Nosocomial Rotavirus Gastroenteritis in Spain

A Multicenter Prospective Study

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Background: The objective of this study was to assess the incidence of nosocomial rotavirus gastroenteritis among children <2 years of age.

Methods: We conducted a prospective active surveillance for acute gastroenteritis (AGE) in the pediatric wards of 3 representative hospitals in Valencia (Spain) from October 2006 to March 2007, among children between 1 and 23 months of age with acute diarrhea. Children were followed up for 3 days after discharge. We obtained clinical and demographic information from participants and tested their stool specimens for rotavirus.

Results: A total of 1576 children were hospitalized at the 3 hospitals and 1300 (82.5%) were followed up as the study cohort. In 69 children, AGE started 48 hours after admission and were considered nosocomial infections. In 35 of the 59 cases where stool samples were obtained, rotavirus (RV) was present (59%), and in 12 of them symptoms started after discharge. The accumulated incidence of nosocomial rotavirus disease during the study period was 2.8 cases per 100 inpatients (95% CI: 1.9–3.8), and the incidence rate was 4.8 cases per 1000 hospital days (95% CI: 3.2–6.5). The most commonly found genotype in nosocomial infection was G9P[8], in 23 cases (66%), followed by G1P[8] in 4 cases (11%). The total economic cost was €883 per case.

Conclusion: Active surveillance demonstrated that the burden of nosocomial rotavirus disease is substantial, and G9P [8] was the genotype found most frequently. Following up children after discharge from hospital allowed the discovery of cases of nosocomial RVAGE which are missed in most other studies.

Key Words: rotavirus, epidemiology, cross infection, gastroenteritis, Spain

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Rotavirus (RV) is the main cause of acute gastroenteritis (AGE) in infants and young children. The incidence of hospital acquired RVAGE is 0.3% to 27.7% of all hospital admissions[1] and represents between 5% to 51% of all RV AGE hospitalizations in children under 5 years old in Europe.[2] Sixty to eighty percent of the cases occur in children between 1 and 23 months of age.[2,3]

The high frequency of hospitalizations for gastroenteritis makes the transmission of rotavirus easier, reinforcing the prevalence of this virus as the leading cause of healthcare acquired diarrhea in pediatric patients.[4,5] Rotavirus infection acquired in the hospital is doubly responsible for a significant economic burden by both prolonging the affected child's hospital stay and by contributing to the further transmission of RV disease from one hospitalized child to another.[6,7]

Very few studies have focused on rotavirus nosocomial gastroenteritis, and most of them have been carried out retrospectively.[4]

The variability in the methodologies, countries, and study periods of different published studies shows the need to carry out more prospective multicenter studies in our country to determine the actual burden of nosocomial rotavirus AGE and the health and economic impact that it could represent.

The aim of this study is to assess burden, clinical, and molecular characteristics and the economic costs of rotavirus nosocomial gastroenteritis in Spain.

PARTICIPANTS AND METHODS

Study Design

For the present project we designed an epidemiologic, observational, multicenter prospective study.

Three hospitals in Valencia (Spain), representing the 3 different levels of care, were identified as investigation sites Hospital Lluís Alcanyís of Játiva (basic, primary hospital), Hospital Dr. Peset (secondary hospital), and Hospital La Fe (tertiary hospital). Hospitals are classified according to the complexity and severity of the cases they handle, which is important to keep in mind, as each level is characterized by inherent variations (number of complex surgical proceedings, subspecialties, intensive care units, and other peculiarities).

Additionally, a centralized national reference laboratory was involved for viral analysis of the study samples: Viral Gastroenteritis Unit, National Center for Microbiology, Instituto de Salud Carlos III, Madrid, Spain.

Study Population

The target population for this study included all children between 1 and 23 months of age hospitalized in the pediatric wards of the 3 participant hospitals during the study period (from October 2, 2006 to March 31, 2007). Children aged less than 1 month were not considered because they are usually admitted to neonatal ward.

The study population was observed by the investigators from the time of hospital admission until 72 hours after hospital discharge to identify the presence of AGE. Follow-up after hospitalization was performed by phone calls to the caretakers of all discharged patients. Three phone call attempts were made from the

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fourth day after discharge to request parents' information on any AGE symptoms developed by the child. If any symptom was present, they were asked to return to the hospital, preferably with a stool sample.

Case Definitions

Acute Gastroenteritis Case

At least 2 loose stools per day or 1 watery stool per day. Cases of chronic diarrhea (persisting for >2 weeks), primary gastrointestinal diseases, or intoxication were excluded from this definition.[8]

Nosocomial Gastroenteritis Case

An AGE was considered to be hospital-acquired when symptoms started between 48 hours after admission and 72 hours after discharge.[9]

Rotavirus Gastroenteritis

The AGE was identified as rotavirus positive when the centralized laboratory provided a positive rotavirus result by RT-PCR VP6 determination (see viral determination section).

Data Collection

The study protocol was reviewed and approved by the Ethics Committee of Lluís Alcanyís Hospital of Játiva and reported to the Ethics Committees of the other participant hospitals, and at least one of the parents of all participating children signed an informed consent for stool sample collection and supply of the rest of the data needed for the study.

In each case, demographic data, including age and gender, were collected by a written questionnaire. Disease characteristics were documented: occurrence and duration of diarrhea, vomiting and fever (>38°C, or 100.4°F rectal), stool characteristics such as the presence of blood or mucus, maximum frequency of diarrhea, and/or vomiting per day, maximum temperature; occurrence and duration of irritability, apathy, seizure, severity of dehydration, and weight loss. Other data relating to recent hospitalization, causes of primary hospitalization, treatment with oral or intravenous fluids and drugs, and parental work absenteeism were also collected.

A 24-point numerical score was used for the clinical severity assessment of the cases.[10] In this score, cases were classified as mild (1–8 points), moderate (9–16 points) and severe (17–24 points).

Data on the total number of admissions and the total duration of hospital stays were obtained from the hospital administration.

Stool Sampling and Laboratory Methods

The stool specimen was obtained by the parents, pediatricians, or research personnel within 48 hours and no more than 14 days after the onset of symptoms, and it was stored at −20°C (−4°F) in each hospital. Samples were periodically sent for analysis to the centralized laboratory.

Determinations performed in the stool samples included a preliminary ELISA test for RV (a microplate-based solid-phase sandwich enzyme immunoassay: IDEIA Rotavirus; Dako Diagnostics, Cambridge, United Kingdom). Positive rotavirus samples were directly genotyped and negative ones were analyzed through RT-PCR for VP6 determination. If a positive VP6 result was obtained, this sample was genotyped and classified as RV positive. Genotyping was focused on group A rotavirus G types (VP7) and P types (VP4) and was carried out using a previously described procedure.[11]

Statistical Analysis

Absolute frequencies and percentages were used to describe qualitative variables. Average, standard deviation, median, 25th percentile, 75th percentile, and minimum and maximum values were used to describe quantitative variables. To compare different groups, the Student t test was used for continuous normal variables, the Mann-Whitney U test for continuous nonparametric variables, and the χ^2 test or Fisher was employed for discreet variables. The significance level was 5% with a confidence interval of 95%. All data were entered twice and reviewed. Statistical analysis was performed with SPSS (version 12.0) (available at: www.spss.com).

The incidence of nosocomial AGE and the nosocomial rotavirus AGE was calculated as follows:

Accumulated incidence = nosocomial AGE cases divided by the total of exposed tracked patients (total tracked patients minus community-acquired AGE cases).

Incidence rate = nosocomial AGE cases divided by days of exposed patients' hospital stay (length of hospital stay for children without AGE + length of hospital stay for children with nosocomial AGE before appearance of AGE symptoms).

Economic Costs

The analysis of direct economic cost was estimated from the average duration of patients' hospital stay due to rotavirus AGE, considering €477.8 to be the daily average cost of pediatric hospitalization in the Valencia region (DOCV 5670, of December 31, 2007. Available at: https://www.docv.gva.es/portal/pages/buscar.jsp). We used the average stay for children admitted for bronchiolitis caused by respiratory syncytial virus (RSV) as a control (5.8 days).[12]

Indirect economic cost was estimated from the hours of work missed by the parents.

For this calculation, we used the average of the salary cost estimated in the fourth quarter of 2006[13] and the first quarter of 2007[14] by the Spanish National Institute of Statistics (10.65 euros per effective hour of work for the Valencia Region).

RESULTS

During the study period, 1576 children were hospitalized in the pediatric wards of the 3 participant hospitals; of these, the condition of 1300 children was fully monitored (82.5%), and this group was considered the study cohort.

A total of 242 children met the AGE case definition (18.6% of the cohort), 217 stool samples were obtained from those children with AGE (89.7%), and rotavirus was positive in 102 cases (47%; 95% CI: 40.1–53.9). Community-acquired AGE was considered in 173 children, and 158 stool samples were obtained. Of these, 67 were rotavirus-positive (42.4%; 95% CI: 34.4–50.4). Nosocomial AGE was observed in 69 children, and 59 stool samples were obtained. Of these, 35 were rotavirus-positive (59.3%; 95% CI: 45.94–72.70).

Therefore, of the 69 nosocomial AGE, 30 began to show symptoms after discharge and were diagnosed by telephone interview. Seven of these patients presented AGE symptoms within 24 hours after discharge, 22 on the second day, and only 1 on the third day following discharge. Stool samples were obtained in 20 cases (3 the first day, 16 the second day, and 1 the third day) resulting in positive diagnosis of rotavirus infection in 12 cases (1RV + on the first day, 10 RV + on the second day, and 1 RV + on the third day), which represents 34.3% (95% CI: 17.1%–51.4%) of the total nosocomial rotavirus AGE.

The accumulated incidence of nosocomial acquired gastroenteritis during the study period was 6.1 (95% CI: 4.7–7.6) cases per 100 inpatients, and for nosocomial rotavirus acquired gastro-

enteritis, the accumulated incidence was 2.8 (95% CI: 1.9–3.8) cases per 100 inpatients.

The incidence rate for nosocomial acquired gastroenteritis was 1.05 cases (95% CI: 0.80–1.3) per 100 hospital days and for nosocomial rotavirus acquired gastroenteritis, it was 0.48 (95% CI: 0.32–0.65) cases per 100 hospital days.

Twenty percent (7 of 35) of the children with nosocomial rotavirus AGE were between 1 and 3 months of age, 20% (7 of 35) between 4 and 6 months of age, and 60% (21 of 35) between 6 and 23 months of age. Nosocomial rotavirus AGE was mild in 37% of the cases and moderate in 63%. None was classified as severe. The average duration of diarrhea was 4.8 (range: 2–8) days with a median maximum frequency of diarrhea of 6 (range: 2–15) stools per day. Mucus was present in 46% of the stool samples, and there was no blood in any of the stool samples. Vomiting was present in 51% of nosocomial rotavirus AGE and the median duration was 3 (range: 1–9) days with an average of 3.4 (range: 1–6) episodes of vomiting per day. Fever was present in 59% of the cases with a median duration of 3 (range: 1–10) days; the average maximum temperature per day was 39.6°C or 103.3°F (range: 38.9°C–40.4°C, 102°F–104.7°F). Irritability was present in 6% of the patients and apathy in 11%. Febrile seizure occurred in 3 children. Twenty-four percent of the patients lost weight and in up to 26% of the AGE cases rehydration was given intravenously with a medium duration of 3 days (range: 2–6). Sixty-nine percent of nosocomial rotavirus AGE were treated with antibiotics (mainly amoxicillin-clavulanic, cefuroxime, ceftriaxone, and trimetoprime-sulfametoxazol).

The causes of hospitalization in children who developed nosocomial rotavirus AGE were mainly respiratory diseases (51.4%), including pneumonia, bronchiolitis, bronchitis, and asthma; followed by nephrourological diseases in (14.3%), including acute pyelonephritis, infections of the urinary tract, and nephrosis. Seizures were present in 8.6% of the cases.

Around 70% of all rotavirus AGE cases were observed in December and January with virtually no differences between community and nosocomial rotavirus AGE.

The genotype found most often in nosocomial RVAGE was G9P[8] (66%), followed by G1P [8] in 11%. There was 1 case of mixed infection with G1 and G9. Other genotypes and undetermined genotypes in community and nosocomial RVAGE are shown in Table 1. There were no differences between community and nosocomial rotavirus types ($P = 0.100$).

TABLE 1. G/P Genotypes in Rotavirus AGE in Hospitalized Children in Valencia, Spain, 2006–2007

Genotype	Community Acquired		Nosocomial Acquired		Total of AGE	
	N	%	N	%	N	%
G1P[8]	8	11.9	3	8.6	11	10.8
G2P[4]	1	1.5	2	5.7	3	2.9
G3P[8]	4	6.0	0	0	4	3.9
G9P[8]	47	70.1	22	62.9	69	67.6
G2P[8]	1	1.5	0	0	1	1.0
G3P[4]	0	0	1	2.9	1	1.0
G1 + G9P[8]	3	4.5	1	2.9	4	3.9
G3 + G12P[8]	0	0	1	2.9	1	1.0
G9PNT	1	1.5	0	0	1	1.0
GNTP[8]	0	0	1	2.9	1	1.0
GNTPNT	2	3.0	4	11.4	6	5.9
Total	67	100	35	100	102	100

NT indicates nontypeable.

Direct Economic Cost

We calculated the prolongation of a hospital stay due to nosocomial rotavirus AGE as 1.7 days. This is based on the fact that hospitalization due to RSV illness lasts, on average, 5.8 days,[12] and the average hospital stay in patients with rotavirus nosocomial AGE is 7.5 ± 3.7 days, so the direct cost is €812.20 per case of rotavirus, or €28,428 for the 35 cases of rotavirus observed.

Indirect Cost

The average number of hours of work missed by parents was 6.6 hours per case (range: 0–48). The indirect cost was €70.29 per case and for the 35 cases, the total indirect economic expense was €2460.15.

The total economic costs of nosocomial rotavirus AGE, then, is €882.49/case and €30,888.15 in total.

DISCUSSION

This was a multicenter and prospective study, with a complete 72-hour follow-up of 82.5% of the children 1 to 23 months old after discharge. The results might be underestimated for different reasons: first, we lacked stools from 11.3% of symptomatic children, and second, we only monitored children with diarrhea, even though up to 7% of asymptomatic children can be infected.[15]

The differences observed in the rotavirus nosocomial AGE incidence in the literature can be attributed to several factors,[1] mainly the variability in the methodology used.

Differences include the ranges of age studied, the population type, the definition of AGE, and the criteria of nosocomial AGE. Other differences include the distribution of beds in the pediatric units, in prevention measures adopted in each hospital and country, and in the duration of the study and study period as well as in the identification (or lack thereof) of asymptomatic carriers. Some differences might even be explained by epidemiologic patterns.

The definition of nosocomial AGE is not consistent in the literature, varying from 1 day,[16–18] 2 days,[8,9,19–21] and 3 days.[15,22–24] If we recognized nosocomial AGE only by the onset of symptoms after 72 hours of hospitalization, a third of the cases would not be diagnosed.[18] The most lenient criterion (nosocomial after 24 hours of admission) is also problematic because up to 14.2% community-acquired AGEs could be mistakenly labeled as nosocomial. AGE cases emerging after discharge began on the same day or up to 2 days later, and only in 1 case did it occur on the third day. Therefore a definition of nosocomial rotavirus AGE that includes the cases that begin after 48 hours of admission and up to 48 hours after discharge would also be a reasonable approach.

Among all AGE cases detected in hospitalized children under 2 years of age, 47% were caused by rotavirus. This information is comparable to other studies carried out in Spain and elsewhere.[2,3,25–27]

Of all rotavirus AGE cases analyzed, 34.3% (35 of 102) were nosocomial. There is a very wide range of estimation published from 5% to 87%.[1,2,6] In Spain, the estimates vary between 20% to 57%.[15,28–30] However, the high proportion of nosocomial AGE caused by rotavirus is notable since they account for 59.3% (35/59) of all nosocomial AGE. These high estimates are consistent with those previously published studies.[8,15]

The fact that 34.3% (12 of 35) of the cases of rotavirus nosocomial AGE take place after hospital discharge must be emphasized; it is consistent with the literature which asserts that it can represent up to a third of all rotavirus nosocomial AGE,[9,15,31]

justifying the follow-up of the children after discharge in this type of study.

The accumulated incidence of rotavirus nosocomial AGE found here (2.8 cases/100 hospitalized) was in the range of most of the published studies[1,2,6]; however Marc et al[32]reported an accumulated incidence of 13.6% and an incidence rate of 22 cases/1000 days of hospital stay in children under 2 years of age. This is despite the lack of follow-up after discharge. The setting of the study was in 4 units comprised mainly of breast-fed babies in individual rooms. There were differences that could explain the results: the study period spanned November to February in 4 successive years, whereas the present study includes 2 more months (October and March) in which the appearance of cases is scarce. Another explanation might be the differences between the Spanish and French healthcare system's criteria of hospitalization as well as variations in the international impact of rotavirus disease.

In Spain, the previously reported incidence was 3.5%[26] to 5%.[15] This higher incidence in the latter study occurred despite a lower proportion of telephone follow-up after discharge (69%), stricter criteria of nosocomial AGE (from 72 hours. after admission up to 72 hours. after discharge), and a 1-year study period. This suggests the existence of variability in rotavirus incidence and severity of cases in the studied years. However, the most likely reason is the bed distribution in wards. While in our 3 hospitals, the maximum number of beds per room was 3, the number of beds per room in the Madrid area was 6 during the study period (E. Román, personal communication, 2007).

The most frequent genotype found was G9P[8] followed by G1P[8]. This is in accordance with recent studies in Spain and in Europe.[33] In Spain, genotype G9 was first detected in the 1998–1999 season as the third G genotype found with high frequency.[34] Before 2005, the most common genotype causing rotavirus AGE was G1,[35,36] but in that year, G9 emerged as the most frequently observed strain.[11]

G12P[8] was associated with the genotype G3. Though this was observed in only 1% of the cases in the current study, it is worth bearing in mind given that in 2005 in Hungary, G12 represented 6.9% of the genotypes found in hospitalized children, suggesting the appearance of a previously undetected genotype.[37]

G2P[4] was found in a lower proportion (3%) as in another Portuguese study[38] (68,6%) carried out in the same period of time.

There is a small number of specimens (1 G2P[8], 1 G3P[4], a total of 2%) which are candidates for having emerged as natural reassortants. This number is in excellent agreement with the percentage of natural reassortants found in a study with a much larger number of specimens.[39]

A small number of apparently mixed infections are prerequisites for natural reassortment events and serve as proof that they could have occurred.

In approximately 8% of the specimens, either the G type or the P type or both could not be determined under the standard conditions used.[11] Attention should be drawn to these isolates as potentially containing genotypes that do not normally circulate in humans but were possibly transmitted from an animal source.

The genotype distribution in nosocomial infections was similar to that of the community acquired AGE, suggesting that rotavirus nosocomial AGE takes place due to the continuous introduction of rotavirus genotypes into the hospital from the community.[4,6,33,40,41]

Our estimation of the nosocomial AGEs direct cost of €812 per case is very conservative and was calculated based on the estimated prolongation of hospital stay. Published costs are difficult to compare as they depend on the methodology used and also on the cost of the Health System.

It is difficult to precisely assess how long rotavirus acquired AGE prolongs the hospital stay. As most of the nosocomial rotavirus AGE occurred in children with bronchiolitis,[12] we calculated the prolongation of the stay based on the average hospitalization calculated for that disease (other approximations have been described in the literature with a wide range of days (1.7–7).[1,2,8,15] Our cost analysis is similar to the €600 per case estimated in direct hospitalization cost by Harrington et al in Ireland,[42] but it differs from the €1900 per case estimated by Piednoir et al,[21] who calculated the prolongation of the hospital stay to be 5 days. The value obtained in the current study is probably underestimated, since not all the children entered with the same pathology. However, it also is important to note that patients with serious pathologies needing a long hospital stay present a higher risk of acquiring the nosocomial infection.[43]

If we add the direct and indirect costs together, €883 is the total cost per case on a nosocomial level. Gleizes et al calculation of total cost is much higher, averaging €2500 per case, with a range of €135 in Poland to €2602 in Austria.[1] The distinct methodologies, study periods, age ranges, healthcare costs, hospital policies, labor costs, and different variables included in the study impede the comparison of studies.

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