Characterizing Pain in Children with Acute Gastroenteritis Who Present for Emergency Care

Samina Ali, MDCM[1,2,3,4], Claudia Maki, BN[3], Jianling Xie, MD, MPH[5], Bonita E. Lee, MD, MSc[1,3,4], James Dickinson, MBBS, PhD[6], Shannon E. MacDonald, PhD, RN[1,3,4,7,8,9], Naveen Poonai, MD, MSc[10], Jennifer Thull-Freedman, MD[11,12,13], Otto Vanderkooi, MD[14], Manasi Rajagopal, MBT[1,3], Mithra Sivakumar, BN[1,3], Linda Chui, PhD[15,16,17], Timothy A. D. Graham, MD, MSc[2,3], Alberto Nettel-Aguirre, PhD, PStat[6], Lawrence W. Svenson, PhD[18], Stephen B. Freedman, MDCM, MSc[11,12,13], on behalf of the Alberta Provincial Pediatric EnTeric Infection TEam (APPETITE Team) and Pediatric Emergency Research Canada (PERC)

Objective To characterize the pain experienced by children with acute gastroenteritis (AGE) in the 24 hours before emergency department (ED) presentation. Secondary objectives included characterizing ED pain, discharge recommendations, overall analgesic use, and factors that influenced analgesic use and pain severity.

Study design A prospective cohort was recruited from 2 pediatric EDs (December 2014 to September 2017). Eligibility criteria included <18 years of age, AGE (≥3 episodes of diarrhea or vomiting in the previous 24 hours), and symptom duration <7 days at presentation.

Results We recruited 2136 patients, median age 20.8 months (IQR 10.4, 47.4) and 45.8% (979/2136) female. In the 24 hours before enrollment, most caregivers reported moderate (28.6% [610/2136, 95% CI 26.7-30.5]) or severe (46.2% [986/2136, CI 44.0-48.3]) pain for their child. In the ED, they reported moderate (31.1% [664/2136, 95% CI 29.1-33.1]) or severe ([26.7% [571/2136, 95% CI 24.9-28.7]) pain; analgesia was provided to 21.2% (452/2131). The most common analgesics used in the ED were acetaminophen and ibuprofen. At discharge, these were also most commonly recommended. Factors associated with greater analgesia use in the ED were high pain scores during the index visit, having a primary care physician, earlier presentation to emergency care, fewer diarrheal episodes, presence of fever, and hospitalization at index visit.

Conclusions Most caregivers of children presenting to the ED with AGE reported moderate or severe pain, both before and during their visit. Future research should focus on the development of effective, safe, and timely pain management plans. *(J Pediatr 2021;231:102-9)*.

Patients with acute gastroenteritis (AGE) typically present with episodes of acute diarrhea often in conjunction with abdominal pain, nausea, vomiting, and fever.[1,2] Globally, there are nearly 1.7 billion cases of childhood diarrheal disease every year,[3] and the World Health Organization reports that diarrheal disease is the second-leading cause of death in children <5 years old, with 525 000 children <5 years dying annually.[3] Although there is extensive literature describing the etiology of AGE and evidence-based management guidelines for this common diagnosis, there is little to no evidence quantifying associated pain and its management.[4-6] Untreated pain in children is associated with many negative effects, including prolonged lengths of hospital stay, slower healing, emotional suffering, anxiety, and medical fears and phobias in adulthood, and should be avoided.[7-9]

We sought to quantify the prevalence and severity of pain experienced by children with AGE in the 24 hours before emergency department (ED) presentation, as reported by their caregivers. Secondary objectives were to describe caregiver-reported pain during the ED visit, analgesic use at home and during the ED visit,

ACH	Alberta Children's Hospital
AGE	Acute gastroenteritis
ED	Emergency department
SCH	Stollery Children's Hospital
VNRS	Verbal numerical rating scale

From the [1]Department of Pediatrics, Faculty of Medicine & Dentistry; [2]Department of Emergency Medicine; [3]Faculty of Medicine & Dentistry, University of Alberta; [4]Women & Children's Health Research Institute (WCHRI), Edmonton; [5]Section of Pediatric Emergency Medicine, Alberta Children's Hospital; [6]Departments of Family Medicine and Community Health Sciences, University of Calgary, Calgary; [7]Faculty of Nursing, University of Alberta, Edmonton; [8]School of Public Health, University of Alberta, Edmonton; [9]Department of Pediatrics, University of Calgary, Calgary, Alberta; [10]Department of Emergency Medicine, Section of Pediatric Emergency Medicine, Schulich School of Medicine & Dentistry, Western University, London, Ontario; [11]Section of Pediatric Emergency Medicine, Department of Pediatrics; [12]Department of Emergency Medicine; [13]Alberta Children's Hospital Research Institute, Cumming School of Medicine; [14]Departments of Pediatrics, Microbiology, Immunology and Infectious Diseases, Pathology & Laboratory Medicine and Community Health Sciences, University of Calgary, Calgary; [15]Provincial Laboratory for Public Health; [16]Alberta Public Health Laboratories-ProvLab; [17]Department of Laboratory Medicine and Pathology, University of Alberta; and [18]Alberta Health, Government of Alberta, Edmonton, Alberta, Canada

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discharge analgesic recommendations, factors that influenced analgesic use in the ED, and factors associated with pain severity.

Methods

This study was a planned secondary analysis of data collected as part of the Alberta Provincial Pediatric EnTeric Infection TEam study.[10] Participants were recruited consecutively between December 2014 and September 2017 from the EDs of 2 Canadian pediatric hospitals: the Alberta Children's Hospital (ACH; Calgary, Alberta) and the Stollery Children's Hospital (SCH; Edmonton, Alberta). The ACH is a tertiary care facility with 141 beds[11]; annual mean census for the ED from 2014 to 2017 was 77 012. The SCH is a 155-bed tertiary care facility[11]; annual mean census for the ED from 2014 to 2017 was 49 646.

Selection of Participants

Eligible participants were 0-18 years of age and presented to the ED with ≥3 episodes of vomiting and/or diarrhea in the previous 24 hours and a duration of symptoms <7 days.[12] Exclusion criteria included enrollment in the study within the preceding 14 days; caregiver inability to complete phone or electronic survey follow-up; chief presenting complaint related to schizophrenia or other significant psychiatric illness; neutrophil count $<1.0 \times 10^9$/L; need for emergent clinical care; and caregiver inability to communicate in English. Children with active mental health concerns or neutropenia were excluded due to the inability to have them complete all study procedures, which included the collection of a rectal swab.

Interventions

Research staff conducted eligibility screening and performed data entry directly into a Research Electronic Data Capture (REDCap) database.[13] Research staff obtained voluntary written informed consent from caregivers along with child assent when appropriate (generally >6 years of age). Research ethics board approval was obtained from the Conjoint Health Research Ethics Board (University of Calgary) and the Health Research Ethics Board (University of Alberta).

Measurements

After enrollment, trained research staff administered an electronic survey to caregivers in the ED to collect details regarding symptoms—illness onset, presence of vomiting and presence of diarrhea, respective maximum number of episodes in a day, and frequencies in the last 24 hours. Pain-related questions focused on the caregiver's rating of their child's pain in the preceding 24 hours and during the ED visit. Verbal children were invited to quantify their level of pain for their caregiver. Medical record review and surveys captured analgesia administered before and during the ED visit. Presence of bloody diarrhea, runny nose, and cough were added to the case report form approximately 18 months after study inception.

Outcomes

The primary outcome was reported as maximum pain in the 24 hours before ED presentation, quantified using an 11-point verbal numerical rating scale (VNRS).[14] Where age-appropriate (minimum 6 years and older), children provided the pain score. For younger children, caregivers provided the score. The VNRS is a recommended pain tool for assessing acute pain in the ED for children aged 6 years and older and has strong psychometric properties.[14,15] Reported pain was categorized as none (0), mild (1-3), moderate (4-6), or severe (7-10).[16,17] In the absence of children's self-reports for pain, caregiver pain scores have been reliably used as a surrogate measure and are recommended over pain scores by nurses and independent observers.[18] Secondary outcomes included the lowest pain reported in the 24 hours before ED presentation (VNRS), the maximum pain reported in the ED (VNRS), analgesic medications administered at home, before ED visit, analgesic medications administered in the ED, and discharge pain management medication recommendations.

Statistical Analyses

Demographic characteristics of participants were summarized with counts and percentages for categorical data and medians and IQRs for continuous data. For the primary outcome (ie, pain categorized as none, mild, moderate, or severe), the bivariate association between pain severity and the symptoms complex of diarrhea and vomiting was estimated using Kruskal–Wallis test. We fit a multivariable generalized ordinal logistic regression model for the primary outcome (ie, categorized pain) to estimate the adjusted association of the a priori–determined covariates,[19] including sex; age in years using the following groups: 0 to <2, 2 to <5, 5 to <12, 12 to <18 years; indigenous status; presence of chronic disease; duration of vomiting and diarrhea before ED presentation; number of vomiting and diarrheal episodes in the 24 hours preceding the ED visit; fever; bloody diarrhea; access to a primary care physician; hospital admission; and enrollment site. All covariates were checked for the parallel lines assumption in the ordinal logistic regression.

The secondary outcome of maximum pain during ED visit was analyzed as described for the primary outcome. Analgesic medication administration before the ED visit, provided in the ED, and recommended at discharge were summarized with counts and percentages. The bivariate association between pain severity and analgesic medication administration (ie, yes vs no) was estimated with the Kruskal–Wallis test. The χ^2 test was used to estimate the association between age group and the use of analgesia medication. We excluded children with an at-home temperature >37.9°C from the bivariate analysis of analgesic use at home to provide a conservative estimate of analgesia use for pain only, as febrile children may have received ibuprofen or acetaminophen to treat their fever as well as their pain. We fit a multivariable logistic regression model for analgesic medication administration in the ED (ie, yes/no) to estimate the adjusted association of the a priori–determined covariates as described for the primary outcome. Results from the regression models

were expressed using ORs and 95% CIs. A type I error rate of 0.05 was used to reject the null hypothesis of no association. To control for multiplicity, we corrected *P* values using the Bonferroni correction within sets of tests. Data were analyzed using Stata 15.0 (2017. Stata Statistical Software: Release 15; StataCorp LLC).

Results

Characteristics of Study Subjects

In total, 2136 eligible participants were enrolled during the study period. Median age was 20.8 months (IQR 10.4, 47.4); 45.8% were female (979/2136) (Table I). Of note, admitting diagnoses for the 149 children requiring admission to hospital included AGE (27%, n = 40), dehydration with or without acute kidney injury (21%, n = 32), vomiting (15%, n = 22), diarrhea/bloody diarrhea (5%, n = 8), appendicitis (10%, n = 15), urinary tract infection (6%, n = 9), intussusception (5%, n = 8), pneumonia/bronchiolitis (5%, n = 8), undifferentiated abdominal pain (4%, n = 6), pyloric stenosis (3%, n = 5), hemolytic uremic syndrome (3%, n = 4), and other (21%, n = 31); multiple admitting diagnoses were permitted.

Pain Experience

Before ED Presentation. The median maximal pain score in the 24 hours before ED presentation was 6 (IQR: 3, 8), representing moderate pain. The proportion of caregivers who reported their child's maximum pain 24 hours preceding ED presentation as moderate was 28.6% (610/2136, 95% CI 26.7-30.5) and as severe was 46.2% (986/2136, 95% CI 44.0-48.3) and 25.3% (540/2136, 95% CI 23.4-27.2) reported no or mild pain (Figure, A). The proportion of children with severe levels of pain 24 hours preceding ED visit was greater in those children with both vomiting and diarrhea (49.5%; 517/1044) compared with the children with either isolated vomiting (43.5%; 369/848; *P* = .001) or isolated diarrhea (40.1%; 100/244; *P* = .007). Median lowest pain in the 24 hours preceding ED presentation was 1 (IQR: 0, 2), representing mild pain.

In the ED. The median maximal pain score in the ED was 4 (IQR 2, 7), representing moderate pain. During the ED visit, 31.1% (664/2136, 95% CI 29.1-33.1) reported maximal AGE-related pain as moderate, 26.7% (571/2136, 95% CI 24.9-28.7) as severe, and 42.2% (901/2136, 95% CI 40.1-44.3) as none to mild (Figure, A). Reported AGE-related pain was greatest in the ED for those with both vomiting and diarrhea; pain was moderate or severe among 61.9% (646/1044) of such children compared with those with isolated vomiting (54.7%; 464/848; *P* = .001) or isolated diarrhea (51.2%; 125/244); *P* = .002). The proportions of children with moderate or severe pain during the 24 hours preceding ED visit and during the ED visit were significantly different among the age groups, with older children reporting more severe pain (Figure, B).

Table I. Demographic characteristics, clinical symptoms, and pain severity for children with AGE (N = 2136)

Characteristics	All patients (n = 2136)
Demographics	
Sex (female), no. (%)	979 (45.8)
Age, mo, median (IQR)	20.8 (10.4, 47.4)
ED where medical care received	
ACH (Calgary), no. (%)	1415 (66.2)
SCH (Edmonton), no. (%)	721 (33.8)
Access to primary care	1976 (92.5)
Family physician, no. (%)	1315 (61.6)
Pediatrician, no. (%)	647 (30.3)
Indigenous status, no. (%)	115 (5.4)
Presence of chronic medical condition, no. (%)	234 (11.0)
Illness duration, h, median (IQR)	42.5 (15.3, 87.4)
Diarrhea, no. (%)	1288 (60.3)
Maximum number of diarrheal episodes in any given 24-h period, median (IQR)	6 (4, 10)
Number of diarrheal episodes in previous 24 h, median (IQR)	
Vomiting, no. (%)	1892 (88.6)
Maximum number of vomiting episodes in any given 24-h period, median (IQR)	6 (4, 10)
Number of vomiting episodes in previous 24 h, median (IQR)	
Bloody stool,* no. (%)	93/973 (7.2)
Fever, no. (%)	975 (45.6)
Runny nose/cough, no. (%)	816/1658 (49.2)
Patient disposition	
Discharged home	1970 (92.2)
Admitted to inpatient ward	147 (6.9)
Admitted to intensive care unit	2 (0.09)
Transferred to another facility	14 (0.7)

*Among those who had diarrhea.

Analgesic Use

In the 24 hours preceding ED presentation, overall, 42.2% (901/2136) of children received analgesic medications at home, but indication of pain vs fever was not specified in this setting (Table II). Among those without reported fever, 26.5% (346/1304) received analgesic medications. Of those who were afebrile and reported moderate or severe pain at home, 30.2% (271/898) received analgesia before ED presentation. Among those who received an analgesic at home, acetaminophen was the most commonly administered medication (77.7%, 700/901), followed by ibuprofen (37.5%, 338/901). Use of other pain medication was minimal, with 1.0% (9/901) receiving other oral analgesic preparations. No opioids were reported in the at-home setting.

A total of 21.2% (452/2131) of children received an analgesic in the ED, specifically for pain. Among children with moderate or severe pain in the ED, 27.4% (338/1230) received an analgesic medication. In the ED, ibuprofen was the most commonly administered medication (68.1%, 308/452), followed by acetaminophen (43.4%, 196/452). Other pain medication use was minimal, with 4.6% (21/452) receiving morphine or fentanyl and 3.5% (16/452) receiving an alternate oral analgesic. A documented discharge recommendation to administer an analgesic at home was identified in 8.7% (186/2129) of children's medical records. Table III provides a description of analgesia use, stratified by age. Of

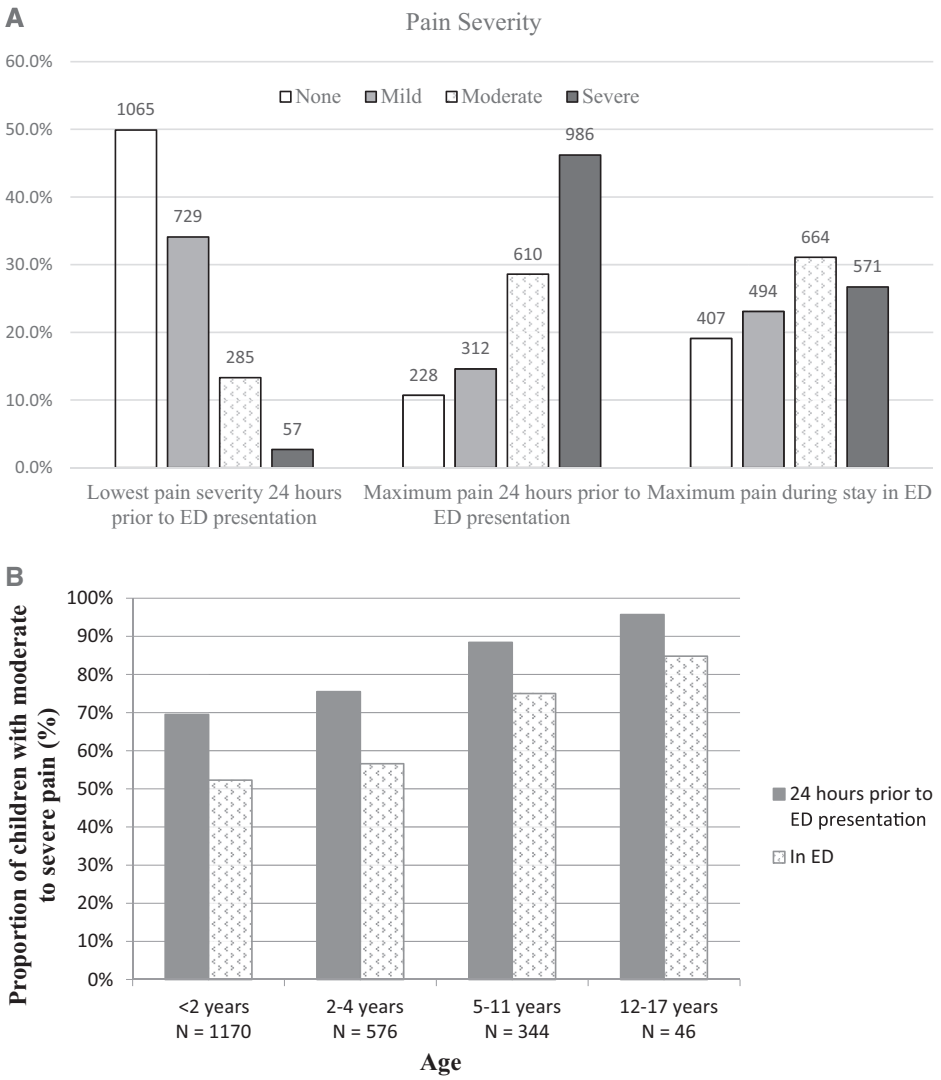

Figure. **A,** Reported pain severity for children (n = 2136). **B,** Proportion of children with moderate to severe pain, stratified by age group (n = 2136). The χ^2 test was used to assess the association between the proportion of participants having moderate-to-severe pain in 24 hours before ED presentation and the age group ($P < .0001$, linear-by-linear association: $P < .0001$) and the association between the proportion of participants having moderate-to-severe pain during ED stay and the age group ($P < .0001$, linear-by-linear association: $P < .0001$).

note, 39.8% (848/2131) of children received antiemetic medication during their ED visit.

Factors independently associated with increased likelihood of receiving analgesia in ED were moderate (OR 1.88; 95% CI 1.27-2.79) and severe (OR 2.70; 95% CI 1.82-4.01) pain in the ED, having a primary care physician (OR 2.17; 95% CI 1.28-3.70), shorter illness duration at time of ED care (OR 1.16; 95% CI 1.09-1.25 for 1-day decrease in duration), diarrheal episodes (OR 1.02; 95% CI 1.01-1.04 for 1-episode decrease in diarrhea), presence of fever (OR 6.70; 95% CI 5.14-8.74), and admission to hospital (OR 4.90; 95% CI 3.34-7.17) (**Table IV**; available at www.jpeds.com).

Between Study Sites

There was no significant difference between study sites in the proportions of children reporting moderate or severe pain during the 24 hours before ED visit (ACH 74.1% [1048/1415] vs SCH 76.0% [548/721]; $P = .33$) or in the ED (ACH 57.8% [818/1415] vs SCH 57.8% [417/721]; $P = .99$). Between the sites, no significant differences were observed for analgesia use at home before ED visit (ACH 27.3% [234/856] vs SCH 25.0% [112/448]; $P = .39$) or in the ED (ACH 21.0% [297/1413] vs SCH 21.6% [155/718]; $P = .78$). SCH documented discharge analgesic advice more frequently than ACH (14.8% [106/717] vs 5.7% [80/1412]; $P < .001$).

Table II. Pain management in relation to maximum pain in the 24 hours preceding pediatric ED visit and maximum pain in the ED

	Received pain medications at home (pre-ED) (n = 2136)		Received pain medications in ED (n = 2131)		Recommended/prescribed pain medications at discharge (n = 2129)	
Pain Ranges	**Number included for analysis**	**No. (%)**	**Number included for analysis**	**No. (%)**	**Number included for analysis**	**No. (%)**
All	1304*	346 (26.5)	2131	452 (21.2)	2129	186 (8.7)
Maximum pain (24 h preceding ED visit)						
No pain (0)	169	28 (16.6)	228	26 (11.4)	228	14 (6.1)
Mild (1-3)	237	47 (19.8)	312	32 (10.3)	311	18 (5.8)
Moderate (4-6)	384	103 (26.8)	610	140 (23.0)	609	49 (8.0)
Severe (7-10)	514	168 (32.7)	981	254 (25.9)	981	105 (10.7)
P value†		<.001		<.001		.019
Maximum pain (in ED)						
No pain (0)	300	61 (20.3)	407	43 (10.6)	407	28 (6.9)
Mild (1-3)	326	75 (23.0)	494	71 (14.4)	494	29 (5.9)
Moderate (4-6)	383	115 (30.0)	662	154 (23.3)	661	56 (8.5)
Severe (7-10)	295	95 (32.2)	568	184 (32.4)	567	73 (12.9)
P value†		.002		<.001		<.001

*Excluded children who had a documented temperature >37.9°C at home.
†Kruskal–Wallis test was used in the between groups comparison; $P < .008$ was considered statistically significant after correction via Bonferroni correction for multiple tests (n = 6).

Factors Associated with Pain

In the regression model for maximum pain before ED visit, increasing age (5-11.99 years: OR 11.12; 95% CI 4.07-30.36; 12-17.99 years: OR 4.41; 95% CI 2.09-9.31), presence of fever (OR 2.15; 95% CI 1.78-2.60), and greater number of diarrheal episodes in the 24 hours before ED presentation (OR 1.04; 95% CI 1.02-1.06) were positively associated with the degree of pain reported in the 24 hours before ED presentation; **Table V** (available at www.jpeds.com). In the regression model for maximum pain reported in the ED, admission to hospital was additionally found to be associated with pain severity (OR 1.75; 95% CI 1.29-2.37); **Table VI** (available at www.jpeds.com).

Discussion

In this observational cohort study, almost three-quarters of caregivers reported that their child suffered from moderate or severe pain at home and nearly 60% reported having moderate-to-severe pain while in the ED. Acetaminophen and ibuprofen were the most commonly administered medications both at home and in the ED, but only one-quarter of children received analgesia for pain. Increasing age, presence of fever, and increasing diarrheal episodes in the 24 hours before ED presentation were positively associated with greater degrees of reported pain for the 24 hours before ED presentation. Factors that were positively associated with ED analgesic medication administration included a greater degree of pain, having a primary care physician, earlier presentation to ED care, fewer diarrhea episodes in the past 24 hours, and the presence of fever. Admission to hospital also was associated with receiving analgesia in the ED.

Acute abdominal pain is among the most common complaints among children brought for ED care, noted as the chief complaint in up to one-third of children.[20,21] Among such children, AGE is the second most common diagnosis,

Table III. Comparison of analgesia use in ED stratified by age (n = 2131)

Medications*	**0-23 months (n = 1170)**		**2-4 y (n = 573)**		**5-11 y (n = 342)**		**12-17 y (n = 46)**		***P* value†**
Any analgesia No. (%)	223 (19.1)		123 (21.5)		91 (26.6)		15 (32.6)		.005
Stratified by severity of pain in ED									
	Total children, n	**Received analgesia, no. (%)**	**Total children, n**	**Received analgesia, no. (%)**	**Total children, n**	**Received analgesia, no. (%)**	**Total children, n**	**Received analgesia, no. (%)**	
No pain (0)	270	26 (9.6)	112	14 (12.5)	24	3 (12.5)	1	0 (0)	.664
Mild (1-3)	288	35 (12.2)	138	29 (21.0)	62	5 (8.1)	6	2 (33.3)	.017
Moderate (4-6)	337	76 (22.6)	182	41 (22.5)	124	32 (25.8)	19	5 (26.3)	.849
Severe (7-10)	275	86 (31.3)	141	39 (27.7)	132	51 (38.6)	20	8 (40.0)	.209
All children given any analgesia		**n = 223**		**n = 123**		**n = 91**		**n = 15**	
Ibuprofen, no. (%)		152 (68.2)		88 (71.5)		60 (65.9)		8 (53.3)	.490
Acetaminophen, no. (%)		96 (43.0)		51 (41.5)		41 (45.1)		8 (53.3)	.810
Morphine/fentanyl, no. (%)		3 (1.3)		3 (2.4)		9 (9.9)		6 (40.0)	<.001
Other,‡ no. (%)		3 (1.3)		2 (1.6)		9 (9.9)		2 (13.3)	<.001

*More than 1 medication could be administered per child.
†The χ^2 test was used in the between groups comparison; $P < .0055$ was considered statistically significant after correction via Bonferroni correction for multiple tests (n = 9).
‡Ketorolac/baclofen/hydromorphone.

accounting for 16% of such presentations.[21] Caregivers in our study described moderate or severe pain being present during the ED visit in almost 60% of AGE cases; yet, only one-quarter of such children received analgesia. It is unclear why so few children in pain received analgesia, although it may be due, in part, to healthcare provider under-recognition of the pain or due to recent patient vomiting and inability to tolerate oral medications for some. It is unlikely due to caregiver refusal, as >90% of families are willing to accept analgesia when offered by their child's healthcare team.[22] In the context of AGE, however, this is further complicated, as children also are often experiencing nausea and vomiting, which might increase the reluctance of prescribing oral medications by physicians and acceptance by families. Having a greater degree of pain and fever were associated with receiving ED analgesia, both of which make intuitive sense, as the former likely indicates a more urgent need, and the latter, an additional reason for using antipyretic/analgesic medications such as ibuprofen and acetaminophen. Similarly, earlier presentation to the ED and admission to hospital were associated with the same and could represent greater pain or disease severity, necessitating earlier ED pain treatment. It is possible that those etiologies of AGE that are associated with fewer diarrheal episodes also are associated with more abdominal pain, but this needs to be explored in future studies. Lastly, the association of more analgesic use in the ED with having a primary care physician may represent greater health literacy for the family and/or a greater family comfort advocating for care; further qualitative study could help clarify this finding.

Children's pain during AGE has not been well described, although 2 small studies of enteric infection have yielded conflicting results regarding the predictive value of pain in identifying a bacterial infection.[23,24] Unfortunately, neither of these studies quantified pain, rather reporting simply its presence or absence. Our documenting both the presence and severity of pain in children with AGE allows clinicians to prioritize children's pain assessment and management. It also highlights the knowledge gap in this field and the importance of future research focused on understanding the mechanism of pain, its relationship to etiology, impact on oral fluid consumption, dehydration severity, and quality of life (eg, return to school, caregiver missed days of work), and most importantly on optimal therapeutic approaches.

Acetaminophen and ibuprofen accounted for 99% of analgesics used at home and 93% in the ED. This is similar to physician treatment of otitis media, where 88% reported ibuprofen and 83% acetaminophen as their first-line treatment options."[25] Similarly, studies of children with musculoskeletal injury have found ibuprofen and acetaminophen to be the 2 most commonly used analgesics.[26,27] Recommendations for analgesia at discharge were similar to physicians' ED choices, with ibuprofen as the top overall recommendation. To our knowledge, there are no guidelines on the treatment of AGE-related pain, and a paucity of rigorous evidence to support a particular pain treatment approach, with the exception of recommendations to avoid the use of diphenoxylate–atropine.[28,29] A systematic review of the safety of ibuprofen for the treatment of children's acute pain has suggested that its use is not associated with a greater occurrence of gastritis and other gastrointestinal complications.[30] However, this study was not focused on children with abdominal pain, who may already have a propensity for gastrointestinal upset or dehydration. Given the paucity of data regarding the safety of nonsteroidal anti-inflammatory drugs as treatment for children with dehydration, fever, or gastrointestinal symptoms, coupled with rare case reports of acute kidney injury after ibuprofen use in dehydrated children, this current study highlights the importance of assessing the safety of short-term ibuprofen use for children with AGE with rigorous clinical trials.[31-33]

Our study reported extremely low rates of documented discharge advice regarding analgesia. A study of children presenting to the ED with musculoskeletal injuries similarly had discharge analgesic recommendations documented on their chart in less than one-quarter of cases, suggesting that documentation of discharge ED pain management recommendations is suboptimal.[34] Unfortunately, both this study and our current study were unable to comment on whether the discharge advice was provided verbally and simply lacked written documentation. At-home pain management advice is critical to evidence-informed at-home AGE management for families, especially as undertreated pain may contribute to healthcare provider revisits and even poor fluid consumption.[35] Clinicians must make efforts to provide and document teaching and education to families to ensure improved and consistent pain management upon discharge.

Although not feasible in our study, the gold standard for assessing pain in children is self-report.[36] Although children >6 years of age quantified their level of pain for their caregiver, the mean child age in our study was 20 months, so we could not include self-reported pain assessment for the vast majority of these pre-verbal children. We did not measure mean pain scores or duration of pain in this study. In addition, we were unable to definitively determine the driver of acetaminophen or ibuprofen use at home, ie, fever vs pain. We attempted to mitigate this by excluding children with fever from relevant analyses to obtain a conservative estimate of analgesic use. However, this does not account for those children who may have received the medications for both symptoms. Although we were able to record the number of children receiving analgesia, we could not comment on the number of patients who were offered analgesia and refused. Provider practice variations may have influenced ED analgesic use and is not controlled for in this study. We did not capture the use of physical and psychological interventions for pain that may have been used in the at-home or ED setting. Lastly, this study was conducted at 2 tertiary care pediatric facilities in 1 province; thus, results may not be generalizable to some settings.

In summary, our study found that large proportions of children with AGE experience moderate or severe pain both before and/or during their ED visit. There is a need to determine the implications of this pain on patient experience

and clinical progression of the illness (eg, dehydration, missed school, and work), and to identify the optimal analgesic treatment approach. ■

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Reprint requests: Dr Samina Ali, MDCM, Department of Pediatrics, 3-583 Edmonton Clinic Health Academy, 11405–87 Ave, Edmonton, Alberta T6G 1C9, Canada. E-mail: sali@ualberta.ca

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50 Years Ago in *The Journal of Pediatrics*

Syndromic Intellectual Disability: A Never-Ending Genomic Odyssey

Palant DI, Feingold M, Berkman MD. Unusual Facies, Cleft Palate, Mental Retardation, and Limb Abnormalities in Siblings - A New Syndrome. J Pediatr 1971;78:686-9.

Intellectual disability is often associated with abnormalities in other systems, resulting in a recognizable syndrome. In 1971, Palant et al described 2 female siblings with global developmental delay, microcephaly, short stature, dysmorphic features including almond-shaped eyes with upslanted palpebral fissures, epicanthal folds, bulbous nasal tip, midline cleft of the hard and soft palate, clinodactyly of fourth and fifth fingers, and nonbony prominences in the ulnar aspect of bilateral wrist. A chromosomal analysis was normal. An autosomal recessively inherited syndrome was considered (Online Mendelian Inheritance in Man 260150). No further reports of similar phenotype have been described to date. Also, although a single gene disorder is more likely in this family in view of 2 affected individuals in 1 generation, the possibility of chromosomal abnormalities too small to be detected on a karyotype cannot be ruled out.

Significant advances in the last 50 years in clinical genetics have enhanced our understanding and unraveled the genetic etiology and underlying pathophysiology of many intellectual disability syndromes and several monogenic syndromes. The development of robust databases for standard vocabulary for description of phenotypic abnormalities (human phenotype ontology); online genetic and phenotypic data like Online Mendelian Inheritance in Man, London Medical Database, POSSUM web; tools for semantic similarity search like Phenomizer; and artificial intelligence based next-generation phenotyping applications like Face2Gene play a complementary role in phenotype analysis and aid the clinical diagnosis of several genetic disorders.

In addition, more advanced cytogenetic and molecular techniques for genetic diagnosis currently available can provide a more precise diagnosis. Advances in clinical cytogenetic testing methodologies like chromosomal microarray have enabled the study of genome wide abnormalities at a greater resolution, making the diagnosis of rare submicroscopic deletions and duplications possible; these would otherwise have been missed on conventional karyotyping. Chromosomal microarray is now used as the first-tier diagnostic test in children with intellectual disability with or without multiple congenital anomalies owing to a higher diagnostic yield of 15%-20%.[1] The advent of next-generation sequencing technology has made the diagnosis and discovery of single gene disorders easier by facilitating massive parallel sequencing of the whole exome or genome. In most chromosomal microarray negative patients with intellectual disability/multiple congenital anomalies, exome or genome sequencing studies have shown a yield of 28%-68%.[2] The genomic journey continues to enlighten our minds regarding the remaining intellectual disability syndromes.

Mounika Endrakanti, MD
Neerja Gupta, MD, DM
All India Institute of Medical Sciences
Delhi, India

Piyush Gupta, MD, FAMS
University College of Medical Sciences
Delhi, India

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Table IV. Logistic regression estimating the association between covariates and the administration of analgesia in the pediatric ED (n = 2130)

Factors	OR (95% CI)	*P* value
Maximum pain in the pediatric ED		
Severe	2.70 (1.82-4.01)	8.095E-7
Moderate	1.88 (1.27-2.79)	.002
Mild	1.12 (0.73-1.73)	.611
None	Ref	
Age		
12-17.99 y	1.60 (0.77-3.33)	.212
5-11.99 y	1.35 (0.97-1.86)	.075
2-4.99 y	0.99 (0.75-1.31)	.955
0-23.99 mo	Ref	
Sex		
Female	0.95 (0.75-1.20)	.681
Male	Ref	
Aboriginal		
Yes	0.78 (0.45-1.36)	.387
No	Ref	
Had a primary care physician		
Yes	2.17 (1.28-3.70)	.004
No	Ref	
Presence of chronic medical condition		
Yes	1.05 (0.73-1.50)	.805
No	Ref	
Symptoms of illness		
Illness duration (per day increase)	0.86 (0.80-0.92)	1.94E-5
Maximum vomiting episodes in past 24 h (per episode increase)	0.99 (0.97-1.01)	.498
Maximum diarrhea episodes in past 24 h (per episode increase)	0.98 (0.96-0.999)	.040
Presence of fever		
Yes	6.70 (5.14-8.74)	<.001
No	Ref	
Disposition in the pediatric ED		
Admitted to hospital	4.90 (3.34-7.17)	3.33E-16
Discharged home	Ref	
Study site		
SCH (Edmonton)	1.02 (0.79-1.32)	.878
ACH (Calgary)	Ref	

Ref, reference.

Table V. Generalized ordinal logistic regression estimating the association between the covariates and the maximum reported pain in the 24 hours before pediatric ED presentation (n = 1654)*†

	No pain vs any pain		No-mild pain vs moderate-severe pain		No-mild-moderate pain vs severe pain	
Covariates*	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Sex						
Male	Ref					
Female	1.03 (0.86-1.24)	.717				
Age						
0-23.99 mo	Ref					
2-4.99 y	1.22 (0.99-1.52)	.065				
5-11.99 y	11.12 (4.07-30.36)	<.001	3.27 (2.19-4.88)	<.001	2.42 (1.82- 3.21)	<.001
12-17.99 y	4.41 (2.09-9.31)	<.001				
Aboriginal						
No	Ref					
Yes	0.73 (0.48-1.11)	.141				
Had a primary care physician						
No	Ref					
Yes	1.01 (0.69-1.48)	.971				
Presence of chronic medical condition						
No	Ref					
Yes	1.01 (0.76-1.35)	.921				
Symptoms of illness						
Illness duration, h	1.002 (1.0002-1.005)	.033				
Maximum vomiting episodes in past 24 h	1.01 (0.997-1.03)	.123				
Maximum diarrhea episodes in past 24 h	1.04 (1.02-1.06)	.001				
Bloody stool						
No	Ref					
Yes	0.84 (0.56-1.28)	.426				
Presence of fever						
No	Ref					
Yes	2.15 (1.78-2.60)	<.001				
Pediatric ED disposition						
Discharged home	Ref					
Admitted to hospital	0.97 (0.69-1.36)	.863				

*Ref.

†For variables that meet the parallel lines assumption for ordinal logistic regression there is 1 OR presented; for variables that do not meet the assumption there are 3 ORs presented.

Table VI. Generalized ordinal logistic regression estimating the association between covariates and the maximum reported pain in the pediatric ED (n = 2130)

Factors	OR (95% CI)	*P* value
Sex		
Male	Ref	
Female	1.05 (0.90-1.23)	.521
Age		
0-23.99 mo	Ref	
2-4.99 y	1.12 (0.93-1.34)	.238
5-11.99 y	2.48 (1.98-3.11)	1.89e-15
12-17.99 y	3.51 (2.05-6.04)	5.39e-6
Aboriginal		
No	Ref	
Yes	0.85 (0.60, 1.20)	.356
Had a primary care physician		
No	Ref	
Yes	0.73 (0.54-0.99)	.041
Presence of chronic medical condition		
No	Ref	
Yes	0.90 (0.70-1.16)	.427
Symptoms of illness		
Illness duration, d	1.02 (0.97-1.06)	.443
Maximum vomiting episodes in past 24 h	1.01 (0.998-1.03)	.087
Maximum diarrhea episodes in past 24 h	1.03 (1.01-1.04)	1.74E-4
Presence of fever		
No	Ref	
Yes	1.89 (1.61-2.21)	3.77E-15
Pediatric ED disposition		
Discharged home	Ref	
Admitted to hospital	1.75 (1.29-2.37)	2.94E-4

All covariates met the parallel lines assumption in the ordinal logistic regression model.