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Mathie Lorrot, Fabienne Bon, M. J. El Hajje, Serge Aho ...+8 more authors





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Epidemiology and clinical features of gastroenteritis in hospitalized children. Prospective survey during a two-year period in a Parisian hospital, France

Mathie Lorrot, MD, PhD ^{1,3*}, Fabienne Bon, PhD², Marie-Joëlle. El-Hajje, MD ³, Serge Aho, MD², Marjorie Wolfer, MD³, Hélène Giraudon, BS², Jérôme Kaplon, BS², Elisabeth Marc, MD, ^{3,4}, Josette Raymond, MD⁵, Pierre Lebon, MD, PhD⁵, Pierre Pothier, MD, PhD², Dominique Gendrel, MD³.

Service de Pédiatrie, Faculté de Médecine Paris VII, CHU Robert Debré, Paris¹; Laboratoire de Virologie, CNR des Virus Entériques, CHU de Dijon, Dijon², Service de Pédiatrie, Faculté de Médecine Paris V, CHU Cochin-Saint Vincent de Paul, Paris³; Service des Urgences Pédiatriques, Faculté de Médecine Paris XI, CHU Bicêtre, Le Kremlin-Bicêtre ⁴; Laboratoire de Microbiologie, Faculté de Médecine Paris V, CHU Cochin-Saint Vincent de Paul, Paris⁵; France.

*Corresponding author :

Dr Mathie Lorrot, Service de Pédiatrie Générale du Pr Faye, Faculté de Médecine Paris VII, Hôpital Robert Debré, Boulevard Sérurier, 75019 Paris-France.

Phone : 33 1 40 03 53 61

Fax : 33 1 40 03 47 45

E-mail: mathie.lorrot@rdb.aphp.fr

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Abbreviated title: Clinical severity of gastroenteritis in hospitalized children

Running head: Viral gastroenteritis severity in children

Abstract

Purpose:

Rotavirus is recognized as the most important agent of severe acute gastroenteritis in young children. In a two-year prospective survey, we investigated the epidemiology and clinical features of the viral and bacterial pathogens in children hospitalized for acute gastroenteritis.

Methods:

The study was performed in a Parisian teaching hospital from November 2001 to May 2004. Clinical data were prospectively collected to assess the gastroenteritis severity (20-point Vesikari severity score, the need for intravenous rehydration, duration of hospitalization). Stools were systematically tested for group A rotavirus, norovirus, astrovirus and adenovirus 40/41, sapovirus and Aichi virus and enteropathogenic bacteria.

Results:

457 children (mean age 15.9 months) were enrolled. Viruses were detected in 305 cases (66.7%) and bacteria in 31 cases (6.8%). Rotaviruses were the most frequent pathogen (48.8%) followed by noroviruses (8.3%) and adenoviruses, astroviruses, Aichi viruses and sapoviruses respectively in 3.5%, 1.5%, 0.9% and 0.4%. Cases of rotavirus gastroenteritis were significantly more severe than those of norovirus with respect to the Vesikari score, duration of hospitalization and the need for intravenous rehydration.

Conclusion:

Rotaviruses were the most frequent and most severe cause in children hospitalized for acute gastroenteritis, noroviruses also account for a large number of cases in this population.

Acute gastroenteritis (AGE) is one of the most common diseases in humans, and continues to be a cause of high morbidity and mortality in children worldwide. Children under 5 years of age are particularly prone, and it is calculated that, in this group, there are more than 700 million cases of acute diarrhoea every year [1]. Worldwide estimates indicate a mean of between 3.5 and 7 episodes of diarrhoea during the first 2 years of life, and over 11 000 deaths per day throughout the world, particularly in developing countries [2]. In developed countries, deaths from diarrhoea are less common, but AGE is a major cause of morbidity in childhood, leading to many hospitalizations and doctor's visits [3-5].

Much of the gastroenteritis in children is caused by viruses. Group A rotaviruses are the leading cause of severe acute gastroenteritis in infants and children throughout the world, causing an estimated 500,000 - 600,000 deaths each year. All children are infected by the age of 2-3 years and the first infection can usually be associated with acute diarrhoea, which can be severe. Other viral agents of AGE are enteric adenoviruses, caliciviruses and astroviruses. With the improvements in molecular methods of viral diagnosis over the past decade, the role of noroviruses in the etiology of childhood diarrhoea is increasingly recognized. In contrast, the role of Aichi viruses, which belong to the picornavirus family, is not well known [6, 7].

To date, there are few data available about the enteric viruses and bacteria in circulation in France. The prevalence and diversity of the four major viruses (rotaviruses, caliciviruses, astroviruses and adenoviruses) are documented for gastroenteritis in children consulting a physician or a hospital emergency service [8-10]. In contrast, their role in community-acquired severe AGE requiring hospitalization have rarely been investigated [11]. The first study of hospitalized gastroenteritis conducted in Saint Vincent de Paul children's hospital (Paris) from January 1997 to December 2000 reported that 50.89% of 725 children hospitalized for AGE were infected with rotavirus. The role of other viral pathogens was not investigated [12].

We have conducted a prospective study to determine the viral and bacterial etiology of AGE in children hospitalized for AGE. In collaboration with the National Reference Center (NRC) of enteric viruses based in Dijon, we systematically searched for viral pathogens (rotavirus, norovirus, sapovirus, astrovirus, enteric adenovirus and Aichi virus) using sensitive molecular methods. Bacterial pathogens (*Salmonella*, *Shigella* and *Campylobacter* spp.) were also systematically screened for. We investigated the clinical pattern of the disease in these

children and the severity of the episodes of AGE. This study provides precise data on the frequency and the severity of bacterial and viral pathogens among children hospitalized for AGE in a Parisian paediatric hospital during a 2-year period.

Patients and methods.

Population, clinical definitions and specimen collection.

The study was carried out in the Parisian teaching hospital Cochin- Saint Vincent de Paul, which is situated at the south of Paris and provides easy access to appropriate medical care. At this hospital, there are a mean of 23,000 consultations for all causes in children every year; 15 to 20 % of the consultations for diarrhoea lead to hospitalization [12].

After its approval by the Ethics Committee of the Cochin-Paris V Faculty of medicine, the study was prospectively performed between November 2001 and May 2004 and included all children between 0 months and 15 years of age hospitalized with acute diarrhoea. Acute diarrhoea was defined as at least 3 looser-than normal stools within a 24-h period. All admissions to the hospital were based on clinical examinations at the request of the hospital emergency team. Patients with chronic diarrhoea (> 10 days) were excluded. For each child, clinical data including, age, sex and admission date were prospectively collected at inclusion. Each episode was graded using the 20-point severity score scale [13, 14]. Furthermore, the occurrence of bloody diarrhoea, the use of intravenous rehydration and the length of hospitalization were documented. Stool samples were systematically collected to screen for etiologic agents of diarrhoea. Bacteria (*Salmonella*, *Shigella* and *Campylobacter* spp.) were detected by routine cultivation in the Bacteriology Laboratory of the Saint Vincent de Paul Hospital. After collection, the samples were stored frozen (- 20°C) at the Virology Laboratory. The stools were sent together to the enteric viruses NRC (Dijon), for viral investigation.

Laboratory methods.

The presence of pathogenic bacteria was determined by routine culture assays on selective media. Stool samples were screened for the presence of group A rotaviruses, adenovirus types 40 and 41 and astroviruses by commercial enzyme immunoassay (EIA) kits (respectively: Biomérieux, France; Oxoid Ltd, UK; Meridian Diagnostics Inc, USA). All positive samples

were confirmed and characterized by molecular biology methods (PCR or RT-PCR). Noroviruses, sapoviruses and Aichi virus were detected by RT-PCR.

Nucleic acids were extracted from 20% stool suspensions in phosphate-buffered saline with a QIA Amp viral RNA kit (Qiagen, Hilden, Germany). The Rotavirus RT-PCR used the primer sets Beg9/End9 [15] and Con2/Con3 [16], The astrovirus RT-PCR used the primers Mon 244 and Mon 245 [17] and the adenovirus PCR used the primers Hex1DEG/Hex2DEG [18]. The norovirus and sapovirus RT-PCR used primer sets in separate reactions. The primer sets SR80/NVP110 [19] and JV12/JV13 [20] were used to amplify a fragment of the RNA polymerase gene of sapoviruses and noroviruses, respectively. The primer sets G1SKF/G1SKR and G2SKF/G2SKR [21] were used to amplify a fragment of the capsid gene of genogroup I and II noroviruses, respectively. The Aichi virus RT-PCR used the primers Ai6261/6779 targeting the RNA polymerase gene [22].

Genotyping of norovirus, sapovirus, astrovirus and Aichi virus was performed by direct sequencing of the PCR products using the ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction Kit and an automated sequencer (model 373A DNA sequencing system, Applied Biosystems).

Statistical methods.

Statistical analysis was performed with the Mann-Whitney U test, which was used to compare the medians of clinical symptoms scores in associated rotavirus and norovirus cases. For comparison of proportions, chi-square or Fisher's exact test was used. All tests were two-tailed and considered significant when the P value was ≤ 0.05 .

Results

Study population and general screening.

A total of 552 children were hospitalized for gastroenteritis between November 2001 and May 2004. Clinical data and stool samples were obtained from 457 (82.8%) children. The mean age of these children was 15.9 months (standard deviation, 22.13; range, 0.2 -156 months) and the median was 9.25 months. The sex ratio was 1.26. The mean Vesikari score was 11.7 (standard deviation, 3.16; range, 4-19). Among the 95 sets of data rejected in this study, 13 were rejected for the lack of clinical data and 82 for the absence of a faecal sample. Comparison of the data of patients at the time of enrolment showed that there was no

significant difference between the data (mean age, sex ratio and Vesikari score) of included and excluded cases ($p > 0.05$, Mann-Whitney U-test), (data not shown).

Laboratory investigations detected at least one pathogen (virus and/or bacteria) in 330 stool samples (72.2%) of the 457. Viral pathogens were detected in 305 (66.7%) samples, and bacterial pathogens in 31 (6.8%) samples.

Among the viruses, group A rotaviruses were detected in 240 samples (223 in single infections, 17 in mixed infection) and the most prevalent G type were G1 (114 isolates, 47.5%), G4 (38 isolates, 15.8%), G3 (38 isolates, 15.8%), G9 (6 isolates, 2.5%) and G2 (6 isolates, 2.5%). The P[8] type was by far the most frequent accounting for 233 rotaviruses strains (97 % of rotaviruses strains). The second most frequent group of viruses was norovirus with 55 isolates (38 in single infections and 17 in mixed infections). Molecular characterization showed that genogroup II (GGII) strains were clearly predominant with 50 isolates (90.9%) including 28 GGII.4 (50.9%), 18 GGIIb (32.7%), 3 GGII.2 (5.5%) and 1 GGII.7 (1.8%). The remaining 5 noroviruses belonged to the GGI (genotypes 1, 2, 4 and 6). The other viruses were less frequently detected: enteric adenoviruses were detected in 16 samples, (3.5%), astrovirus in 7 (1.5%), Aichi in 4 samples (0.9%) and sapovirus in 2 samples (0.4%). Bacterial pathogens were 13 *Campylobacter*, 14 non typhi *Salmonella*, 5 *Shigella*.

Single pathogen infections were responsible for 307 cases of gastroenteritis, most of which were viral agents (283 samples versus 25 samples (24: 1 bacterium; 1: 2 bacteria) for bacteria). Among these, rotaviruses were responsible for 223 cases (48.8%) and noroviruses for 38 cases (8.3%). The other enteric viruses were adenovirus type 40/41, astrovirus, Aichi virus and sapovirus respectively in 16, 3, 2 and 1 cases. Single bacterial pathogens were found in 24 cases (12 *Campylobacter*, 9 non typhi *Salmonella sp.*, 3 *Shigella*).

Mixed infections were detected in 23 samples and mainly involved combinations of viruses (16 samples) especially rotavirus and norovirus. Dual infections with rotavirus and norovirus were detected in 10 samples, with norovirus and astrovirus or sapovirus in 1 sample, with rotavirus and astrovirus or Aichi virus in 1 sample. Triple infections with norovirus, rotavirus and astrovirus were detected in 2 samples. Mixed infections involving viruses and bacteria were detected in 6 samples: non typhi *Salmonella* was associated with rotavirus in 2 samples, with norovirus in 1 sample and with norovirus-rotavirus in 1 sample; *Campylobacter* was

associated with norovirus and *Shigella* with Aichi virus in 1 sample. There was only one dual bacterial infection, which associated *Salmonella* and *Shigella* (Table 1).

Monthly distribution.

The peak of the gastroenteritis epidemic was due to rotavirus and was observed during the winter months, the highest peak occurred in January. Interestingly, a second lower peak of rotavirus incidence was observed in September. Rotaviruses continued to be detected in the interepidemic season but, during these 2 years of surveillance, rotaviruses were not detected in June

Norovirus AGE have a seasonal pattern similar to that of rotavirus AGE with a main peak observed in January and a second peak in September (Figure 1). No consistent seasonal pattern was observed for enteric adenovirus, astrovirus and bacterial AGE.

Etiology of hospitalized AGE in relation to age of the children.

The proportion of the pathogens detected among children in different age groups is presented in Table 1.

Most hospitalizations for AGE were reported in children less than 2 years of age (385 children, 84.2%). In these children, 267 (69.3%) had a viral etiology: rotavirus and norovirus were detected in 210 (54.5%) and 47 (12.2%) stool samples, respectively; a single bacterial etiology was identified in 14 stool samples (3.6%) and mixed bacterial and viral infections in 5 stool samples (1.3%). In 99 cases of AGE (25.7%), no acknowledged pathogen was identified.

One hundred and seventy-seven hospitalized children (38.7%) were less than 6 months of age. In these children, 97 (54.8%) had a viral etiology: rotavirus and norovirus were detected in 77 (42.4%) and 15 (8.5%) stool samples respectively. Single bacterial etiology was identified in 8 stool samples (4.5%) and mixed bacterial and viral infections in 2 stool samples (1.1%). In 67 cases of AGE (37.8%), no acknowledged pathogen was identified.

Clinical severity criteria in children hospitalized for rotavirus or norovirus AGE.

The clinical severity of the disease was analyzed in children infected by a single virus (rotavirus or norovirus). The 223 children infected with rotavirus and the 38 children infected with norovirus were similar in terms of age and sex ratio ($p > 0.05$, Mann-Whitney U-test). The mean age was 13.65 months (median: 9 months) for rotavirus infections versus 14.9

months (median: 9.5 months) for norovirus infections. The sex ratio was 1.27 for rotavirus infections versus 1.23 for norovirus infections.

The correlation between the severity of the AGE (severity score, intravenous rehydration, length of hospitalization) and the virus (rotavirus and norovirus) is reported in table 2.

Rotavirus AGE were more severe in infants above 6 months than in infants from 0 to 6 months ($p < 0.0001$). Rotavirus AGE were significantly more severe than norovirus AGE with respect to the Vesikari score (12.6 versus 10.47, $p < 0.001$), the duration of the hospitalizations (3.2 days versus 1.85, $p < 0.001$) and the requirement for intravenous rehydration (77.13% versus 55.26%, $p = 0.005$). This contrast was more marked in children above 6 months ($p < 0.007$ for severity score and $p < 0.001$ for the length of hospitalization and $p = 0.03$ for the need for intravenous rehydration).

These differences in severity according to age were not observed in norovirus gastroenteritis.

DISCUSSION

This is the first prospective study to provide data for cause-specific hospitalizations due to community acquired gastroenteritis in children in France. This study was conducted from November 2001 to May 2004 in a Parisian paediatric hospital, but these results are still relevant today. The management of acute gastroenteritis is currently the same with use of an oral rehydration solution and/or intravenous fluid replacement; the trends of hospitalization should continue to show the same pattern. The two rotavirus vaccines (RotaTeq and Rotarix) were licensed in France in 2006, but rotavirus vaccination is not included in the French official recommendations for childhood immunizations, and vaccine coverage is still very low, less than 10 percent.

Our results show that group A rotavirus caused more than 50 % of the total hospitalizations for gastroenteritis per year in a paediatric unit in Paris (France) and was the leading cause of severe diarrhoea in young children. In addition, they highlight the role of norovirus in France as the second viral etiologic agent causing 12% of hospitalizations for AGE in children. In contrast, the other enteric viruses including adenovirus type 40 and 41, astrovirus, sapovirus and Aichi virus were a minor cause of hospitalization for childhood gastroenteritis. Altogether, our results show that viruses are by far the most frequent etiology in children hospitalized for gastroenteritis (66.7%), whereas a bacterial etiology was found in 6.8% of cases, and the etiology of 27.8% of the AGE was not elucidated.

Previous studies underlined the importance of viruses in children hospitalized for gastroenteritis especially in developed countries [23, 24]. However, few studies have investigated prospectively the relative contributions of the different enteric viruses and bacteria in children admitted to hospital for gastroenteritis in developed countries. In accordance with our results, studies conducted in other developed countries in hospitalized children found a large predominance of viruses (56 to 70%) versus bacteria (4 to 17%) [25, 26]. A large retrospective study conducted in Australia found the same ratio between viral and bacterial etiologies in children [27]. In contradiction with these studies, Boga et al [28] in a study conducted in Asturias found bacteria and viruses with a similar frequency, *Campylobacter jejuni* and *Salmonella* spp were respectively the second and third main cause of gastroenteritis in children. Among the bacterial etiologies, we also found a large predominance of *C. jejuni* and *Salmonella* spp, but, on the whole, bacteria were a minor cause of hospitalization for diarrhoea in children.

Among the viruses, rotaviruses were by far the main cause of gastroenteritis in hospitalized children, far ahead of noroviruses, which were found in 8-15% of children hospitalized for gastroenteritis [8, 25, 29-31]. These studies and our results contrast with other sentinel studies conducted by physicians in the general population [5, 7, 10], in which the incidence of norovirus ranged from 10 to 20%. This is close to and in some cases even higher than the incidence of rotavirus infections [10]. One possible explanation of the relatively higher incidence of norovirus is that these sentinel studies highlight the diagnosis of mild infections, whereas more severe cases of gastroenteritis are admitted to the emergency department of the hospital.

Sequence typing of the rotavirus strains showed that the main type was G1;P[8] (47.5%) followed by the two other conventional types: G3;P[8] (15.8%) and G4;P[8] (15.8%) whereas the G9;P[8] type was seldom detected (2.5%). This pattern of genotype distribution with the low prevalence of the G9 type was close to that reported in our previous works since 1995 [8, 10], but considerably different from that we reported during the 2004/2005 season following the present study. In this latter season, G9;P[8] emerged as by far the major genotype (54.7%) whereas G1;P[8] was very rarely detected [32].

Among noroviruses, there was a clear predominance of genogroup II, and especially the GGII.4 genotype, which is currently reported in adult gastroenteritis outbreaks [33]. Norovirus genotype GII.4 has also been reported as the main norovirus genotype in sporadic cases of gastroenteritis in children [9, 25, 28]. In accordance with these previous reports, our results show that norovirus GGII.4 was predominantly detected in the faeces of children. GGII.4 norovirus was observed throughout the study with a peak during the winter of 2002/2003. It is important to note that this peak corresponded to an increase in gastroenteritis outbreaks throughout Europe caused by a new variant (HU/NoV/Farmington Hill/2002/USA, accession number AY502023)[34, 35]. The second most frequent norovirus genotype found in this study was GGII.b. Several studies have reported this genotype as a cause of sporadic and outbreak cases of gastroenteritis in children, and some of these studies suggested that GGII.b was closely associated with infections in children [36-40]. In this study, the highest rates of GGII.b detection were observed in January-February 2002 and the fall and winter of 2003-2004. These periods coincide with GGII.b adult outbreaks in France [41]. So, the rate of detection of GGII.b and GGII.4 norovirus strains identified in children are similar to those circulating in the adult population in the same period. These results and more recent data (data

not shown) do not support the hypothesis that one of these strains could play a predominant role in children.

The severity of norovirus and rotavirus gastroenteritis excluded mixed infections and was evaluated on three criteria, the severity score defined by Vesikari [13], the need for intravenous rehydration and the length of the hospitalization. In the population of children studied, norovirus infections were significantly less severe than rotavirus infections. The literature concerning symptom severity in norovirus and rotavirus gastroenteritis is heterogeneous [42]. A number of previous studies found lower levels of disease severity in norovirus than in rotavirus gastroenteritis, and most of these were carried out in developed countries [7, 43-47]. In contrast, other studies found no significant differences between the severity of rotavirus and norovirus infections [48-51]. One such study was conducted by us in Tunisia, and we attributed the severity of the norovirus infection to a lack of medical care at home and the delay to hospitalization for children infected with norovirus. This could also be the case for the studies conducted in countries with poor sanitation and hygiene.

In conclusion, these results highlight the main role of rotavirus in hospitalized gastroenteritis among French children less than 2 years of age. During the study until the end of the 2003-2004 winter season the G1;P[8] genotype was widespread while G9;P[8] remained rare. A majority of severe rotavirus gastroenteritis requiring hospitalization may be prevented by the widespread use of rotavirus vaccines [52-54]. Noroviruses are the second leading causative agent of gastroenteritis in hospitalized young children and such infections are less severe than those caused by rotavirus. The norovirus genotype pattern in children shows a clear predominance of genotype GII.4 followed by genotype GGIIb. This pattern reflects the norovirus genotypes in circulation within the population rather than a predominance of particular genotypes in children.

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Table 1: Etiology of gastroenteritis in 457 hospitalized children in relation to age.

	Age (months)					Total
	0-6	>6-12	>12-24	>24-60	>60-180	
Rotavirus	77 (43.5%)	63 (59.4%)	59 (57.8%)	22 (44.9%)	4 (17.4%)	223 (48.8%)
Norovirus	15 (8.5%)	10 (9.4%)	8 (7.8%)	3 (6.1%)	2 (8.7%)	38 (8.3%)
Adenovirus	6	5	5	0	0	16 (3.50)
Astrovirus	1	2	0	0	0	3
Aïchivirus	0	0	1	0	1	2
Sapovirus	0	0	1	0	0	1
Bacteria	8	2 ^a	4	6	5	25 ^a (5.4%)
Virus + Bacteria	2 ^{b; c}	0	3 ^{d; e}	1 ^f	0	6
Virus + virus	3 ^{g; h; i}	9 ^{j; k; l; m}	4	0	0	16 (3.5%)
NPI*	67 (37.8 %)	15 (14.1 %)	17 (16.7 %)	17 (34.7 %)	11 (47.8 %)	127 (27.8 %)
Total	177 (38.7%)	106 (23.2%)	102 (22.32%)	49 (10.72%)	23 (5.03%)	457

Values are numbers of cases, with percentages in parentheses.

* NPI: No acknowledged enteric pathogens.

a : 1 Salmonella + shigella
b : 1 Salmonella + norovirus
c : 1 campylobacter + norovirus
d : 1 Salmonella + norovirus + rotavirus
e : 2 Salmonella + rotavirus
f : 1 Shigella + Aichi virus
g : 1 norovirus + astrovirus
h : 1 norovirus + rotavirus
i : 1 norovirus + rotavirus
j : 2 norovirus + rotavirus + astrovirus
k : 1 rotavirus + Aichi virus
l : 1 rotavirus + astrovirus
m : 5 norovirus + rotavirus

Table 2: Clinical features according the etiologic agent (rotavirus or norovirus, mixed infections excluded) related to the age of the children with gastroenteritis.

Age	0-6 months (177)			6-24 months (208)			> 24 months (72)		
	Rotavirus (75)	Norovirus (15)	<i>p value</i>	Rotavirus (122)	Norovirus (18)	<i>p value</i>	Rotavirus (26)	Norovirus (5)	<i>p value</i>
Severity score, 1-20 points: mean value (+/-sd)	11.1 ^a (+/-2.89)	9.93 ^b (+/-2.46)	NS	13.48 ^a (+/-2.54)	11.39 ^b (+/-3.05)	$p < 0.002$	12.88 ^a (+/-2.94)	8.8 ^b (+/-2.28)	$p = 0.008$
Length of hospitalization in days (+/-sd)	3.26 (+/-1.84)	2.17 (+/-1.06)	$p = 0.0293$	2.90 (+/-1.39)	1.78 (+/-1.06)	$p = 0.0013$	2.85 (+/-1.26)	1.2 (+/-0.45)	$p = 0.0001$
Intravenous rehydration (%)	40 (53.3%)	5 (33.33%)	NS	107 (87.7%)	12 (66.67%)	$p = 0.031$	25 (96.1%)	4 (80%)	NS
Bloody stools (%)	0	0		3 (2.46%)	2 (11.11%)		1 (3.8%)	0 (0%)	

NS= Not significant

- a) Rotavirus severity score: 0-6 months versus 6-24 months ($p < 0.0001$) or >24 months ($p = 0.008$).
- b) Norovirus severity score: p not significant for all age groups.

Figure 1: Monthly distribution of viruses in children hospitalized for gastroenteritis (January 2002- May 2004)

