SUBSTANTIAL MORBIDITY FOR HOSPITALIZED CHILDREN WITH COMMUNITY ACQUIRED ROTAVIRUS INFECTIONS

2005–2007 IMPACT SURVEILLANCE IN CANADIAN HOSPITALS

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Abstract: We describe community-acquired rotavirus illness in 1359 children hospitalized at 12 centers in Canada between January 2005 and December 2007. The median age was 1.5 years. Almost half (48.6%) had significant dehydration, almost one-fifth (19%) had clinical sepsis and 7% had seizures at presentation. The median hospital stay was 3.4 days. Severe clinical presentations are less commonly described in surveillance programs.

Key Words: rotavirus infections, hospitalizations, children, morbidity from rotavirus infections, pediatric hospital surveillance

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Despite its effect on parents, outpatient visits, and hospital admissions, rotavirus diarrhea in developed countries is generally accepted as a common, relatively benign infection.[1–3] As such, testing is not routinely performed in outpatient settings and since rotavirus is not a reportable disease provincially or nationally, the burden of disease in Canada is unknown.

Currently, there are 2 licensed live attenuated rotavirus vaccines available for purchase in Canada: a human-bovine reassortant vaccine (RotaTeq; Merck and Co, Inc) licensed in August 2006 and a G1P[8] human rotavirus vaccine (Rotarix; GlaxoSmithKline Biologicals) licensed in July 2007. Publicly funded rotavirus immunization programs do not yet exist in Canada. In 2006 and 2007, 3339 and 38,878 doses respectively of RotaTeq were sold for a birth cohort of 722,481 for both years (available at: http://cansim2.statcan.ca/cgi-win/cnsmcgi.pgm), whereas Rotarix was not sold until after 2007 in Canada (personal communication Merck and Co. Inc and GlaxoSmithKline Biologicals). Clinical trials for both vaccines have demonstrated efficacy of 85% or greater against severe disease.[4,5]

The aim of this 3-year surveillance study was to examine the epidemiology of illness associated with rotavirus hospital admissions and to describe the morbidity associated with infection.

METHODS

Active, metropolitan area surveillance for hospital admissions related to infection with rotavirus was conducted by the 12 centers of the Canadian Immunization Monitoring Program, Active (IMPACT). This network of pediatric centers accounts for approximately 90% of the pediatric tertiary care beds in the country, with referrals from all provinces and territories.[6]

The nurse monitor at each center identified all laboratory-confirmed rotavirus cases admitted to the IMPACT hospitals between January 1, 2005 and December 31, 2007 in children 0 to 16 years of age. All centers used the same case finding strategies, case definition, and report form. Identification of rotavirus gastroenteritis was based on laboratory diagnosis and clinical symptoms of acute gastrointestinal infection. Cases were identified on a prospective basis, while the chart abstraction occurred after discharge. Medical records searches were also used regularly to identify any missed cases of diarrhea or viral gastroenteritis using the following ICD10 codes: A08 (viral and other intestinal infections), A09 (diarrhea and gastroenteritis of infectious origin), K52.9 (noninfectious gastroenteritis), R11 (nausea and vomiting), and R15 (fecal incontinence). Any identified cases were then cross checked for a laboratory diagnosis of rotavirus and cases with a laboratory positive rotavirus diagnosis were included.

The following information was retrieved from the medical record: demographic data, underlying illnesses or immune compromising conditions, details concerning diagnosis, health care utilization, and outcome. The determination of dehydration or dehydration complications was based on health record notes.

All hospital acquired cases were excluded from this analysis. SAS version 9.1.3 (SAS Institute, Cary, NC) was used for all analyses. Continuous variables were tested with analysis of variance, categorical variables were tested with Fisher exact test and χ^2 tests when appropriate.

RESULTS

A total of 1359 children were hospitalized with laboratory-confirmed, community-acquired rotavirus gastroenteritis at the 12 IMPACT centers over the 3-year period. Seasonal distributions of admissions by age group are shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A477. More than 90% of cases occurred between December and May. The majority of cases (43% [234/537]) in 2005, 42% [173/413] in 2006 and, 49% [199/409] in 2007) occurred in March and April.

Yearly totals and characteristics of the cases are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A478. The majority of cases (63%) occurred in children <2 years. The age distribution was as follows: 129 (9.5%) <3 months, 99 (7.3%) 4 to 6 months, 195 (14.3%) 7 to 11 months, and 431 (31.7%) 12 to 23 months of age. The mean age was 2.4 years while the median age was 1.5 years. This did not differ over the 3 years of surveillance ($P = 0.7$).

Healthy children constituted 61% of admissions, whereas an additional 7% were considered healthy, but had a concurrent acute infection. Among others, the most common underlying health conditions are shown in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A478. Gastrointestinal disorders were responsible for more than 25% of underlying conditions, Crohn's disease (n = 22), and gastroesophageal reflux disorder (n = 19) being most frequent. Older children (10–16 years) were significantly more likely to have underlying health conditions compared with younger children ($P < 0.0001$). None of the 1321 cases whose vaccination status was known had been vaccinated against rotavirus.

Laboratory Detection. Rotavirus was most commonly detected using antigen detection enzyme immunoassays (1034 cases, 76.1%) followed by electron microscopy (245 cases, 18.0%) or both (79 cases, 5.8%). One case (0.1%) was detected by polymerase chain reaction.

Clinical Manifestations. Table 1 describes the clinical manifestations of infection. Vomiting/diarrhea, dehydration, and suspected sepsis were the most frequent presentations among admitted cases. Prior to admission, 1210 (89%) had diarrhea, 1225 (90%) had vomiting, and 923 (69%) had fever. Bloody diarrhea occurred most often in children 10 to 16 years of age (40%, 20/50) all of whom had underlying gastrointestinal conditions. Children <2 years were significantly more likely to present with a clinical picture suggestive of sepsis (22.1%) compared with children between 2 and 16 years (13.7%) ($P < 0.001$) with 50% of children 0 to 3 months of age presenting with sepsis-like picture, a rate significantly higher than among children 4 to 23 months of age ($P < 0.001$). Otherwise, there were no differences in clinical manifestations according to age.

Health Care Utilization and Outcome. Of available data for 1357 children, 191 (14%) had had at least 1 prior outpatient visit elsewhere. Including the emergency room visit that led to the current admission, 897 (68.5%) had 1 visit, 359 (26.4%) had 2, 54 (4%), had 3, and 14 children (1%) had 4 visits to the emergency department. The average length of stay in emergency was 7.9 hours (range: 0–41 hours) with a median of 7 hours. The mean duration of hospital stay was 3.4 days with a median of 3 days (Table 1). A total of 4555 hospital days were used for more than 3 years (1782, 1474, and 1299 days each year). In total, 48 children (3.5%) required intensive care for a mean duration of 2.4 days.

Among 835 children who were healthy and 97 who were healthy with concurrent infections, 49% (460/932) received antimicrobials on admission while 59% (252/427) who had underlying health conditions or who were premature (but otherwise healthy) did ($P = 0.07$).

There were no deaths during the study period from rotavirus infection; all children recovered from infection and were discharged. Over the 3 years of surveillance, 2% (n = 27) were readmitted to hospital within 14 days of hospital discharge and of these 48% (13/27) had an underlying illness.

DISCUSSION

This report describes the first national surveillance for pediatric rotavirus hospitalizations in Canada. The span of surveillance provides evidence of substantial burden of disease and morbidity associated with community-acquired rotavirus and provides some evidence that this infection consumes significant resources, even in tertiary care institutions. Yearly, in these institutions, 1300 to 1800 hospital days are used for treatment of admitted cases with community-acquired rotavirus infection. Consistent with other countries in the developed world, children <2 years represented the majority of children hospitalized in the 3-year period with community acquired disease.[1,2,7] Assuming at least 85% efficacy of vaccine in infants, vaccination could have prevented approximately 726 admissions and a median of 2178 hospital days over the course of the 3 years in the these 12 institutions in children under 2 years. The length of stay including the stay in the emergency department was just under 4 days per case, in keeping with prior North American and European reports.[1,2,7,8]

As in other northern climates, the rotavirus season over the 3-year period lasted from 20 to 26 weeks or between December and April during each year. Although previously similar in the United States, their rotavirus season has been delayed and shortened with the introduction of rotavirus vaccine.[9] Compared with Switzerland, where 19% were noted to have upper airway infections at admission, 7% of healthy children in our study had concomitant infections.[10] Prevention of rotavirus illness especially during respiratory viral season would not only decrease comorbidity inherent in dual infections but would favorably effect the health care system during peak respiratory viral season.

This 3-year study consistently demonstrated that about one-third of patients hospitalized had significant underlying illnesses. Other similar studies have shown that 13% to 22% of hospitalized patients had underlying conditions.[8,10,11] The presence of older children in this cohort is likely due to the provision of secondary

TABLE 1. Clinical Manifestations and Course of Hospitalized Rotavirus Cases, 2005–2007

Manifestations	Year 2005 N = 537 N (%)	Year 2006 N = 413 N (%)	Year 2007 N = 409 N (%)	Total N = 1359 N (%)
Vomiting/diarrhea without significant dehydration	293 (54.6)	202 (48.9)	146 (35.7)	641 (47.2)
Dehydration	226 (42.1)	195 (47.2)	239 (58.4)	660 (48.6)
Hypotension	23 (4.3)	19 (4.6)	18 (4.4)	60 (4.4)
Sepsis	101 (18.8)	81 (19.6)	76 (18.6)	258 (19)
Seizure	32 (6)	24 (5.8)	39 (9.5)	95 (7)
Bloody diarrhea	25 (4.7)	18 (4.4)	23 (5.6)	66 (4.9)
Other manifestations*	27 (5)	37 (9)	44 (10.8)	108 (7.9)
Mean, median duration of diarrhea prior to admission (min, max)	2.3, 2 (0, 14)	2.5, 2 (0, 21)	2.3, 2 (0, 14)	2.4, 2 (0, 21)
Mean, median duration of vomiting prior to admission (min, max)	2.2, 2 (0, 14)	2.4, 2 (0, 21)	2.2, 2 (0, 12)	2.3, 2 (0, 21)
Mean, median duration of fever prior to admission (min, max) (N = 1350)	1.4, 1 (0, 11)	1.5, 1 (0, 13)	1.5, 1 (0, 17)	1.5, 1 (0, 17)
ICU	17 (3.2%)	17 (4.1%)	14 (3.4%)	48 (3.5%)
Mean, median duration of stay in ICU (min, max)	2.3, 2 (1, 9)	2.5, 2 (1, 8)	2.3, 1 (1, 7)	2.4, 2 (1, 9)
ICU underlying condition	8 (47.1%)	12 (70.6%)	9 (64.3%)	29 (60.4%)
If underlying condition, mean, median duration of stay in ICU (min, max)	2.8, 1.5 (1, 9)	2.4, 2 (1, 8)	2.9, 2 (1, 7)	2.7, 2 (1, 9)
Mean, median duration of hospital stay (min, max)	3.3, 3 (1, 26)	3.6, 3 (1, 46)	3.2, 2 (1, 23)	3.4, 3 (1, 46)

*Altered level of consciousness (41), hematemesis (15), rash (21), cardiac arrest (2), intestinal perforation (1), hepatitis (3), neutropenia or anemia (9), acute renal failure (13), worsening of underlying disease (4), acute hepatic failure (1), elevated lipase (1), and concomitant bacteremia (1) (4 children presented with more than one other clinically significant manifestation).

and tertiary care at sites within the network but may also indicate a particularly vulnerable population who are more likely to be hospitalized when ill. Although universal vaccination would initially effect infants, once significant herd immunity is reached, it is expected that transmission to older or more vulnerable groups would decrease.

Despite its pedigree of benignity in developed countries, our data highlighted the morbidity of rotavirus infection (19% of children presented with signs and/or symptoms suggestive of sepsis, 8% presented with other serious manifestations, and 7% with seizures).[7,10] Rotavirus vaccine also has the potential to decrease these less common manifestations that are associated with greater morbidity.

This study has several limitations. The surveillance is not population based and some of the hospitals preferentially manage healthy children as outpatients or at other primary care institutions in the area, thus biasing the cohort to children with underlying diseases or more severe illness. The strength of these data, however, rests with a network that uses standardized data collection, case ascertainment is comprehensive, covers several years and is national in scope allowing for capture of less common presentations.

Universal vaccination programs for rotavirus have potential to decrease disease severity, hospitalization rates, and length of the rotavirus season in Canada.[12]

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