Septicemia Following Rotavirus Gastroenteritis

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ABSTRACT: **Background:** Rotavirus gastroenteritis is a prevalent childhood illness rarely complicated by secondary bacterial sepsis. Although there are case reports of septicemia after rotavirus infection, there are no recent reviews on this topic.
Objectives: To add new cases of septicemia after rotavirus to the literature, review the few cases of septicemia after rotavirus that have been reported, calculate the incidence of septicemia in children hospitalized for rotavirus gastroenteritis, and discuss the characteristics of septicemia after rotavirus infection and implications for current pediatric practice.
Methods: We identified children whose illness was complicated by septicemia from among all hospitalizations at our facility for rotavirus gastroenteritis from May 1999 through May 2010. We also review the few cases reported in the English literature.
Results: We identified two cases of septicemia from among 632 hospitalizations for rotavirus gastroenteritis in this time period, for an incidence rate of 0.32%, which is comparable to other estimates in the English literature. The typical course for cases of bacterial superinfection involves a second peak of high fever; other clinical signs are variable.
Conclusions: Septicemia after rotavirus gastroenteritis is a rare but dangerous entity. Early identification of a child developing bacterial superinfection after rotavirus, as in any case of sepsis, is of the utmost importance, as is obtaining blood cultures in a child with a rotavirus infection and a second fever spike.

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The majority of the world's children will experience rotavirus gastroenteritis by the age of 5 years [1]. Despite the availability of effective vaccines, rotavirus gastroenteritis continues to place heavy demands on emergency rooms and hospitals in Israel and worldwide [2-7]. Complications of rotavirus infection are well known and include not only gastroenteritis and dehydration but also seizure [8] and meningoencephalitis [9]. Rotavirus has been associated with respiratory illness as well [10] and is known to increase the risk for co-infection with Salmonella species [11]. The literature contains a limited number of case reports of septicemia after rotavirus gastroenteritis. To date, only four authors have compiled case series of more than a single patient, and the most comprehensive case series in any one publication involves four patients [1,12-14].

We present two cases of rotavirus-associated sepsis that presented to our facility over an 11 year period. Table 1 delineates the characteristics of the cases in the literature which could help physicians identify the clinical, laboratory and demographic characteristics that may predispose a child with rotavirus gastroenteritis to secondary bacterial infection.

PATIENTS AND METHODS

A retrospective study was conducted in the Pediatric Division of Barzilai Medical Center, a medium-size secondary hospital that serves a population of 500,000 people in southern Israel. The pediatric division has 36 beds. The population comprises both urban and rural inhabitants of diverse ethnic backgrounds characteristic of the Israeli population. Both authors supervised the medical treatment of the patients.

A search was done for all children hospitalized in Barzilai Medical Center from May 1999 through May 2010 whose admission or discharge diagnoses included either sepsis or bacteremia as a diagnosis and either gastroenteritis or diarrhea as a second diagnosis. To be eligible for inclusion, children had to be without prior intestinal disease or immunodeficiency. On presentation, initial stool had to be positive for rotavirus antigen and negative for Salmonella, Shigella or Campylobacter. Initial blood cultures and urine cultures had to be sterile, with growth of a pathogen on a subsequent blood culture while subsequent urine cultures remained sterile. Two children were found to be eligible for inclusion.

MICROBIOLOGIC EXAMINATIONS

Rotavirus was detected using the Combi-Strip™ fecal rapid detection system (Coris Bioconcept, Belgium). The Combi-Strip kit uses two monoclonal antibodies directed against Group A VP6 proteins of human rotavirus. The Combi-Strip documentation cites a sensitivity and specificity for rotavirus of 99.1% and 100% respectively.

RESULTS

From May 1999 through May 2010 there were 3682 admissions to the pediatric division coded as either acute gastroenteritis or

Table 1. Summary of cases of rotavirus gastroenteritis and superimposed bacterial sepsis

No.	Author [ref]	Patient age (mos)	Gender	Origin	Organism	Day of septicemia diagnosis	Findings on clinical exam that suggested septicemia	Leukocyte count (cells/μl) and/or CRP (mg/dl) at sepsis onset
1	Current case 1	16	Male	Israel	*Klebsiella pneumoniae*	6	Fever to 40.8°C, chills, febrile seizure	WBC 2900 CRP 15
2	Current case 2	10	Female	Israel	*Acinetobacter*	8	Fever 39.2°C, chills	WBC 17,100, CRP 7.24
3	Nakatani et al. [23]	60	Female	Japan	*K. pneumoniae*	7	High fever to 40°C, chills, generalized abdominal pain	CRP 9.25
4	Kashiwagi et al. [21]	12	Male	Japan	*K. oxytoca*	2	GI hemorrhage, fever 38°C, tachycardia to 160	WBC 104,000 CRP 5.8
5	Carneiro et al. [24]	10	Female	Brazil	ESBL-producing *E. coli*	4	Fever 39.1°C, tachycardia, tachypnea, lethargy, shock	Not reported
6	Mel et al. [22]	16	Female	Israel	ESBL-producing *E. coli*	5	High fever 39.8°C	WBC 28,000
7	Lowenthal et al. [13]	6	Male	Israel	*E. cloacae*	7	High fever 40°C	WBC 17,360
8	Lowenthal et al. [13]	4	Female	Israel	*E. cloacae*	3	Fever to 39.5°C	WBC 9160
9	Lowenthal et al. [13]	0.5	Female	Israel	*K. pneumoniae*	4	Fever to 38.2°C	WBC 18,650
10	Lowenthal et al. [13]	13	Female	Israel	*E. cloacae*	4	Fever to 39.3°C	WBC 21,080
11	Gonzalez-Carretero et al. [12]	1.5	Male	Spain	*Streptoccocus viridans*	4	Fever to 39.3°C	Not reported
12	Gonzalez Carretero et al. [12]	10	Male	Spain	*E. cloacae*	13	Fever to 38.3°C	Not reported
13	Ciftci et al. [1]	1.5	Male	Turkey	ESBL-producing *K. pneumoniae*	5	Fever to 38.5°C, tachycardia, tachypnea, abdominal distension	CRP 7
14	Ciftci et al. [1]	9	Male	Turkey	*E. coli*	3	Fever to 39°C	CRP 7.2
15	Ciftci et al. [1]	36	Male	Turkey	*P. aeroginosa* and *C. albicans*	7	Fever to 39.3°C	Not reported
16	Ciftci et al. [1]	5	Male	Turkey	*C. albicans*	3	Fever to 39°C	Not reported
17	Adler et al. [14]	9	Male	Israel	*K. pneumoniae*	4	Fever 39.5°C, distended non-tender abdomen. Pneumatosis intestinalis on abdominal X-ray, one episode of hematochesia	WBC 14,400
18	Adler et al. [14]	9	Male	Israel	*E. coli*	4	Fever 40°C, poor perfusion	WBC 29,000
19	Adler et al. [14]	0.75	Female	Israel	*K. pneumoniae*	5	Fever 39°C, lethargy	WBC 8720
20	Cicchetti et al. [25]	18	Male	Italy	*Pantea agglomerans*	3?	High fever, irritability, seizures, shock, DIC	Not reported

WBC = white blood cells, CRP = C-reactive protein, GI = gastrointestinal, ESBL = extended-spectrum beta-lactamase

diarrhea, of which 632 children had initial positive rotavirus antigen in stool. Two of these cases of rotavirus were shown to have co-infection with Salmonella and were thus excluded from our current series. Two of the remaining cases (0.32%) developed gram-negative rod septicemia.

CASE REPORTS

Patient 1 was a 16 month old male presenting with 3 days of emesis and non-bloody diarrhea. He was born at term and his past medical history was unremarkable. He was noted on examination to have mild to moderate dehydration. His initial leukocyte count, blood chemistry and C-reactive protein levels were all within normal limits. His initial stool sample at admission was positive for the rotavirus antigen. Stool culture was negative for pathogenic bacteria. During the initial days of hospitalization the patient seemed clinically improved on intravenous fluid therapy. On the third day of hospitalization, he was noted to have a new fever of 40.8°C and chills; he subsequently had a prolonged febrile seizure. Laboratory tests demonstrated leukopenia of 2600 cells/μl. CRP peaked at 174 mg/L. Intravenous ceftriaxone was started due to presumed bacterial infection. During that day, he developed thrombocytopenia and diffuse intravascular coagulation. Blood culture taken on that day grew *Klebsiella pnuemoniae* resistant to cephalosporins. After completing 10 days of treatment with

CRP = C-reactive protein

meropenem and amikacin, and 14 days after presentation, he was discharged home in good health.

Patient 2 was a 10 month old female who presented with 3 days of watery stool, emesis, and fever reaching 39.2°C. She was born at term and her past medical history was unremarkable. She was noted on physical examination to be moderately to severely dehydrated. Initial laboratory tests were remarkable for a leukocyte count of 14,000 cells/µl, CRP 8.4 mg/L and bicarbonate level 14 mEq/L. Stool was positive for rotavirus antigen. Fever and emesis resolved with intravenous fluid therapy, but the diarrhea continued. On day 5 of hospitalization, she developed fever reaching 39.2°C and chills. Leukocyte count at onset of septicemia was elevated to 17,100 cells/µl but CRP at 7.24 mg/L was lower than at admission. The patient was given intravenous ceftriaxone and she defervesced within 24 hours. Blood culture grew Acinetobacter species resistant to ampicillin, amoxicillin-clavulanate, cefonicid and ceftriaxone. Gentamicin completed the antibiotic course. After 10 days of antibiotic therapy, on the 17th day of hospitalization, the patient was discharged home in good health.

DISCUSSION

We describe two infants with rotavirus gastroenteritis who developed gram-negative sepsis. We reviewed the medical literature and identified a total of 18 pediatric cases of laboratory-proven septicemia that developed during rotavirus gastroenteritis [Table 1]. This phenomenon is exceedingly rare; the prevalence in our study was 0.32% over 11 years, which compares with the prevalence rates of 0.22% and 0.35% in two other retrospective studies covering 9 and 2 years, respectively [12,15]. In a prospective study over a 2 year period that drew blood cultures from children hospitalized with severe rotavirus who had persistent or recurrent fever, 3.8% of the study population had bacteremia and/or candidemia [1]. Since rotavirus infection can present with only non-specific symptoms such as fever, headache and nausea, the true incidence of rotavirus infection in the community is difficult to quantify, though one recent study conducted over a 3 year period in England estimated the prevalence rate of rotavirus infection presenting with non-specific symptoms in children under 2 years of age to be almost one-third, and in children under 5 years of age to be 24% [16]. Another limitation inherent to the retrospective nature of our study was the limitation on testing: blood cultures were not obtained in all cases of fever that occurred during hospitalization, and not all diarrheal stools were tested for rotavirus on admission. However, our figures should assess the prevalence of septicemia in children hospitalized with rotavirus gastroenteritis. Superinfection likely remains underdiagnosed because many pediatricians do not obtain blood cultures in the recrudescence of fever in a child with rotavirus gastroenteritis. Indeed, patient 2 in the series of Lowenthal et al. [13] developed bacteremia with concurrent rotavirus that resolved without antibiotic treatment. This supports the possibility that increased surveillance might increase the reported prevalence of this rare complication.

Ciftçi et al. [1], in explaining why the incidence calculated over a 2 year period in Turkey was higher than that reported elsewhere, suggest that a more virulent strain might be implicated [1]. The rotavirus exists in several different strains with geographic preference: while serotypes G1 through G4 and G9 account for 95% of rotavirus infections worldwide, G1 accounts for 70% of infections in North America, Australia and Europe, but 20–30% in South America, Asia and Africa. In contrast, G9 has the highest rates in South America and Australia [17]. However, the 20 cases of bacterial superinfection following rotavirus infection were reported from only a handful of countries: Japan, Brazil, Israel, Spain, Turkey and Italy. Although it is feasible that cases of bacterial superinfection after rotavirus would occur in countries with higher rates of malnutrition, these six countries all enjoy a relatively high standard of living. Aside from Japan, these are all warm-weather countries, hinting at a possible geographic limitation to this rare complication. In fact, we are not aware of a single case of septicemia following rotavirus infection in the United States.

In addition, regional and/or ethnic variation may provide diversity in an intestinal bacterial milieu, with possible consequences on the predisposition of children to develop septicemia from occult bacteremia. This was described for Klebsiella bacteremia, with Bedouin children having more than twice the rate of Klebsiella bacteremia than Jewish children [18]. It remains unclear whether certain strains of rotavirus create a milieu favorable for translocation of enteric gram-negative rods, or whether geographic or ethnic factors predispose patients to superinfection.

Although it is thought that translocation of enteric flora across intestinal epithelium damaged by rotavirus puts a patient at risk for secondary septicemia [13], how septicemia develops from rotavirus infection is not fully understood. While rotavirus has been shown to cause intestinal epithelial metaplasia and dysfunction, and rotavirus-infected enterocytes are more vulnerable to bacterial invasion [19], rotavirus has never been shown to cause substantial destruction of enterocytes or mucosal inflammation [14]. In 18 of the 20 cases the age of the children ranged between several weeks (indeed, the rotavirus itself is thought to be involved in a large percentage of necrotizing entercolitis in neonates) [17] and 18 months, with only two patients above 3 years of age. It is presumed that immaturity of the intestinal barrier predisposes young infants to bacterial translocation [13], and this age distribution appears to be a factor.

Early identification of a child developing bacterial superinfection after rotavirus, as in any case of sepsis, is of the utmost importance. The typical course for cases of bacterial superinfection involves a second peak of high fever. Other clinical signs are variable and range from fever alone to signs of sepsis. Presentation of symptoms can appear from the third day of illness to over a week, and patients do not seem to present with a markedly elevated leukocyte count or inflammatory markers at the onset of septicemia. Signs of colitis are rare, with only one patient presenting with gastrointestinal hemorrhage and one patient with abdominal pain.

One of the patients in our series developed DIC. Although DIC has been presumed to be a complication of rotavirus itself [20], in this case it was attributed to septicemia which underscores the importance of vigilance and early detection. Kashiwagi et al. [21] describe a case of nosocomially acquired rotavirus gastroenteritis that did not survive the septicemia, emphasizing the importance of infection control in hospitalized patients. Mel and colleagues [22] reported a patient with recurrent hospitalizations requiring multiple courses of broad-spectrum antibiotics that likely resulted in intestinal colonization of the extended-spectrum beta-lactamase-producing *Escherichia coli* that later caused her septicemia. Thus, judicious antibiotic treatment is also highlighted.

Other questions remain to be answered: why is secondary bacteremia so rarely encountered, and given the high burden of rotavirus infection, are there any protective factors that prevent the development of septicemia in rotavirus infection? Is breastfeeding protective against septicemia as it is against rotavirus infection? Rotavirus infections peak during a given time of year, which can vary by location [17]. Is there a seasonality to septicemia after rotavirus infection?

This study demonstrates the importance of obtaining blood cultures in a child with a rotavirus infection and a second fever spike. It supports vaccination as well as preventing unnecessary hospital admissions, limiting antibiotic use, and maintaining impeccable hygiene in the inpatient setting in order to prevent nosocomial rotavirus infection. Further studies are warranted to uncover the pathogenic mechanism of septicemia in rotavirus infection and to identify specific risk factors for these sequelae.

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DIC = diffuse intravascular coagulation

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