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Etiology of Severely Dehydrating Diarrheal Illness in Infants and Young Children Residing in Low- and Middle-Income Countries

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Background. Severe dehydration due to acute infectious diarrhea remains a leading cause of death among young children worldwide. Diarrhea with severe dehydration is a clinical syndrome with distinct management per the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) and the WHO Global Task Force on Cholera Control (GTFCC) guidelines. We sought to characterize the pathogens causing severe dehydration using data from the Global Enteric Multicenter Study.

Methods. We used the IMCI and GTFCC guidelines to define severe dehydration and quantitative polymerase chain reaction–based attribution models to assign the etiology of diarrhea associated with severe dehydration.

Results. The IMCI or GTFCC guidelines classified 2284 of the 5304 (43%) cases with moderate-to-severe diarrhea as having severe dehydration. In one-third of the cases with severe dehydration, no pathogens were attributed. The top pathogens attributed to children with guidelines-classified severe dehydration varied by age and were similar among those requiring intravenous hydration and hospitalization. Rotavirus (30.9%), *Cryptosporidium* (12.0%), and heat-stable (ST) enterotoxigenic *Escherichia coli* (ETEC) (10.3%) were the most common pathogens for ages 0–11 months, while *Shigella*/enteroinvasive *E coli* (EIEC) (25.8%), rotavirus (19.3%), and ST-ETEC (10.9%) were the most common for ages 12–23 months. *Shigella*/EIEC (25.9%), *Vibrio cholerae* (10.4%), and rotavirus (9.2%) were the most common among ages 24–59 months.

Conclusions. The findings inform prioritization of pathogens, in addition to *V cholerae*, that cause severe dehydration for future preventive and treatment efforts. The schema for prioritization is driven primarily by age stratifications.

Keywords. diarrhea; dehydration; pediatric.

Diarrheal illness, primarily acute infectious diarrhea, remains a leading cause of death among young children globally, causing 500 000 deaths per year primarily in low- and middle-income countries (LMICs) [1, 2]. In addition to morbidity and mortality from an acute episode, diarrheal illness can also result in additional sequelae including impaired growth and cognitive development [3]. Deaths due to diarrheal illness in young children occur primarily due to severe dehydration, associated with hypovolemic shock and electrolyte disturbances. Thus, the prevention and optimized management of severe dehydration can save lives.

In LMICs, the management of diarrheal illness, including of severe dehydration, is syndromic [4]. The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) guidelines provide guidance on treatment of pediatric diarrhea using the dehydration level, chronicity, and presence of blood in the stool [5, 6]. Notably, the level of dehydration determines the rehydration plan (ie, oral vs intravenous [IV] fluid resuscitation) and indication to use antibiotics. If children >2 years of age are diagnosed with severe dehydration in a cholera-endemic area, IMCI guidelines recommend antibiotics for treatment of presumed cholera [5]. Notably, in those with severe dehydration, cholera endemicity is the only

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pathogen-specific factor in the consideration for empiric antibiotic use. The Global Task Force on Cholera Control (GTFCC) also provides a definition for severe dehydration associated with diarrhea that aids in the identification and treatment of potential cholera cases [7]. If children >2 years of age with suspected cholera and severe dehydration are hospitalized, GTFCC guidelines recommend antibiotic treatment [8]. With cholera, antibiotics have the potential to shorten the duration of symptoms and shedding as well as reduce the volume of stool loss in the setting of a cholera infection [9, 10]. However, global overuse of antibiotics is associated with increasing population-level antibiotic resistance in addition to individual-level adverse effects [11].

Asymptomatic and convalescent shedding of diarrheal pathogens has complicated the interpretation of epidemiologic studies. The emergence of molecular diagnostic techniques, paired with case-control study design, has allowed for the attribution of infectious etiologies associated with pediatric diarrhea. Although prior studies have described pathogens associated with varying levels of diarrheal illness severity, data on the etiologies attributed specifically to severe dehydrating diarrhea are limited [12–14]. While *Vibrio cholerae* is well known to cause acute watery diarrhea leading to severe dehydration [15], other pathogens have the potential to cause severe diarrhea and dehydration [16, 17], and use of antibiotics in viral and protozoal infections may result in more harm than benefit. Thus, our primary objective was to use a large dataset from a multicountry study of pediatric diarrhea to examine the pathogens associated with severe dehydration [18]. A secondary objective was to assess the test performance of the IMCI case definition in identifying *V cholerae*.

METHODS

Study Population

Our study is a secondary analysis of data from the Global Enteric Multicenter Study (GEMS). GEMS was a prospective, case-control study of children aged 0–59 months with moderate-to-severe diarrhea (MSD) at 7 sites in sub-Saharan Africa (Kenya, Mali, Mozambique, and The Gambia), and South Asia (Bangladesh, India, and Pakistan). Data collection occurred during December 2007–March 2011, prior to the widespread use of the rotavirus vaccine [19]. The methods have been described in detail previously [12, 18, 20]. In brief, cases were identified when presenting for care with the new onset (after 7 diarrhea-free days) of acute (<7 days' duration) and moderate-to-severe (defined as at least 1 of the following: sunken eyes, loss of skin turgor, IV rehydration administered or prescribed, visible blood in loose stool, hospitalized with diarrhea or bloody stools) diarrhea. A total of 9439 cases with MSD were enrolled along with 1 to 3 matched nondiarrheal controls; for this analysis, we used only diarrhea cases. Demographic and clinical information was collected from caregiver interviews at enrollment and approximately 60-day follow-up. Clinicians also examined cases to assess signs of dehydration and to determine treatment. Stool specimens were collected from cases and controls. Our analysis was restricted to cases with MSD.

Definition of Diarrhea With Severe Dehydration

We used 2 definitions of diarrhea with severe dehydration in this analysis: (1) WHO IMCI criteria and (2) GTFCC criteria. GTFCC guidance aims to strengthen surveillance for cholera. The guideline includes criteria for severe dehydration that could apply to diarrhea caused by any pathogen. Severe dehydration per the WHO IMCI criteria is defined as 2 of the following signs: lethargic or unconscious, sunken eyes, not able to drink or drinking poorly, skin pinch goes back very slowly [5]. All variables were available using the data collected in GEMS. Severe dehydration per the GTFCC guidelines is defined as 1 or more of the following: lethargic or loss of consciousness, absent or weak pulse, respiratory distress; or at least 2 of the following: sunken eyes, not able to drink or drinks poorly, skin pinch goes back very slowly [7]. The GEMS data did not include pulse, and this was excluded from the definition in our analysis. We also compared the IMCI and GTFCC clinical criteria to clinical outcomes that would suggest severe dehydration: need for IV hydration and need for hospitalization.

Etiology

We used the quantitative real-time polymerase chain reaction–based (qPCR) majority attribution models developed by Liu et al to ascribe the etiology of diarrhea [21]. qPCR data were available for 5304 of the cases and thus our analysis was restricted to these cases. The subset of cases with qPCR data was previously randomly selected from each age strata and study site [21]. Using previously derived episode-specific attributable fraction (AFe) of etiology, we used a cut-off of >0.5 to designate attribution of a pathogen to a particular episode [22]. Of note, the invasion plasmid antigen H (i*paH*) qPCR target was used for identification of *Shigella* and is also described in enteroinvasive *Escherichia coli* (EIEC); thus, we were unable to distinguish between *Shigella* and EIEC [21].

Statistical Analysis

We performed all analyses using R version 4.2.3 software [23]. We stratified the cases of MSD with qPCR data by dehydration severity: (1) severe as defined by the IMCI definition, (2) severe as defined by a modified (excluding pulse) GTFCC definition, (3) severe as defined by IMCI and GTFCC definitions, (4) severe as defined by either IMCI or GTFCC definition, and (5) not severe by either definition. We also stratified using other clinical proxies for severe dehydration: cases receiving IV hydration and cases requiring hospitalization. We examined the etiologies in each severity class. Data were further stratified

by age (<12 months, 12–23 months, and 24–59 months). We also calculated descriptive statistics for demographic and clinical characteristics. Unadjusted and age-adjusted odds ratios (ORs) were calculated for severe dehydration by etiology using logistic regression.

Additionally, we assessed the test performance of the IMCI clinical case definition in identifying diarrhea of cholera etiology (Supplemental Table 1). The IMCI case definition outlines when antibiotics would be given for presumed cholera and was as follows: diarrhea with severe dehydration in a child aged ≥2 years in a cholera-endemic area [5]. An AFe cut-off of >0.5 (as defined above) for *V cholerae* was used as the gold standard to define true test positivity for sensitivity and specificity calculations to remain consistent with the other analyses. We also used *V cholerae* culture positivity as a gold standard for comparison. Areas with known cholera at the time of the study were defined as the following 4 sites: India, Pakistan, Bangladesh, and Mozambique.

Patient Consent Statement

The GEMS study protocol was approved by ethics committees and applicable scientific review boards at each field site and the University of Maryland, Baltimore. Individual, informed consent was obtained [18].

RESULTS

Of the 9439 children with MSD in GEMS, qPCR was available from 5304 cases, and these were included in this analysis. Among the 5304 cases, 2284 (43%) were classified as having severe dehydration by either the IMCI or GTFCC guidelines. The GTFCC guidelines had a broader definition of severe dehydration, and all cases that were labeled as severe with the IMCI guidelines were also labeled as severe with the GTFCC guidelines (n = 1893); an additional 391 were only categorized as severe with the GTFCC guidelines (SupplementalTable 2). Approximately 40% of children with severe dehydration were aged <1 year, compared to 32% in those without severe dehydration (Table 1).

Clinical Characteristics

We did not identify any difference in diarrheal episode duration at time of presentation between those with and without severe dehydration. Most children with severe dehydration had sunken eyes and/or slow skin recoil (99.0% and 93.7% had sunken eyes and 52.4% and 43.9% had slow skin recoil per IMCI and GTFCC classifications, respectively, Supplemental Table 3). Twenty-eight percent of children with severe dehydration received IV rehydration and 27.0% were hospitalized. Death by 60 days of follow-up was more common in the cases with severe dehydration; 4.1% died compared to 1% of those without severe dehydration (Table 1).

Etiologies

Among the children with severe dehydration, approximately one-third did not have any attributable pathogens (33% for IMCI definition, 35% GTFCC). Most children had 1 attributable pathogen (53% for IMCI definition, 52% GTFCC) and some had ≥2 attributable pathogens (14% for IMCI definition, 13% GTFCC). The most common attributed pathogens varied by age group. In children 0–11 months of age, the most common pathogens in those with severe dehydration meeting either criteria were rotavirus (30.9%), *Cryptosporidium* (12.0%), heat-stable (ST) enterotoxigenic *E coli* (ETEC) (10.3%), *Shigella*/EIEC (7.3%), and adenovirus 40/41 (7.0%). In those 12–23 months of age, they were *Shigella*/EIEC (25.8%), rotavirus (19.3%), ST-ETEC (10.9%), *Cryptosporidium* (7.6%), and adenovirus 40/41 (4.6%). In those 24–59 months of age, *Shigella*/EIEC (25.9%), *V cholerae* (10.4%), rotavirus (9.2%), ST-ETEC (7.8%), and *Helicobacter pylori* (6.7%) were the most common (Table 2). Among those without severe dehydration, the top 5 etiologies were the same for each age group as for those with severe dehydration, though the proportion varied. In those 0–11 months of age, rotavirus was attributed in one-third (30.9%) of the cases compared to one-fourth (23.7%) in those without severe dehydration; *Cryptosporidium* and ST-ETEC were also attributed more frequently in those with severe dehydration. For the cases in children aged 24–59 months, *V cholerae* was attributed in 10.4% of cases with severe dehydration compared to 2.6% of the cases without severe dehydration (Table 2).

In children with MSD, the highest odds of having severe dehydration was in those episodes attributed to *V cholerae* (OR, 3.05 [95% confidence interval {CI}, 2.17–4.33]) when adjusted for age. Episodes attributed to *Shigella*/EIEC had among the lowest odds of having severe dehydration (OR, 0.50 [95% CI, .44–.57]) (Table 3).

Measures of Dehydration

Overall, the pathogen hierarchy did not change when severe dehydration was restricted to IMCI-only guidelines compared to GTFCC (Supplemental Table 4). The IMCI and GTFCC guidelines classified many more children as severely dehydrated than using the clinical outcomes of IV rehydration (16.4% of children) and hospitalization (21.9%) as proxies for severe dehydration (Table 2). Although the total number of children classified as severely dehydrated varied if using a clinical measure such as IV hydration or hospitalization, the top pathogen remained similar in each age group (Table 2 and Supplemental Table 5). Notable exceptions were that rotavirus, rather than *Shigella*/EIEC, represented the most common pathogen identified in children aged 12–23 months requiring IV rehydration or hospitalization and that *V cholerae* was attributed to 20.5% of the children requiring IV hydration compared to 10.4% of the children classified as severely dehydrated by GTFCC or IMCI guidelines (Table 2).

Table 1. Demographic and Clinical Characteristics of Included Cases

Characteristic	Severe Dehydration: GTFCC or IMCI	Severe Dehydration: IMCI and GTFCC Criteria Met	Severe Dehydration: GTFCC Criteria Only	Not Severe Dehydration: Neither IMCI Nor GTFCC Criteria Met	Total
No. of cases	2284	1893	391	3020	5304
Female sex	998 (43.7)	823 (43.5)	175 (44.8)	1288 (42.6)	2286 (43.1)
Male sex	1286 (56.3)	1070 (56.5)	216 (55.2)	1732 (57.4)	3018 (56.9)
Age, mo					
0–11	939 (41.1)	764 (40.4)	175 (44.8)	970 (32.1)	1909 (36.0)
12–23	778 (34.1)	642 (33.9)	136 (34.8)	1057 (35.0)	1835 (34.6)
24–59	567 (24.8)	487 (25.7)	80 (20.5)	993 (32.9)	1560 (29.4)
Study site					
Bangladesh	106 (4.6)	56 (3.0)	50 (12.8)	771 (22.5)	877 (16.5)
India	383 (16.8)	356 (18.8)	27 (6.9)	466 (15.4)	849 (16.0)
Kenya	448 (19.6)	356 (18.8)	27 (6.9)	466 (15.4)	849 (16.0)
Mali	308 (13.5)	279 (14.7)	29 (7.4)	526 (17.4)	834 (15.7)
Mozambique	284 (12.4)	173 (9.1)	111 (28.4)	200 (6.6)	484 (9.1)
Pakistan	446 (19.5)	392 (20.7)	54 (13.8)	342 (11.3)	788 (14.9)
The Gambia	309 (13.5)	264 (13.9)	45 (11.5)	376 (12.5)	685 (12.9)
Diarrheal episode duration prior to presentation, d, mean (SD)	2.77 (1.35)	2.79 (1.36)	2.64 (1.29)	2.82 (1.34)[a]	2.80 (1.34)
Lethargy/loss of consciousness	576 (25.2)	558 (29.5)	18 (4.6)	0 (0)	576 (10.9)
Respiratory distress	806 (35.3)	429 (22.7)	377 (96.4)	0 (0)	806 (15.2)
Sunken eyes	2139 (93.7)	1875 (99.0)	264 (67.5)	2151 (71.2)	4290 (80.9)
Poor drinking	902 (39.5)	883 (46.6)	19 (4.9)	89 (2.9)	991 (18.7)
Slow skin recoil	1002 (43.9)	992 (52.4)	10 (2.6)	38 (1.3)	1040 (19.6)
Predominant stool type					
Bloody	123 (5.4)	92 (4.9)	31 (7.9)	373 (12.4)	496 (9.4)
Rice watery	171 (7.5)	159 (8.4)	12 (3.1)	132 (4.4)	303 (5.7)
Simple watery	1466 (64.2)	1239 (65.5)	227 (58.1)	1609 (53.3)	3075 (58.0)
Sticky/mucoid	524 (22.9)	403 (21.3)	121 (30.9)	906 (30.0)	1430 (27.0)
Rehydration					
None	119 (5.2)	44 (2.3)	75 (19.2)	242 (8.0)	361 (6.8)
Oral	1523 (66.7)	1281 (67.7)	242 (61.9)	2551 (84.5)	4074 (76.8)
IV	642 (28.1)	568 (30.0)	74 (18.9)	227 (7.5)	869 (16.4)
Antibiotics given	1688 (73.9)	1380 (72.9)	308 (78.8)	2443 (80.9)	4131 (77.9)
Hospitalized	617 (27.0)	451 (23.8)	166 (42.5)	546 (18.1)	1163 (21.9)
Death by ~60-d follow-up[b]	85 (4.1)	68 (4.0)	17 (4.8)	28 (1.0)	113 (2.3)
Median time from enrollment to death, d	10.0	10.0	12.0	21.0	13.0

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: GTFCC, World Health Organization Global Task Force on Cholera Control; IMCI, World Health Organization Integrated Management of Childhood Illness; IV, intravenous; SD, standard deviation.

[a]One case (not severe dehydration) missing data for diarrheal episode duration.

[b]Missing status at 60-day follow-up for 483 cases. Percentages were calculated using observed sample sizes as follows: IMCI and GTFCC criteria, n = 1698; GTFCC only, n = 351; GTFCC or IMCI, n = 2049; neither IMCI nor GTFCC, n = 2772; Total, n = 48.

Test Performance

Given that IMCI case definition serves to identify potential cholera cases, such that they could be provided appropriate rehydration and antibiotics, we examined the performance of this case definition in identifying *V cholerae*–attributed episodes. The test performance of the IMCI case definition at identifying *V cholerae* in countries with known cholera, using AFe >0.5 as the gold standard, showed sensitivity of 67% and specificity of 72%. The positive predictive value (PPV) was 19% and the negative predictive value (NPV) was 96% (Supplemental Table 6). Test performance was similar using *V cholerae* culture positivity as a gold standard (Supplemental Table 7).

DISCUSSION

In this analysis of children seeking medical care for MSD with severe dehydration, we showed that the most common pathogens associated with severe dehydration as classified by WHO IMCI or GTFCC criteria varied by age group. Rotavirus was

Table 2. Pathogens and Dehydration Severity, Stratified by Age Group

	Dehydration Measure and Age Group											
	Age 0–11 mo (n = 1909)				Age 12–23 mo (n = 1835)				Age 24–59 mo (n = 1560)			
Pathogen	GTFCC or IMCI Guidelines	Received IV Rehydration	Hosp.[a] Required	Not Severely Dehydrated[b]	GTFCC or IMCI Guidelines	Received IV Rehydration	Hosp. Required[a]	Not Severely Dehydrated[b]	GTFCC or IMCI Guidelines	Received IV Rehydration	Hosp. Required[a]	Not Severely Dehydrated[b]
No. of cases	939	380	460	970	778	284	397	1057	567	205	306	993
Rotavirus	290 (30.9)	149 (39.2)	181 (39.3)	230 (23.7)	150 (19.3)	77 (27.1)	136 (34.3)	196 (18.5)	52 (9.2)	21 (10.2)	34 (11.1)	62 (6.2)
Shigella/EIEC	69 (7.3)	21 (5.5)	34 (7.4)	96 (9.9)	201 (25.8)	67 (23.6)	125 (31.5)	444 (42.0)	147 (25.9)	61 (29.8)	139 (45.4)	437 (44.0)
ST-ETEC	97 (10.3)	48 (12.6)	35 (7.6)	49 (5.1)	85 (10.9)	36 (12.7)	39 (9.8)	84 (7.9)	44 (7.8)	18 (8.8)	19 (6.2)	54 (5.4)
Cryptosporidium spp	113 (12.0)	49 (12.9)	48 (10.4)	76 (7.8)	59 (7.6)	29 (10.2)	31 (7.8)	47 (4.4)	7 (1.2)	1 (0.5)	4 (1.3)	4 (0.4)
Adenovirus 40/41	66 (7.0)	37 (9.7)	46 (10.0)	57 (5.9)	36 (4.6)	11 (3.9)	13 (3.3)	42 (4.0)	10 (1.8)	1 (0.5)	4 (1.3)	16 (1.6)
Vibrio cholerae	16 (1.7)	13 (3.4)	4 (0.9)	8 (0.8)	26 (3.3)	21 (7.4)	10 (2.5)	18 (1.7)	59 (10.4)	42 (20.5)	30 (9.8)	26 (2.6)
Helicobacter pylori	6 (0.6)	5 (1.3)	5 (1.1)	5 (0.5)	13 (1.7)	3 (1.1)	4 (1.0)	14 (1.3)	38 (6.7)	12 (5.9)	18 (5.9)	57 (5.7)
Astrovirus	20 (2.1)	10 (2.6)	6 (1.3)	22 (2.3)	23 (3.0)	3 (1.1)	6 (1.5)	31 (2.9)	7 (1.2)	0 (0)	2 (0.7)	9 (0.9)
Salmonella spp	7 (0.7)	2 (0.5)	3 (0.7)	0 (0)	17 (2.2)	8 (2.8)	10 (2.5)	16 (1.5)	14 (2.5)	7 (3.4)	7 (2.3)	13 (1.3)
Norovirus GII	19 (2.0)	7 (1.8)	9 (2.0)	19 (2.0)	4 (0.5)	1 (0.4)	4 (1.0)	6 (0.6)	9 (1.6)	0 (0)	4 (1.3)	15 (1.5)
Sapovirus	3 (0.3)	0 (0)	0 (0)	5 (0.5)	7 (0.9)	1 (0.4)	2 (0.5)	19 (1.8)	20 (3.5)	4 (2.0)	6 (2.0)	21 (2.1)
Campylobacter jejuni/C coli	28 (3.0)	17 (4.5)	22 (4.8)	47 (4.8)	0 (0)	0 (0)	0 (0)	6 (0.6)	0 (0)	0 (0)	2 (0.7)	5 (0.5)
tEPEC	16 (1.7)	11 (2.9)	13 (2.8)	10 (1.0)	10 (1.3)	6 (2.1)	5 (1.3)	6 (0.6)	1 (0.2)	0 (0)	0 (0)	0 (0)
Aeromonas spp	8 (0.9)	1 (0.3)	6 (1.3)	5 (0.5)	1 (0.1)	0 (0)	2 (0.5)	5 (0.5)	16 (2.8)	9 (4.4)	6 (2.0)	25 (2.5)
Entamoeba histolytica	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	2 (0.2)	7 (1.2)	0 (0)	0 (0)	18 (1.8)
Cyclospora cayetanensis	2 (0.2)	1 (0.3)	1 (0.2)	2 (0.2)	2 (0.3)	0 (0)	2 (0.5)	5 (0.5)	2 (0.4)	0 (0)	1 (0.3)	3 (0.3)
Cystoisospora belli	2 (0.2)	1 (0.3)	1 (0.2)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
EAEC	0 (0)	0	0 (0)	0 (0)	1 (0.1)	0	1 (0.3)	0 (0)	0 (0)	0	0 (0)	0 (0)
LT-ETEC	0	0	0	0	0	0	0	0	0	0	0	0
STEC	0	0	0	0	0	0	0	0	0	0	0	0

Estimates are shown as No. (%).

Abbreviations: EAEC, enteroaggregative *Escherichia coli*; EIEC, enteroinvasive *Escherichia coli*; ETEC, enterotoxigenic *Escherichia coli*; GTFCC, World Health Organization Global Task Force on Cholera Control; Hosp., hospitalization; IMCI, World Health Organization Integrated Management of Childhood Illness; IV, intravenous; LT, heat-labile; ST, heat-stable; STEC, Shiga toxin–producing *Escherichia coli*; tEPEC, typical enteropathogenic *Escherichia coli*.

[a]Hospitalization refers to admission to the hospital; some children received treatment without requiring admission.

[b]Not meeting either GTFCC or IMCI criteria.

Table 3. Odds Ratios for Severe Dehydration (as Defined by World Health Organization Global Task Force on Cholera Control or Integrated Management of Childhood Illness Guidelines) in Children With Moderate-to-Severe Diarrhea, by Pathogen

Pathogen	OR (95% CI)	Adjusted[a] OR (95% CI)
Rotavirus	1.42 (1.24–1.64)	1.30 (1.13–1.50)
Shigella/EIEC	0.46 (.41–.53)	0.50 (.44–.57)
ST-ETEC	1.66 (1.36–2.04)	1.62 (1.33–1.99)
Cryptosporidium spp	1.94 (1.53–2.45)	1.74 (1.37–2.21)
Adenovirus 40/41	1.30 (1.00–1.70)	1.19 (.91–1.56)
Vibrio cholerae	2.64 (1.89–3.73)	3.05 (2.17–4.33)
Helicobacter pylori	0.99 (.70–1.40)	1.21 (.85–1.73)
Astrovirus	1.07 (.73–1.55)	0.99 (.68–1.44)
Salmonella spp	1.74 (1.08–2.86)	1.91 (1.18–3.15)
Norovirus GII	1.06 (.66–1.69)	1.04 (.64–1.65)
Sapovirus	0.88 (.55–1.39)	0.98 (.61–1.56)
Campylobacter jejuni/C coli	0.63 (.40–.99)	0.55 (.34–.86)
tEPEC	2.25 (1.22–4.27)	2.01 (1.09–3.82)
Aeromonas spp	0.94 (.56–1.57)	1.08 (.63–1.80)
Entamoeba histolytica	0.50 (.21–1.09)	0.69 (.28–1.47)
Cyclospora cayetanensis	0.79 (.27–2.14)	0.84 (.28–2.28)
Cystoisospora belli	2.65 (.25–56.96)	2.27 (.22–48.83)
EAEC	NA	NA
LT-ETEC	NA	NA
STEC	NA	NA

Odds ratios were unable to be calculated for EAEC, LT-ETEC, and STEC due to the low number of cases (1, 0, and 0, respectively).

Abbreviations: CI, confidence interval; EAEC, enteroaggregative *Escherichia coli*; EIEC, enteroinvasive *Escherichia coli*; ETEC, enterotoxigenic *Escherichia coli*; LT, heat-labile; NA, not applicable; OR, odds ratio; ST, heat-stable; STEC, Shiga toxin–producing *Escherichia coli*; tEPEC, typical enteropathogenic *Escherichia coli*.

[a]Adjusted for age at enrollment.

the most common in those aged <12 months, and *Shigella*/EIEC was the most common attributable etiology in those 12–59 months of age. Rotavirus was also among the top 5 pathogens in 12–23 months of age as well as 24–59 months of age. *Cryptosporidium* was also common among those <24 months of age (attributed to approximately 10% of cases), while *V cholerae* was common among those 24–59 months of age (attributed to approximately 10% of cases). The prevalence of rotavirus is less surprising given that the data collection occurred prior to the widespread use of the rotavirus vaccine. However, the prevalence of other etiologies aside from *V cholerae* has implications for both public health, such as prioritization of vaccine development efforts, and the clinical management of individual patients, through informing syndromic guidance of diarrheal treatment.

The leading 6 identified etiologies of children with diarrhea presenting with severe dehydration as classified by WHO IMCI or GTFCC criteria were rotavirus, *Shigella*/EIEC, ST-ETEC, *Cryptosporidium*, adenovirus, and *V cholerae*. These also represented the top 6 identified etiologies of children who received IV fluids and required hospitalization in the study. While *Shigella*/EIEC is a leading cause of severe dehydration, episodes of MSD attributed to *Shigella*/EIEC had among the lowest odds of having severe dehydration. This finding could be related to the high burden of diarrhea attributable to *Shigella*/EIEC in the GEMS population. The other most common pathogens had higher odds of having severe dehydration. *Salmonella* and enteropathogenic *E coli* both had higher odds of severe dehydration but were not frequently attributed as etiologies of diarrhea; further evaluation of their potential to cause severe dehydration is warranted.

Our findings are similar to other multisite studies of pediatric diarrheal illnesses using molecular detection that occurred after the implementation of the rotavirus vaccine. In the Global Pediatric Diarrhea Surveillance network (GPDS), which examined children aged <5 years with diarrhea requiring hospitalization after the introduction of the rotavirus vaccine, rotavirus was the leading cause of diarrhea requiring hospitalization, with *Shigella*/EIEC as the second most prevalent cause [13]. Interestingly, norovirus was the third most common cause in GPDS, while norovirus was only attributed in 1.4% of children with severe dehydration in our study [13]. In the Malnutrition and Enteric Disease Study (MAL-ED), which was a longitudinal study of diarrheal episodes, a modified Vesikari score was used to define severity of diarrheal episode, and rotavirus, *Shigella*/EIEC, adenovirus, and *Cryptosporidium* were associated with high severity [14]. Additionally, previous analyses of the GEMS dataset have described etiologies associated with MSD (which includes children with and without severe dehydration) and showed similar findings with *Shigella*/EIEC, adenovirus, ST-ETEC, *V cholerae*, rotavirus, and *Cryptosporidium* representing the top 6 pathogens [21]. Overall, these findings highlight the importance of considering pathogens other than *V cholerae* in children presenting with severe dehydration. *Shigella*/EIEC is of particular importance as antibiotic treatment is also recommended but may differ from that for *V cholerae*.

Overall, the IMCI and GTFCC clinical criteria for severe dehydration identified similar cases. The GTFCC criteria categorized slightly more patients as severely dehydrated compared to the IMCI criteria. However, the distribution of pathogens was very similar between the 2. Although previous studies have demonstrated that the IMCI guidelines are not accurate for predicting severe dehydration compared to a gold standard of weight loss [24], the pathogens that are associated with severe dehydration in our analysis are similar to pathogens in studies that used different metrics for dehydration, such as the Vesikari scale [14, 25, 26].

We found that severe dehydration alone in a child aged >2 years is poorly predictive of diarrhea due to *V cholerae*. Using the IMCI clinical criteria, in GEMS countries that were cholera endemic, only 19% of children >2 years of age with severe dehydration were attributed to *V cholerae*. Additionally, the PPV of the IMCI criteria, 19%, is not clinically useful. The IMCI guidelines recommend that all children >2 years

of age meeting criteria for severe dehydration in cholera-endemic countries should be treated with antibiotics. The low PPV suggests that a significant number would be inappropriately deemed in need of antibiotics for treatment of *V cholerae*. Conversely, the NPV is 96% and therefore 96% of patients without severe dehydration do not have *V cholerae*, suggesting that few *V cholerae*–positive patients would be missed using these clinical criteria. Those with MSD and *V cholerae* had the highest odds of severe dehydration, emphasizing the already known risk of severe dehydration with cholera [27]. The inadequacy of the clinical criteria highlights the importance of the development of better diagnostic tools to help guide appropriate treatment [28, 29].

While IMCI guidelines recommend that children presenting with severe dehydration should receive IV fluids, we found that only 30% of children who met IMCI criteria for severe dehydration received IV fluids (Table 1). Previous research has shown that adherence to the WHO guidelines for management of diarrheal diseases may be near impossible due to a combination of factors including inadequate staffing, limited resources, and differences between patient and clinician expectations, among others [30–32]. Additionally, a small number of children classified as severely dehydrated did not require any hydration (oral or IV) at the healthcare center. The IMCI and GTFCC definitions of severe dehydration incorporate both provider and caregiver assessment and it is possible that provider gestalt, which determined need for rehydration, differed from the clinical criteria classification that has been observed in prior studies [24]. Furthermore, structural barriers such as accessibility and availability of supplies as well as training of staff affect ability to adhere to treatment guidelines [32]. Technologies to provide clinical decision support for this challenge may improve guideline adherence [33, 34].

Our study has several limitations. First, GEMS only included children presenting with MSD, and thus we are unable to determine the proportion of each etiology that presents with severe dehydration. Second, the GTFCC guidelines also include pulse as a factor to determine dehydration severity, and our analysis was limited by the absence of pulse in the GEMS dataset. The inclusion of pulse data would have potentially added more cases to the severe category that were not captured with the other criteria, and it is unclear if these missing severe dehydrated cases would have similar or different etiologies. Additionally, our analysis represents a subset of all the cases in GEMS as qPCR data were only available for 5304 of 9439 total cases, which limits the generalizability of the results. Finally, GEMS data represent an older dataset and were collected prior to the availability of the rotavirus vaccine and may not represent the current landscape.

Overall, our study highlights important pathogens aside from *V cholerae* that cause diarrhea with severe dehydration, a leading cause of death in young children worldwide. Rotavirus was a leading pathogen in our study and remained so in the GPDS study after introduction of the rotavirus vaccine, highlighting the importance of improving rotavirus vaccine coverage. *Shigella*/EIEC, ST-ETEC, *Cryptosporidium*, and *V cholerae* also are important causes of severe dehydration. Vaccine and treatment advances should be targeted at these pathogens to reduce the mortality associated with severe dehydration. *Shigella*/EIEC was prevalent across all age groups and was also an important cause of hospitalization in the GPDS study and severe diarrhea in MAL-ED, suggesting that *Shigella*/EIEC represent an important high-priority target for vaccine development. Besides rotavirus, *V cholerae* is the only other pathogen with an approved vaccine, although unfortunately with supply issues, brief length of protection, and suboptimal effectiveness in young children, its use as a preventive strategy is limited [35]. Additionally, the IMCI and GTFCC clinical criteria are poor predictors of a *V cholerae* infection, which emphasizes the importance of continued work on development of readily available diagnostics to guide appropriate treatment.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Concept and design: S. M. A. and D. T. L. Data analysis: A. J. Drafting of the primary manuscript: A. J. Critical revision of the manuscript for important intellectual content: All authors. Administrative, technical, or material support: All authors.

Data availability. This submitted manuscript is a secondary analysis. GEMS data are publicly and freely available by request through ClinEpiDB.org. The previously derived attributable fractions (AFe) for etiologies will be made available upon request.

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