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ORIGINAL ARTICLE

Hospital-acquired gastroenteritis at a referral hospital in Gaborone, Botswana

Henry D. Welch[1], David M. Goldfarb[2,3,4,5], Banno Moorad[2], Margaret Mokomane[3], Marek Smieja[4], Unoda Chakalisa[6], Andrew P. Steenhoff[1,2,3], Rodney Finalle[1], Susan E. Coffin[1]

[1]Children's Hospital of Philadelphia, Philadelphia, PA, United States
[2]Botswana-UPenn Partnership, Gaborone, Botswana
[3]The University of Botswana, Gaborone, Botswana
[4]McMaster University, Hamilton, Canada
[5]University of British Columbia, Vancouver, Canada
[6]Botswana Harvard AIDS Institute, Gaborone, Botswana

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Abstract

Hospital-acquired infections, including hospital-acquired gastroenteritis (HAGE), are well documented in Western countries but little is known about these infections in sub-Saharan Africa. The aim of this study was to determine the incidence of and explore modifiable risk factors for HAGE.

A prospective cohort study of children <13 years with HAGE admitted to Princess Marina Hospital in Gaborone, Botswana was performed. HAGE was defined as new-onset gastroenteritis (GE) >72 hours after admission or upon admission after recent discharge for a non-GE illness. Children were followed until discharge to ascertain therapies used and adverse outcomes. Enteric pathogens were identified by multiplex polymerase chain reaction.

Virtually all of the 32 children with HAGE were < 2 years (n=30, 94%) and most were male (n=19, 59%). Few had human immunodeficiency virus infection (n=6, 19%), severe malnutrition (n=8, 25%), or a history of vitamin A use in the past 6 months (n=2, 6%). The mean monthly incidence of HAGE was 2.3 per 1000 patient days, and was associated with the monthly number of community-acquired gastroenteritis (CAGE) admissions (IRR 1.02, 95% CI 1.00, 1.04, p=0.025). A stool pathogen was detected in 15/27 (56%) children, including

Corresponding Author

Andrew Steenhoff
The Children's Hospital of Philadelphia, Global Health Center, Department of International Medicine.
3535 Market St 13th Floor, Suite 1300 Philadelphia PA 19104
Email: henrydwelch@gmail.com

norovirus (n=7, 26%) and rotavirus (n=5, 18%). Most children received oral rehydration solution (n=26, 81%), or intravenous fluids (n=9, 28%). Antibiotics were administered to 5 (16%) children. Two (6%) children with HAGE were admitted to the intensive care unit and 4 (12%) died.

In conclusion, we found HAGE was relatively common and associated with severe outcomes. The monthly incidence of HAGE was associated with CAGE admissions. Common pathogens included norovirus and rotavirus.

Keywords: nosocomial infection, gastroenteritis, hospital-acquired gastroenteritis, paediatrics, international health, Botswana

Background

Hospital-acquired infections (HAI), including hospital-acquired gastroenteritis (HAGE) are well documented in European and Western countries.[1-5] Although less frequently studied than HAI due to medical devices or surgical procedures, HAGE occurs frequently related to both endemic transmission as well as outbreaks. A United Kingdom study found 39% of all episodes of acute gastroenteritis (GE) among hospitalized patients were healthcare acquired and that rotavirus was the most common cause (31%).[1] Other studies documented that rotavirus accounted for up to 87% of paediatric HAGE cases.[5,6] A recent meta-analysis found that the incidence of healthcare-associated rotavirus infections was 8.1 per 100 hospitalizations for children under two years of age during epidemic months,[4] however a single-centre study suggested that the introduction of the rotavirus vaccine was associated with a substantial reduction in the incidence of both community and hospital-acquired rotavirus.[3] Our understanding of the aetiologies of paediatric HAGE other than rotavirus is limited.

Few studies have examined the epidemiology of paediatric HAI in Africa or other regions of the developing world. One prospective study performed in South Africa found that 14.3% of hospitalized children developed an HAI and that GE was the second most common type of HAI, accounting for 12.4% of paediatric HAI cases.[7] However, this study did not report the etiological agents causing HAGE or examine potential modifiable risk factors for in-hospital transmission. In Guinea-Bissau a study implementing World Health Organization's (WHO's) generic protocols for hospital-and community-based surveillance of rotavirus GE found a rotavirus infection rate of 1.6 per 1000 child-days.[8]

The aim of this prospective cohort study of children hospitalized at a large academic hospital in Botswana was to determine the incidence and aetiology of HAGE, and explore potential modifiable risk factors for infection. This project was conducted in parallel with an ongoing study of community-acquired gastroenteritis (CAGE).[9]

Methods

Study design, setting, and population

Between February 1st, 2012 and February 28th, 2013 we performed a prospective cohort study of HAGE in Batswana children 13 years of age and younger who were admitted to the general paediatric ward at Princess Marina Hospital, the primary referral and teaching hospital in Gaborone, Botswana. The general paediatric medical unit is composed of five cubicles and 30 beds. Children with CAGE are admitted to one of the cubicles, in an effort to cohort the patients and limit HAI. Additionally, the bed mats are cleansed with a disinfectant after patient use. In total, there were five hand hygiene stations located throughout the paediatric ward. This study was approved by Ethics Boards of Botswana's Ministry of Health, Princess Marina Hospital, and The Children's Hospital of Philadelphia. Written informed consent was obtained from a caregiver for each participant.

Case finding

A research assistant performed active surveillance by reviewing inpatient medical files daily from Monday to Friday for any documented diarrhoea, in addition

to speaking with physicians and nurses on the ward to identify patients with new-onset diarrhoea. Cases from the weekend were identified on the subsequent Monday. Gastroenteritis was defined using the WHO definition of three or more loose or watery stools/day.[11] HAGE was defined as new-onset GE after 72 hours of hospital admission or upon admission for a patient who had been discharged less than seven days prior due to a non-GE illness.

Data collection

Baseline demographic, clinical and laboratory data were obtained by systematic review of the medical record. All enrolled children were followed until either hospital discharge or in-hospital death to capture associated outcomes. Additional covariates captured through structured review of the medical record included age, sex, human immunodeficiency virus (HIV) status, feeding practice (breast or bottle feeding), vitamin A use, malnutrition status, clinical symptoms (vomiting, diarrhoea, blood in stool), exposure to sick contacts inside and outside the hospital, and potential food exposures.

Stool was collected after admission in conjunction with the ongoing CAGE study. Stool was immediately frozen at -80°C. Stool samples collected from February 1st, 2012 until November 5th, 2012 were shipped on dry ice in batches to McMaster University, Hamilton, Canada, for pre-treatment and nucleic acid extraction with the QIA symphony™ (Qiagen, Germantown USA) using the DSP Virus/Pathogen Mini-Kit. Enteric pathogen polymerase chain reaction (PCR) detection was performed using the commercial multiplex xTAG Gastrointestinal Pathogen Panel™ (GPP) assay (Luminex Molecular Diagnostics, Toronto, Canada), which has previously been validated.[11,12] This assay simultaneously detects 19 enteric pathogen targets (*Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica, Yersinia enterocolitica, Salmonella* spp., *Escherichia coli ST, E. coli LT, Shigella* spp., *Clostridium difficile toxin A, C. difficile toxin B, Campylobacter jejuni, Vibrio cholera, E. coli O157*, Shiga Toxin 1 and 2, norovirus GI and GII, rotavirus A, and adenovirus 40/41). After November 5th, 2012 PCR testing was established on site in Gaborone, to allow for rapid identification of outbreaks. Briefly, two laboratory-developed multiplex PCR assays, one targeting the three most prevalent bacterial pathogens (*Salmonella* spp., *Shigella* spp. and *Campylobacter* spp.) and the other targeting rotavirus A, norovirus GI/GII, and all adenoviruses were utilized. Stool was extracted with the Nuclisense easyMAG™ platform (BioMerieux, Durham NC) and multiplex PCR performed using the Applied Biosystems ABI 7500 (Life Technologies, Carlsbad CA). An extensive validation was performed for each assay target and there was close concordance with the Luminex GPP™ assay for each target of the new in house assays as described previously.[13] A portion of samples was also sent for testing to McMaster University for ongoing external quality assurance.

Measured outcomes

The primary outcomes were in-hospital death, intensive care unit (ICU) admission, and the administration of therapies to treat HAGE (intravenous fluids, oral rehydration solution, or antibiotics).

Statistical analysis

Data were entered into a standardized data collection form and analyzed using Stata 11 (Stata Corp., College Station, TX). Continuous variables were described using mean, median, interquartile range, and range values as appropriate. Categorical variables were described using frequencies and percents. Bivariable Poisson regression analysis was done to assess the association between the monthly incidence of HAGE and unit-based exposures such as 1) availability of hand hygiene resources, 2) CAGE admissions, and 3) inpatient census.

Results

Patient and clinical characteristics

A total of 32 cases of HAGE was identified, corresponding to an incidence of 2.3 cases of HAGE per 1000 patient days. During the study period there were a total of 1,776 admissions to the paediatric ward, 406 (23%) of which were due to CAGE. The majority of children who developed HAGE were male (n=19, 59%) and less than two years of age (n=30, 94%). Most children did not have a chronic medical condition although six (19%) children were infected with HIV (Table II). Eight (25%) children who developed HAGE had severe acute malnutrition at the time of hospital admission, and only two (6%) children had a history of vitamin A supplementation in the last six months.

Table I. Pathogen primers and probes used in testing done in Gaborone, Botswana[14]

Target pathogen	Forward primer	Reverse primer	Probe sequence	Target
Campylobacter[12]	CTGCTTAA CACAAGTT GAGTAGG	TTCCTTAGGTA CCGTCAGAA	TGTCATCCTCCAC GCGGCGTTGCTG C	16SrRNA
Salmonella[13]	CTCACCAG GAGATTAC AACATGG	AGCTCAGACC AAAAGTGACCA TC	CAC CGA CGG CGA GAC CGA CTT T	ttr gene
Shigella[14]	CCTTTTCC GCGTTCCT TGA	CGGAATCCGG AGGTATTGC	CGC CTT TCC GAT ACC GTC TCT GCA	ipaH gene
Rotavirus A[15]	GGAKGTYCT GTACTCMTT GTCA	CCAGTTTGRAA STCATTTCC	GAATATAAT/ZEN/G TACCTTCRACAATT TTGTCYCTAGCATC	VP6 gene
Norovirus GI[16-17]	CGYTGGAT GCGNTTYC ATGA	CTTAGACGCC ATCATCATTYA C	AGATYGCGRTCYC CTGTCCA	RNA polymerase/ capsid
Norovirus GII[16-17]	CARGARBC NATGTTYA GRTGGATG AG	TCGACGCCAT CTTCATTCACA	TGGGAGGGCGAT CGCAATCT	RNA polymerase/ capsid
Adenovirus[18]	CAGGACGC CTCGGRGT AYCTSAG	GGAGCCACVG TGGGRTT	CCGGGTCTGGTG CAGTTTGCCCGC	Hexon

All children had diarrhoea at the time of onset of HAGE and 14 (44%) also had vomiting. Mucus in the stool was reported by the parents of 25 (78%) children. Only two (6%) had blood in the stool. The median length of stay prior to onset of HAGE was six days (IQR 4, 12) (Table III). Of the 32 children who developed HAGE, 10 (31%) were admitted for respiratory conditions. Other reasons for admissions are shown in Table II.

Exposures prior to HAGE onset

Most children with HAGE ate hospital-prepared food, although seven (22%) were exclusively breast-fed (Table IV). Only two (6%) patients were known to have had a recent visit from a sick person. Of the 32 patients that developed HAGE, two (6%) had shared a bed surface with another patient (one patient had GE, the other patient a non-GE related illness) prior to onset of HAGE.

Many children developed HAGE during times that the ward was overcrowded; the average daily census for the three days prior to HAGE onset was 36 patients. Additionally, while the average daily GE census was 5.6 patients during the study period, children developed HAGE when the average daily census of GE cases was 6.1 patients for the three days prior to onset of HAGE. The unit had five hand hygiene stations consisting of three hand washing stations and two aseptic hand sanitizers. Most episodes of HAGE occurred when there were multiple non-functional hand hygiene stations; on average 65% of hand hygiene stations were functional during the three days

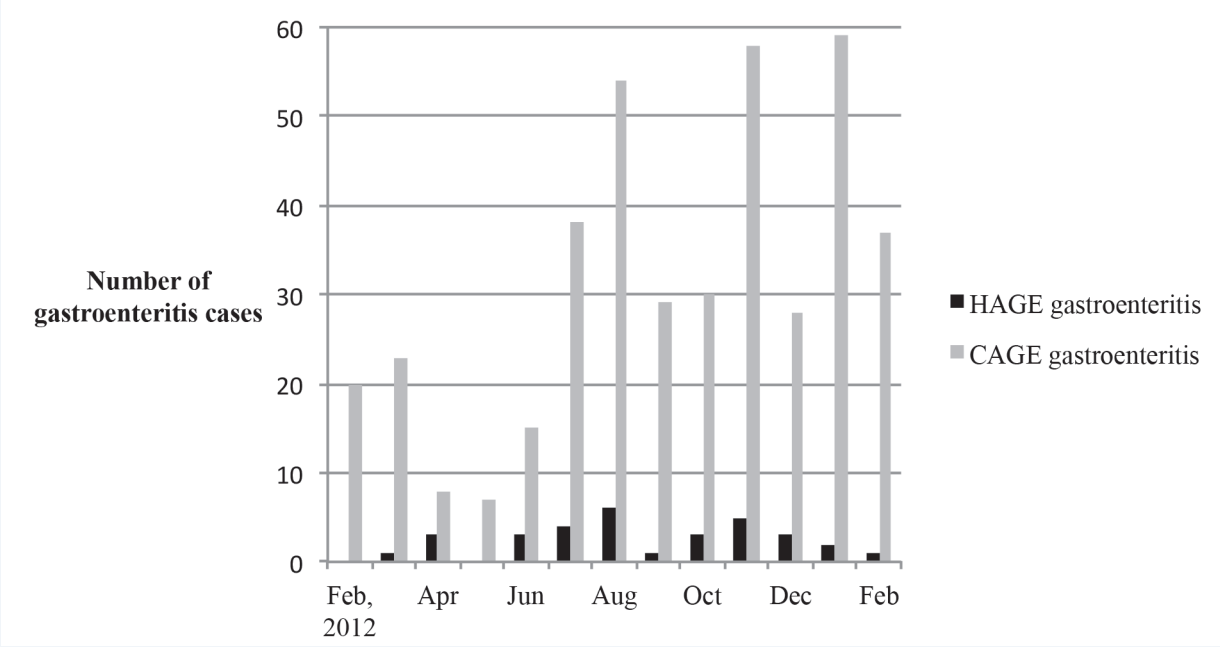

Figure 1. Monthly cases of community acquired and hospital acquired gastroenteritis

prior to HAGE onset (Table IV). In contrast, 54% of the functional hygiene stations were functional over the entire study period. Using bivariable analysis, the monthly incidence of HAGE was associated with the monthly number of CAGE admissions (IRR 1.02, 95% CI 1.00, 1.04, p=0.025) (Figure 1).

Pathogen detection rates

During the study period 27/32 (84%) children had a stool specimen tested and a pathogen was detected in 15 (56%) samples (Table V). Norovirus was the most frequent pathogen detected (n=7, 26%), followed by rotavirus (n=5, 18%). One patient tested positive for both rotavirus and norovirus. Three children had non-viral pathogens detected (*Shigella* spp. n=2; *Giardia* spp. n=1).

Therapies and outcomes

Most children with HAGE received oral-rehydration solution (n=26, 81%), while intravenous fluid administration was relatively uncommon (n=9, 28%) (Table VI). Antibiotics were started in 5 (16%) children although the indication for antibiotics is unknown. Two (6%) children with HAGE were admitted to the ICU and four (12%) experienced an in-hospital death.

Discussion

In this paediatric ward in sub-Saharan Africa, we found that HAGE was relatively common and appeared to be associated with severe outcomes, including death. Although limited resources, including space and hand hygiene stations, were common during the three days prior to most cases of HAGE, only the number of CAGE admissions was significantly associated with risk of HAGE. Additional studies will be needed to identify whether these factors were associated with an increased risk of HAGE onset.

Most children with HAGE were under two years old (94%). Viral pathogens (norovirus and rotavirus) were the most common pathogens isolated. Not surprisingly, the incidence of HAGE increased from June to November (Figure 1) mirroring the peak season for CAGE cases and corresponding to the rotavirus season in Botswana.[9] Of note, 18% of the tested stools were positive for rotavirus, suggesting that rotavirus HAGE may arise as a consequence of patient-to-patient transmission during times of increased disease activity in the community as well as increased burden in the hospital.[2,4] This is similar to what has been reported in a UK hospital where

Table II. Sample characteristics of 32 children who developed hospital acquired gastroenteritis

Characteristic	Overall [1]
Age, months	
< 6 months	14 (44%)
6-11 months	12 (38%)
12-23 months	4 (13%)
24-35 months	1 (3%)
36-47 months	1 (3%)
Median months (Q1,Q3)	6 (3,10.5)
Male sex	19 (59%)
HIV status	
Positive	6 (19%)
Negative	20 (63%)
Unknown	6 (19%)
Chronic conditions, non-HIV	
1. Tuberculosis	6 (19%)
2. Neurologic [2]	2 (6%)
3. Cardiac [3]	1 (3%)
4. None	21(66%)
Reason for admission	
1. Respiratory related [4]	10 (31%)
2. Anemia [5]	4 (13%)
3. Failure to thrive	3 (9%)
4. Other [6]	15 (47%)

[1] Column percent unless otherwise noted (Note: values may not sum to 100% due to rounding)

[2] 1 patient with seizure disorder, 1 patient with cerebral palsy

[3] 1 patient with Down syndrome and an endocardial cushion defect

[4] 8 patients with pneumonia, 1 bronchiolitis, 1 pulmonary tuberculosis

[5] 3 patients with AZT induced anemia, 1anemia and thrombocytopenia of unknown etiology

[6] 2 severe acute malnutrition, 2 seizures, 2 congenital anomalies, 2 HAGE, 2 sepsis,1 pericardial effusion, 1 congestive heart failure, 1 paraffin ingestion, 1 jaundice, 1 meningitis

Q1-first quartile; Q3-third quartile; SD-standard deviation; HIV-human immunodeficiency virus

rotavirus (31%) and norovirus (16%) were the most common pathogens responsible for viral HAGE.[1] With the introduction of rotavirus vaccine into the Botswana immunization schedule in July 2012, we anticipate there will be a decrease in HAGE cases due to rotavirus.

In our large (n=617) prospective study of community onset GE[15] where we also used a sensitive multiplex PCR assay, we detected at least one pathogen target in 83% of all children, which is a higher pathogen detection rate than we have found in these hospital associated cases described in this study. However, some of the leading pathogens detected in the community onset study were bacteria (e.g. *Shigella* spp. 17%, *Campylobacter* spp. 14%, *Salmonella* spp. 8.5%) and parasites (e.g. *Cryptosporidium* 8.3%). After children are admitted to the study hospital, they are less likely

Table III. Clinical characteristics of 32 children with hospital acquired gastroenteritis

Characteristic	Overall
Vomiting	14 (44%)
Diarrhea	32 (100%)
Blood in stool	2 (6%))
Mucous in stool	25 (78%)
Number of days in hospital until gastroenteritis started	
Mean (SD)	10.4 (10.1)
Median (IQR)	6 (4,12)

to be exposed to these water-borne, food-borne and zoonotic pathogens and this might explain why the total number of pathogens detected was lower in the HAGE group. Also, some of the pathogens particularly associated with paediatric hospital transmission (e.g. sapovirus and astrovirus) were not included in our molecular assays and this might also help explain this observed gap in pathogen detection between the two groups.

There is a paucity of data on exposures related to HAGE and other HAI in Africa. We found that the monthly incidence of CAGE was associated with the incidence of HAGE but the mechanisms of transmission remain unclear. Outbreaks of rotavirus and norovirus HAGE have been commonly reported. Several shared characteristics may explain why these pathogens are more common causes of paediatric HAGE: 1) the relative resistance to commonly used hospital antiseptic solutions[5]; 2) the ability of viral particles to survive on surfaces and hands for prolonged periods, and 3) the small inoculum needed to establish infection.[4] In this study, we observed that crowding and limited resources for hand hygiene products were common, which likely led to increased contamination of the healthcare environment. Additionally, many of the patients with HAGE were exposed to bottle-feeding (57%) and/or hospital-prepared food (78%), raising the possibility of food-borne transmission of enteric pathogens. However, our study design did not allow us to examine whether this was a risk factor for HAGE. Finally, at least one patient with HAGE had shared a bed surface with a CAGE patient suggesting that some cases may arise as a result of direct patient-to-patient transmission.

HAGE was associated with significant morbidity. The majority of children with HAGE needed fluid supplementation and 16% were treated with antibiotics. Two patients were admitted to the ICU, one of whom died. An additional three deaths occurred within two weeks of HAGE onset, although the exact cause of death was not available for these patients so it is unknown whether HAGE contributed to any of these deaths. Reducing rates of HAGE would decrease the need to utilize additional hospital resources, an important goal in both resource limited and abundant settings.

In summary, this study describes the epidemiology and aetiology of HAGE in the major tertiary care hospital in Gaborone, Botswana. We found that most cases of HAGE occurred in children under two year of age and that the incidence of HAGE was associated with the monthly incidence of hospitalized CAGE. Additional studies are needed to define risk factors and assess the impact of interventions, such as increased hand hygiene resources, patient cohorting, and environmental disinfection.

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Table IV. Exposures of 32 children who developed hospital acquired gastroenteritis

Characteristic	Overall
Household size	
Median (IQR)	6 (4,8)
Feeding practice in children	
Exclusively breast fed	7 (22%)
Exclusively bottle fed	18 (57%)
Mixed feeding	2 (14%)
Solid food	5 (16%)
Food exposures	
Hospital prepared food	25 (78%)
Non-hospital prepared food	7 (22%)
Daily census, average (SD)	
Overall	36 (7.7)
3 days prior to HAGE onset	37.1 (6.4)
Functional hand hygiene stations, average percent (SD)	
Overall	53% (32%)
3 days prior to HAGE onset	65% (28%)
Daily GE census, average (SD)	
Overall	5.6 (3.9)
3 days prior to HAGE onset	6.1 (3.1)

Table V. Detection of Rotavirus A and Norovirus using PCR in stool specimens from 27 children with hospital acquired gastroenteritis

Pathogen	PCR Positive[1]
Norovirus	
Positive	7/27 (26%)
Negative	20/27 (74%)
Rotavirus	
Positive	5/27 (19%)
Negative	22/27 (79%)

[1] *Shigella* species was detected in 2 samples, Adenovirus in 2 samples,
Enterotoxigenic *Escherichia coli* stable toxin (ST) or labile toxin (LT) in 1 sample, and *Giardia* species in 1 sample.
PCR - polymerase chain reaction.

Table VI. Therapies and outcomes of 32 children with hospital acquired gastroenteritis

Characteristic	Overall
Gastroenteritis therapies used	
Oral rehydration solution	26 (81%)
Intravenous fluids	9 (28%)
Antibiotics	5 (16%)
Unknown	1 (3%)
Discharged alive	28 (88%)
Intensive care unit admission	2 (6%)
In-hospital death	4 (12%)

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