calibration in our combined datasets, both for the prediction of the primary outcome of moderate-severe AGE as well as subsequent hospitalization. Although the accuracy of the PAGER score will need to be reassessed in external validation studies before clinical use, it has the potential to individualize anticipatory guidance and inform the need for follow-up care.

Several prior studies have evaluated clinical predictors of undesirable outcomes in children with AGE. A retrospective cohort study examined data from 3356 AGE-related visits to a Canadian pediatric ED and found intravenous rehydration at the index ED visit to be associated with ED revisits (5). Similarly, a secondary analysis of data from 226 children with AGE who received intravenous rehydration in a Canadian pediatric ED found that a higher baseline serum bicarbonate level, absence of a primary care provider, and administration of ondansetron predicted an ED revisit (6). Inversely, lower baseline Clinical Dehydration Scale scores and a smaller volume of administered fluid were found to be independent predictors of a successful ED discharge (6). The variables identified in these prior studies align with those identified in our international, multicenter cohort as predictive of both worse outcomes overall and future ED revisits in children with AGE.

Although several studies have evaluated various clinical diagnostic models to assess dehydration severity in young children presenting with AGE, including the Clinical Dehydration Scale (CDS) score, the World Health Organization's dehydration algorithm, and the Dehydration: Assessing Kids Accurately (DHAKA) score, no prior studies have attempted to develop clinical prognostic models for the specific purpose of predicting the

future course of illness in young children with AGE (16,17,26–33). The PAGER score, in contrast, was developed for the prediction of moderate-to-severe AGE in the 2 weeks after an index ED visit.

Lastly, our algorithm enables physicians to apply a simple point system at a patient's bedside to accurately inform the anticipated course of illness, thereby guiding providercaregiver interactions. During instances of AGE, caregivers report very high stress scores, with 93.6% of parents in one cohort reporting high or medium distress (34). Identifying those children most likely to experience a more severe and prolonged disease course will enable clinicians to provide parents with important prognostic information that may help them better prepare for missed school and work, or alternatively, reassure them of a likely benign course, thereby reducing the stress associated with their child's illness.

Limitations

The 2 study cohorts were enrolled during days and evenings, so eligible children who presented to participating EDs after hours or whose caregivers declined to participate are not represented. Furthermore, the 2 study cohorts had different inclusion criteria, which may affect the baseline patient characteristics used in our secondary analysis. In particular, the PERC cohort included only those with a maximum symptom duration smaller than 72 hours, whereas the PECARN cohort extended their inclusion to those with symptoms up to 7 days. Although this is a significant limitation, a sensitivity analysis applying the PAGER score to patients with a maximum symptom duration of 72 hours did not appear to affect its accuracy.

Furthermore, our dataset is also largely reliant on caregiver reports of symptoms and adverse outcomes, raising the possibility of inaccurate recall. To reduce the potential impact of this bias on the data, caregivers regularly provided updates using a standardized data collection tool with high follow-up rates. Study staff also conducted chart reviews to identify potentially missed revisits and hospitalizations. Such efforts could not, however, detect visits to other institutions, so some pertinent outcomes may have been missed. Finally, the study includes patients presenting to North American pediatric EDs between 3 months and 4 years of age. Thus, the sample population may not be representative of EDs in general, and the findings may not be generalizable to older or younger children. As with other potential clinical tools, prospective external validations will be necessary and important to further evaluate the score. Particularly as this analysis was conducted in a variety of settings both within and outside of North America, as well as with pediatric patients of other ages.

CONCLUSION

Although the majority of young children presenting for AGE will experience a relatively benign course after an ED visit, a significant proportion will experience moderate-to-severe disease, resulting in missed school for the child and work for parents, repeat healthcare visits, and hospitalizations. The PAGER score uses age, number of prior vomiting episodes, dehydration status, intravenous fluid administration, and prior ED visits to aid clinicians in identifying children at higher risk for poor outcomes and, thus, provide better guidance to

parents on the likely course of their child's illness and set reasonable expectations. Before the score can be applied in clinical practices, however, there must be further validation of the tool in other patient populations. Upon external validation, the PAGER score could be an important tool for clinicians to use in managing one of the most common illnesses in young children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

The researchers would like to thank Ms Viani Dickey and Ms Carla Hall-Moore at Washington University, the staff at the data coordinating center, the research coordinators and clinicians at all participating sites, and the investigators and subcommittees of the Pediatric Emergency Care Applied Research Network (PECARN) and Pediatric Emergency Research Canada (PERC), without whose support these trials could not have been conducted; Ms Gabriela Gil for her contributions to this manuscript; Ms Sheila Mason and Dr. Richard Buller for stool testing; Dr Carey-Ann Burnham, Dr Erik Dubberke, and Ms Tiffany Hink for *L rhamnosus* GG sample testing; and the members of the data and safety monitoring board (Dr David Reboussin [chair], Dr Anupam Kharbanda, Dr Oscar Gomez, Dr George Fuchs, and Dr Robert Shulman).

Sources of Funding:

All phases of this study were supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant R01HD071915); the Washington University Biobank Core, supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (grant P30DK052574) and the Canadian Institutes of Health Research (grants 286384 and 325412); S.F. is supported by the Alberta Children's Hospital Foundation Professorship in Child Health and Wellness.

Lactobacillus GG and placebo were provided in-kind by iHealth, the distributors of Culturelle in the United States; Lacidofil and placebo were provided in-kind by Lallemand Health Solutions. Neither company contributed financially to the trials or to the investigators, and their employees did not have access to the trial data. Personnel at iHealth and Lallemand Health Solutions had no role in the design or conduct of the trials; in the collection, management, analysis, or interpretation of the data; in the preparation of the manuscripts; or in the decision to submit the manuscripts for publication.

D.S. is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant R01HD071915). D.S. has received in-kind study drug and placebo from iHeath Inc. and is supported in part by the Richard and Barbara Ruddy Endowed Chair in Emergency Medicine at Cincinnati Children's Hospital Medical Center.

P.T. is a consultant to, a holder of equity in, and a member of the Scientific Advisory Board of MediBeacon Inc, which is developing technology to test intestinal permeability in people. He is also a co-inventor on a patent that might generate royalties on this technology in the future. He is also a consultant to Takeda Pharmaceuticals on childhood intestinal disorders.

S.B.F. is supported by the Alberta Children's Hospital Foundation Professorship in Child Health and Wellness (to S.B.F.).

PECARN is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS), the Emergency Medical Services for Children (EMSC) program through the following grants: DCC-University of Utah (U03MC 00008), GLEMSCRN-Nationwide Children's Hospital (U03MC 00003), HOMERUN-Cincinnati Children's Hospital Medical Center (U03MC22684), PEMNEWS-Columbia University Medical Center (U03MC00007), PRIME-University of California at Davis Medical Center (U03MC00001), SW NODE-University of Arizona Health Sciences Center (U03MC28845), WBCARN-Children's National Medical Center (U03MC00006), and CHaMP-Medical College of Wisconsin (H3MC26201).

S.B.F. provides consulting services to RedHill Biopharma LTD, Takeda Pharmaceutical Company, and Eligo Bioscience.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work, including appropriately investigating and resolving questions related to the accuracy and integrity of any part of the work.

REFERENCES

- Freedman S, Steiner M, Chan K. Oral ondansetron administration in emergency departments to children with gastroenteritis: an economic analysis. PLOS Med 2010;7:e1000350. [PubMed: 20967234]
- 2. Burke RM, Mattison C, Pindyck T, et al. The burden of Norovirus in the United States, as estimated based on administrative data: updates for medically attended illness and mortality, 2001–2015. Clin Infect Dis 2020;73:e1–8.
- Anon. Diarrhoeal disease. World Health Organization. https://www.who.int/news-room/fact-sheets/ detail/diarrhoeal-disease. Published May 2, 2017. Accessed May 20, 2020.
- Freedman SB, Gouin S, Bhatt M, et al. Pediatric Emergency Research Canada. Prospective assessment of practice pattern variations in the treatment of pediatric gastroenteritis. Pediatrics 2011;127:e287–95. [PubMed: 21262881]
- 5. Freedman SB, Thull-Freedman JD, Rumantir M, et al. Emergency department revisits in children with gastroenteritis. J Pediatr Gastroenterol Nutr 2013;57:612–8. [PubMed: 23820403]
- Freedman S, DeGroot J, Parkin P. Successful discharge of children with gastroenteritis requiring intravenous rehydration. J Emerg Med 2014;46:9–20. [PubMed: 23993936]
- Bahm A, Freedman S, Guan J, et al. Evaluating the impact of clinical decision tools in pediatric acute gastroenteritis: a population-based cohort study. Acad Emerg Med 2016;23:599–609. [PubMed: 26824763]
- Arnold B, Wade T, Benjamin-Chung J, et al. Acute gastroenteritis and recreational water: highest burden among young US children. Am J Public Health 2016;106:1690–7. [PubMed: 27459461]
- 9. Coffin S, Elser J, Marchant C, et al. Impact of acute rotavirus gastroenteritis on pediatric outpatient practices in the United States. Pediatr Infect Dis J 2006;25:584–9. [PubMed: 16804426]
- Freedman S, Sherman P, Willan A, et al. Pediatric Emergency Research Canada (PERC). Emergency department treatment of children with diarrhea who attend day care: a randomized multidose trial of a Lactobacillus helveticus and Lactobacillus rhamnosus combination probiotic. Clin Pediatr (Phila) 2015;54:1158–66. [PubMed: 25669920]
- Freedman S, Williamson-Urquhart S, Farion K, et al. PERC PROGUT Trial Group. Multicenter trial of a combination probiotic for children with gastroenteritis. N Engl J Med 2018;379:2015–26. [PubMed: 30462939]
- Schnadower D, Tarr P, Casper T, et al. Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children. N Engl J Med 2018;379:2002–14. [PubMed: 30462938]
- 13. Freedman SB, Williamson-Urquhart S, Schuh S, et al. Pediatric Emergency Research Canada (PERC) Gastroenteritis Study Group. Impact of emergency department probiotic treatment of pediatric gastroenteritis: study protocol for the PROGUT (Probiotic Regimen for Outpatient Gastroenteritis Utility of Treatment) randomized controlled trial. Trials 2014;15:170. [PubMed: 24885220]
- Schnadower D, Tarr PI, Casper TC, et al. Randomised controlled trial of Lactobacillus rhamnosus (LGG) versus placebo in children presenting to the emergency department with acute gastroenteritis: the PECARN probiotic study protocol. BMJ Open 2017;7:e018115.
- Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594. [PubMed: 25569120]
- 16. Friedman J, Goldman R, Srivastava R, et al. Development of a clinical dehydration scale for use in children between 1 and 36 months of age. J Pediatr 2004;145:201–7. [PubMed: 15289767]
- 17. Goldman R, Friedman J, Parkin P. Validation of the clinical dehydration scale for children with acute gastroenteritis. Pediatrics 2008;122:545–9. [PubMed: 18762524]

- Schnadower D, Tarr P, Gorelick M, et al. Validation of the Modified Vesikari Score in children with gastroenteritis in 5 US emergency departments. J Pediatr Gastroenterol Nutr 2013;57:514–9. [PubMed: 23676445]
- Kinlin L, Freedman S. Evaluation of a clinical dehydration scale in children requiring intravenous rehydration. Pediatrics 2012;129:e1211–9. [PubMed: 22529270]
- Freedman S, Eltorky M, Gorelick M, et al. Pediatric Emergency Research Canada Gastroenteritis Study Group. Evaluation of a Gastroenteritis Severity Score for Use in Outpatient Settings. Pediatrics 2010;125:e1278–85. [PubMed: 20439605]
- 21. Raghunathan T, Lepkowski J, Van Hoewyk J, et al. A multivariate technique for multiply imputing missing values Using a sequence of regression models. Surv Methodol 2001;27:85–95.
- 22. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons, Incorporated; 1987.
- 23. Yuan M, Lin Y. Model selection and estimation in regression with grouped variables. J R Stat Soc Ser B Stat Methodol 2006;68:49–67.
- 24. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128–38. [PubMed: 20010215]
- 25. Van der Wielen M, Giaquinto C, Gothefors L, et al. REVEAL Study Group. Impact of communityacquired paediatric rotavirus gastroenteritis on family life: data from the REVEAL study. BMC Fam Pract 2010;11:22. [PubMed: 20230601]
- 26. Levine A, Glavis-Bloom J, Modi P, et al. Empirically derived dehydration scoring and decision tree models for children with diarrhea: assessment and internal validation in a prospective cohort study in Dhaka, Bangladesh. Glob Health Sci Pract 2015;3:405–18. [PubMed: 26374802]
- 27. Levine A, Glavis-Bloom J, Modi P, et al. External validation of the DHAKA score and comparison with the current IMCI algorithm for the assessment of dehydration in children with diarrhoea: a prospective cohort study. Lancet Glob Health 2016;4:e744–51. [PubMed: 27567350]
- 28. Anon. Handbook IMCI: integrated management of childhood illness. Geneva: World Health Organization, Dept. of Child and Adolescent Health and Development; 2005.
- Gorelick M, Shaw K, Murphy K. Validity and reliability of clinical signs in the diagnosis of dehydration in children. Pediatrics 1997;99:E6.
- 30. Pomorska D, Dziechciarz P, Mduma E, et al. Comparison of three dehydration scales showed that they were of limited or no value for assessing small children with acute diarrhoea. Acta Paediatr 2018;107:1283–7. [PubMed: 29461647]
- 31. Levine A, Munyaneza R, Glavis-Bloom J, et al. Prediction of severe disease in children with diarrhea in a resource-limited setting. PLoS One 2013;8:e82386. [PubMed: 24349271]
- Jauregui J, Nelson D, Choo E, et al. External validation and comparison of three pediatric clinical dehydration scales. PLoS One 2014;9:e95739. [PubMed: 24788134]
- Pringle K, Shah S, Umulisa I, et al. Comparing the accuracy of the three popular clinical dehydration scales in children with diarrhea. Int J Emerg Med 2011;4:58. [PubMed: 21902838]
- 34. Marchetti F, Vetter V, Conforti G, et al. Parents' insights after pediatric hospitalization due to rotavirus gastroenteritis in Italy. Hum Vaccines Immunother 2017;13:2155–9.

What Is Known

- Previous studies have evaluated clinical tools to determine hydration status in young children with gastroenteritis.
- No prior research has developed a clinical risk score that predicts which children will experience a moderate-to-severe course after their index visit.

What Is New

- We derived the Pediatric Acute Gastroenteritis Risk score to assist clinicians with evaluating the prognosis of young children with acute gastroenteritis in clinical settings.
- The score can be used to identify which young children are likely to develop moderate-to-severe acute gastroenteritis and adverse secondary outcomes following an emergency department visit.



FIGURE 1. Patient flow diagram.

		TABLE 1.		
Baseline characteristics of s	study cohort and predictors of mod	erate-to-severe acute	gastroenteritis (h	Modified Vesikari Scal
		Nur	nber (row %) of parti	cipants
	Number (%) of participants (N = 1770)	MVS 0 to 8 $(n = 1267)$	MVS $9 (n = 215)$	MVS Unknown (N = 288)
Age group in months				
3.0 to <12.0	589 (33.3)	392 (66.6)	85 (14.4)	112 (19.0)
12.0 to <24.0	652 (36.8)	465 (71.3)	79 (12.1)	108 (16.6)
24.0 to <36.0	325 (18.4)	249 (76.6)	33 (10.2)	43 (13.2)
36.0 to <48.0	204 (11.5)	161 (78.9)	18 (8.8)	25 (12.3)
Sex				
Female	794 (44.9)	576 (72.5)	88 (11.1)	130 (16.4)
Male	976 (55.1)	691 (70.8)	127 (13.0)	158 (16.2)

Age group in months 3.0 to <12.0 12.0 to $<24.02.0$ to $<36.036.0$ to $<38.036.0$ to $<48.036.0$ to <23.0 hours ⁴ Yes Unknown Yomiting episodes, median (Q1-Q3), hours4 $YesYesVomiting episodes, median (Q1-Q3), hours4YesYesVomiting episodes, median (Q1-Q3), hours4YesYesVomiting episodes, median (Q1-Q3), hours4YesYesVomiting episodes, median (Q1-Q3), hours4YesVomiting episodes, median (Q1-Q3), hours4YesVomiting Platentarion (Q1-Q3), hours4YesVomiting Platentarion (Q1-Q3), hours4YesVon the median (Q1-Q3)$	Had prior ED visit for the current illness		Unknown	Yes	No	Fever	Vomiting episodes, median (Q1–Q3) $^{\sharp}$	Vomiting duration, median (Q1–Q3), hours ${}^{\dot{\tau}}$	Unknown	Yes	No	Presence of vomiting at presentation	Diarrheal episodes, median (Q1–Q3) \sharp	Diarrhea duration, median (Q1–Q3), hours $^{\neq}$	Male	Female	Sex	36.0 to <48.0	24.0 to <36.0	12.0 to <24.0	3.0 to <12.0	Age group in months	Age group in months 3.0 to <12.0 12.0 to <24.0 24.0 to <36.0 36.0 to <48.0 36.0 to <48.0 Sex Female Male Diarrhea duration, median (Q1–Q3), hours ^{t^{+}} Diarrheal episodes, median (Q1–Q3), t^{+} Presence of vomiting at presentation No Yes Unknown Vomiting episodes, median (Q1–Q3), t^{+} Fever No Yes Unknown Had prior ED visit for the current illness Had prior ED visit for the current illness
--	--	--	---------	-----	----	-------	---	--	---------	-----	----	--------------------------------------	---	--	------	--------	-----	---------------	---------------	---------------	--------------	---------------------	--

<0.001

[Reference]

2.56 (1.79-3.65)

219 (16.2)

191 (14.1) 23 (5.5)

941 (69.7) 326 (78.0)

0(0.0)

0 (0.0)

1(100.0)

69 (16.5)

0.003

0.01

37.8 (23.3–57.8)

40.0 (22.8-67.4)

48.3 (26.0-70.0)

46.0 (25.3–68.1)

5.0 (4.0-8.0)

418 (23.6) 351 (76.3) 1 (0.1)

5.0 (3.0-8.0)

6.0(4.0-10.0)

5.0 (4.0-8.0)

<0.001

0.02

[Reference]

153 (18.4)

76 (9.1)

603 (72.5)

664 (70.9)

937 (52.9)

1 (0.1)

832 (47.0)

 $0\,(0.0)$

135 (14.4)

138 (14.7)

0 (0.0)

1 (100.0)

1.35 (1.06–1.72)

0.01

1.11 (1.02-1.20) 1.64 (1.44–1.85)

24.2 (0.0-51.0)

32.7 (14.6-56.0)

23.5 (0.0-53.0)

25.2 (0.0-52.8)

2.0 (0.0-5.0)

3.0 (0.0-6.0)

4.0 (2.0-8.0)

2.0 (0.0-5.0)

J Pediatr Gastroenterol Nutr. Author manuscript; available in PMC 2022 June 17.

Author Manuscript

Author Manuscript

Author Manuscript

Levine et al.

P value

Unadjusted odds ratio (95 CI)*

<0.001

[Reference]

0.66 (0.50-0.88) 0.54 (0.37-0.77) 0.46 (0.29-0.73) 0.52

[Reference]

1.08 (0.85–1.38) 0.88 (0.80-0.97) 1.21 (1.07-1.36) 0.98

[Reference]

154 (16.0)

118 (12.2)

693 (71.8)

965 (54.5)

Received a vaccine against rotavirus

Yes

No or Unsure

<0.001

[Reference]

2.04 (1.34-3.10)

26 (21.5)

22 (18.2)

73 (60.3)

194 (72.4)

649 (93.2)

121 (6.8)

262 (15.9)

193 (11.7)

		Num	ther (row %) of parti	icipants		
	Number (%) of participants (N = 1770)	MVS 0 to 8 $(n = 1267)$	MVS $9 (n = 215)$	MVS Unknown (N = 288)	Unadjusted odds ratio (95 CI)*	P value
Yes	805 (45.5)	574 (71.3)	97 (12.0)	134 (16.6)	1.00 (0.78–1.27)	
Attended daycare						
No	971 (54.9)	696 (71.7)	121 (12.5)	154 (15.9)	[Reference]	0.48
Yes	799 (45.1)	571 (71.5)	94 (11.8)	134 (16.8)	0.91 (0.72–1.17)	
Dehydration Scale						
None	1065 (60.2)	819 (76.9)	102 (9.6)	144 (13.5)	[Reference]	<0.001
Mild to moderate	660 (37.3)	423 (64.1)	101 (15.3)	136 (20.6)	1.92 (1.50–2.45)	
Severe	39 (2.2)	21 (53.8)	10 (25.6)	8 (20.5)	4.35 (2.18–8.70)	
Unknown	6 (0.3)	4 (66.7)	2 (33.3)	0 (0.0)		
Intravenous fluids administered during index ED visit						
No	1537 (86.8)	1121 (72.9)	158 (10.3)	258 (16.8)	[Reference]	<0.001
Yes	233 (13.2)	146 (62.7)	57 (24.5)	30 (12.9)	2.29 (1.67–3.13)	
Ondansetron administered during index ED visit						
No	1160 (65.5)	827 (71.3)	123 (10.6)	210 (18.1)	[Reference]	0.07
Yes	610 (34.5)	440 (72.1)	92 (15.1)	78 (12.8)	1.26 (0.98–1.61)	
Antibiotics administered during index ED visit						
No	1713 (96.8)	1225 (71.5)	207 (12.1)	281 (16.4)	[Reference]	0.98
Yes	57 (3.2)	42 (73.7)	8 (14.0)	7 (12.3)	1.01 (0.51–2.00)	
CI = confidence interval; ED = emergency depa	rtment; MVS = Modified Vesikari S	Scale; Q1 = first quartile; Q3	3 = third quartile.			
* Odds-ratios and confidence interval estimates :	are pooled from 10 imputed dataset	s using standard methods; C)Rs >1 indicate a grea	ter odds of MVS 9 compared	with the reference.	

J Pediatr Gastroenterol Nutr. Author manuscript; available in PMC 2022 June 17.

 $\dot{\tau}_{\rm OR}$ is calculated per 24 hours.

 ‡ OR is calculated per 5 episodes.

Levine et al.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

$\mathbf{\Sigma}$
<
<u> </u>
t
5
5
_
~
<u> </u>
\geq
a
J ar
/lan
/anu
Janus
/lanus
Janusc
Januscr
/anuscri
Januscrip

TABLE 2.

Pediatric Acute Gastroenteritis Risk score model with the odds ratios for selected predictive variables for moderate-to-severe acute gastroenteritis (MVS 6

Levine et al.

Predictive variables	Number of risk points	Adjusted odds ratio (95% CI)	P value
Age group in months			
>12	0	[Reference]	[Reference]
3 to 12	2	1.92(1.48-2.48)	<0.001
No. of vomiting episodes in the prior 24 h			
0	0	[Reference]	[Reference]
1 to 4	1	1.64 (1.16–2.33)	0.005
S	ŝ	3.04 (2.13-4.35)	<0.001
Dehydration status			
None	0	[Reference]	[Reference]
Mild/moderate	1	1.63 (1.25–2.13)	<0.001
Severe	ŝ	2.52 (1.18–5.39)	0.02
Intravenous fluids administered at index ED visit			
No	0	[Reference]	[Reference]
Yes	1	1.52 (1.07–2.16)	0.02
Prior ED visit(s)			
No	0	[Reference]	[Reference]
Yes	1	1.67 (1.07–2.61)	0.02

CI = confidence interval; ED = emergency department; MVS = Modified Vesikari Scale.

Risk category according to PAGER score	PAGER score	Model-predicted probability of outcome, % (95% CI)	% with MVS 9 out of total number of patients (number with MVS 9, total number)
Low	0	7.4 (5.7, 9.2)	5.9 (13, 212)
	1	10.3 (8.5, 12.2)	11.6 (42, 361)
	2	14.2 (12.4, 16.1)	12.7 (40, 317)
	б	19.3 (17.3, 21.3)	19.3 (73, 375)
	4	25.6 (23.0, 28.2)	26.6 (62, 233)
Medium	5	33.0 (29.2, 36.9)	34.8 (51, 147)
	9	41.5 (36.0, 47.0)	45.1 (37, 81)
	7	50.5 (43.4, 57.7)	40.0 (14, 35)
High	8	59.5 (51.1, 67.9)	66.7 (2, 3)
	6	67.8 (58.8, 76.8)	50.0 (2, 4)
	10	75.2 (66.3, 84.1)	50.0 (1, 2)

J Pediatr Gastroenterol Nutr. Author manuscript; available in PMC 2022 June 17.

Author Manuscript

TABLE 3.