

## ORIGINAL ARTICLE

# Epidemiology and burden of Rotavirus-associated hospitalizations in Ferrara, Italy

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## Key words

Rotavirus • Hospitalization • Epidemiology

## Summary

*Objective of this study was to provide data on hospitalizations for rotavirus gastroenteritis (RVGE) in Ferrara, Italy.*

*The study was conducted analyzing the hospital discharge forms of all children admitted to the Pediatric Department of the University of Ferrara, Arcispedale Sant'Anna, from January 2001 through December 2005. The database was searched for all gastrointestinal diseases and in particular RVGE.*

*During the period under study 3277 children, of which 2038 < 60 months of age, were hospitalized; 247 children < 5 years old were admitted for acute gastroenteritis and 89 (4.4% of all and 36% of*

*gastroenteritis-related hospitalizations) had rapid screening tests positive for rotavirus. A seasonal pattern was observed for RVGE with an increase in winter and early spring. The average length of hospital stay was 5.7 days. The median cost of each hospitalized case of RVGE ranged between 1417 and 1595 €.*

*The present research confirms that rotavirus gastroenteritis represents an important cause of hospitalization in children and is responsible for significant costs for the Public Health Care System. An effective vaccination program could significantly reduce the incidence of hospitalization and the associated costs.*

## Introduction

Rotavirus represents the main cause of acute gastroenteritis (GE) in children worldwide [1, 2]. Virtually every child will be infected by Rotavirus before age 3-5, some of them more than once in this period of time [1].

Clinically, the infection can vary from the asymptomatic form to the severe one with dehydration, which, if not adequately treated, can be fatal. In comparison to other viruses, Rotaviruses (RV), usually, determine a more severe diarrhea, often associated to dehydration; nevertheless, there is no way of foreseeing the gravity and the evolution of the disease [1, 3]. RV are endemic in both developing and industrialized countries, and their transmission is independent from social-economic and hygienic-sanitary conditions [1].

Globally, it is estimated that every year RV are responsible for over 125 million cases of acute GE in children and 600,000 deaths, which mostly (82%) occur in developing countries [2, 4]. In industrialized countries, the possibility to access to equipped healthcare centers and consequently receive adequate treatments correlates to a low mortality (about 231 deaths/year in Europe) and a higher hospitalization incidence rate [4].

In Europe it is estimated that every year 3.6 million cases of rotavirus gastroenteritis (RVGE), 87,000 hospitalization and more than 700,000 clinic visits occur, on a total of 23.6 million children under 5 years of age [5]. Epidemiological studies in Italy indicate that RV are responsible on the average for 26% of hospital admissions in children [6, 7].

Considering that RV are also an important cause of nosocomial infections in children and health care workers, RVGE represent a considerable problem for public health care systems with a significant impact, even in economical terms (direct and indirect costs), on society and families [8].

Two new live attenuated oral vaccines are available on the world market. Considering the microbiological characteristics of RV, these vaccines represent the most effective system to prevent moderate/severe forms of RVGE and, therefore, to contain the associated costs.

The purpose of this study was to provide data on hospitalization of children with acute gastrointestinal diseases, in particular Rotavirus gastroenteritis, in Ferrara, Italy.

## Materials and methods

The study was conducted in the Pediatric Department of the University of Ferrara, Arcispedale Sant'Anna, Italy; this Institute has 12 beds and covers a population of 20,933 children and adolescents between 0 and 18 years of age, of which 6,759 under 60 months.

In this retrospective study we analyzed the hospital discharge forms (SDO) of all children between 0-18 years old admitted to the Pediatric Department from January 2001 through December 2005.

Hospital discharge forms represent an important instrument, which provides information about every patient discharged from all public and private hospitals nationwide; they are filled out by the physicians who

had the patient in care and contain information regarding clinical (diagnosis, relevant symptoms, surgery, diagnostic and therapeutic procedures, prosthetic implants, discharge status) and organizational aspects of the hospitalization (hospital division of admission and discharge, transfers to other wards, expected source of payment). The hospital discharge forms are then coded and transmitted to the Regions and from these to the National Ministry of Health [9].

Hospitalization records for gastrointestinal diseases were selected. The hospital database was searched to investigate all intestinal infections, using ICD codes: cholera (ICD 001), typhoid and paratyphoid fever (ICD 002), other salmonella infections (ICD 003), shigellosis (ICD 004), other food poisonings (ICD 005), amebiasis (ICD 006), other protozoal intestinal diseases (ICD 007), bacterial intestinal infections (ICD 0080, 0081, 0082, 0083, 0084, 0085), enteritis due to specified virus (ICD 0086), intestinal infections due to other organism not classified elsewhere (ICD 0088), ill-defined intestinal infections (ICD 009). For RV enteritis the ICD code used is 00861, belonging to enteritis due to specified virus. In the same class we also searched for enteritis due to other viruses: adenovirus (ICD 00862), enterovirus NEC (Not Elsewhere Classified) (ICD 00867) and other viral enteritis (ICD 00869).

Demographic-anamnestic (particularly age and gender) and clinical data (symptoms, length of stay, diagnosis at admission, concomitant disease) were obtained anonymously for each patient.

Data were stratified by age (0-6 months, 7-12 months, 13-24 months, 25-36 months, 37-60 months, > 60 months), gender and symptoms (diarrhea and/or fever and/or vomiting and/or dehydration).

Diagnosis of rotavirus infection was confirmed in the Microbiology Laboratory through rapid immuno-chromatographic tests on stool specimens obtained in the Pediatric Department. The determination of costs related to hospitalizations was evaluated through Diagnosis Related Group (DRG) rates.

According to the DRG reimbursement system, every hospitalized patient belongs to a group of diagnostically homogeneous cases; therefore patients within each category are similar clinically and are expected to use

the same level of hospital resources. As a result patients in the same DRG group are assigned the same reimbursement charges. In case of outliers (patients with a length-of-stay superior or inferior to that individually established for every DRG), the cost-weight increases or decreases for every day more or less compared to the average length-of-stay [10].

A specific DRG for rotavirus gastroenteritis does not exist, therefore DRG 184 (esophagitis, gastroenteritis, and miscellaneous digestive disorders, age < 18) and 298 (nutritional and miscellaneous metabolic disorders, age < 18) were assigned to patients discharged from the Pediatric Department, referring to the Emilia Romagna Regional DRG reimbursement system (HCFG-DRG 19th version, 2005).

## Results

From January 2001 through December 2005, 3,277 children were admitted to the Pediatric Department, of which 2,038 < 60 months of age; 12.1% (247) of the patients had symptoms referable to a gastroenteritis. Most (53.4%) discharges for gastrointestinal disease were classified as ill-defined intestinal infections (ICD 009): infectious (ICD 0090) or presumed infectious (ICD 0091) colitis, enteritis, and gastroenteritis and infectious (ICD 0092) or presumed infectious (ICD 0093) diarrhea.

Viral enteritis represented 45.7% of admissions for gastrointestinal disease, while only 0.9% were due to other organisms.

Rotaviruses were responsible for 78.8% of viral enteritis, followed by adenovirus (16.8%), enterovirus NEC (2.7%) and other viruses (1.7%).

Considering all admissions of children from 0 to 18 years old in the period of time studied, positivity of rapid tests for rotavirus and adenovirus was obtained in 120 and 25 cases, respectively. Regarding children < 5 years old, 89 cases were found positive for rotavirus and 19 for adenovirus, which correspond to 4.4% and 0.9% of all admissions and 36% and 7.7% of admissions for acute gastroenteritis, respectively (Tab. I).

Tab. I. Admissions (< 60 months of age) to the Pediatric Department in Ferrara, 2001-2005.

Total admissions		GE-associated admissions		Rotavirus positive GE		Adenovirus positive GE		% GE-associated admissions	
		N	% total admissions	N	% total admissions	N	% total admissions	RV positive	AV positive
2001	356	51	14.3	13	3.7	1	0.3	25.5	2
2002	435	61	14	25	5.7	2	0.5	41	3.3
2003	397	19	4.8	10	2.5	3	0.8	52.6	15.8
2004	396	36	9.1	15	3.9	9	2.3	41.7	25
2005	454	80	16.5	26	5.7	4	0.9	32.5	5
Total	2038	247	12.1	89	4.4	19	0.9	36	7.7

N = number; GE = gastroenteritis; RV = rotavirus; AV = adenovirus

The annual incidence rate of hospitalization for RVGE, referred to the Pediatric Department's population, was 2.6/1000 children < 60 months of age; the estimated average cumulative incidence rate for RVGE hospitalizations was 1 in 74 children.

The number of monthly admissions was nearly constant, while admissions for acute gastroenteritis showed an increase in winter and spring and an evident reduction in summer, with the highest hospitalization rate for GE in April (29.2%) and the lowest in June (2%). RVGE hospitalizations also showed a seasonal pattern, with an increase in winter and spring (maximum peak 12.9% in April) and a decrease in summer and autumn (minimum peak 0.6% in June) (Fig. 1).

Regarding the age of the patients (Fig. 2), 74.2% (89/120) of RVGE hospitalizations involved children below 5 years old; admissions for RVGE were more frequent in males (60%). In children < 5 yrs, 34.8% (31/89) of cases occurred within the first 12 months of life and the remaining 65.2% (58/89) between 12 and 60 months.

Considering children < 60 months of age, diarrhea was present in all cases. Vomiting and fever were described in 73.7% and 62.4% of the cases, respectively. The simultaneous observation of diarrhea, vomiting and fever occurred in 63% of patients. These symptoms led to dehydration in 64% of cases. In 25% of these patients a co-morbidity was found (acute upper and lower respiratory infections, urinary tract infections, seizures, growth retardation, iron deficiency anemia, etc.).

Rotavirus gastroenteritis was responsible for about 101 days of hospitalization per year, with an average length of hospital-stay of 5.7 days. This length of stay was longer than that for adenovirus gastroenteritis (4.8 days).

Concerning the economic impact of rotaviral disease, using the Emilia Romagna Regional reimbursement charges (HCFG-DRG 19<sup>th</sup> version, 2005), the median cost for each hospitalized case of RVGE ranged from 1417.44 € (DRG 298) to 1595.05 € (DRG 184). In 2005, 1 outlier case of rotavirus disease was observed, for which the DRG 298 charge was applied with a daily increase of 218.77 € (total 1636.2 €).

Noteworthy, 31 (25.8%) cases of RVGE were observed in children and adolescents 5-16 years old, accounting for 9.5% of the hospitalizations for diarrhea in patients aged between 0 and 16 years. The median age for these cases was 8.1 years old and 96% of them presented co-morbidities.

## Discussion and conclusions

The availability of anti-rotavirus vaccines has stimulated numerous studies to determine both the epidemiological and social-economic impact of this disease. However, rotavirus infections in Italy, as in other countries, are not subject to a specific active surveillance system, thus it is difficult to obtain an accurate evaluation of the incidence of the disease.

Hospital discharge forms, even though with some limits, represent a valid instrument for the measurement of hospitalization rates and for the estimate of the incidence of a specific illness, including rotavirus gastroenteritis. In the present study it was possible to consult the database not only for the main diagnosis, which often determines underestimation of rotavirus infections, but even for the secondary ones.

This study confirms that acute gastroenteritis is an important cause of hospital admission in children < 5 years old. Researches conducted locally [6, 11, 12] and nationally [7, 13] show that rotaviruses are on the average responsible for 26% of all diarrhea-associated hospitalizations in children. In particular a recent analysis, which consulted the national hospital discharge database, found that rotaviruses are responsible for about 17% of all hospitalizations for intestinal infections and 84% of hospitalizations for viral enteritis [13]. The first percentage is significantly lower than the one registered in this (36%) and in other Italian studies [7, 14], even though the rate of cases coded as ill-defined intestinal infections was similar (54% vs 53.4%) in both researches. International active surveillance studies, conducted in hospitals, have found that rotaviruses are present in about 35-60% of stool specimens from children with diarrhea [15-18].

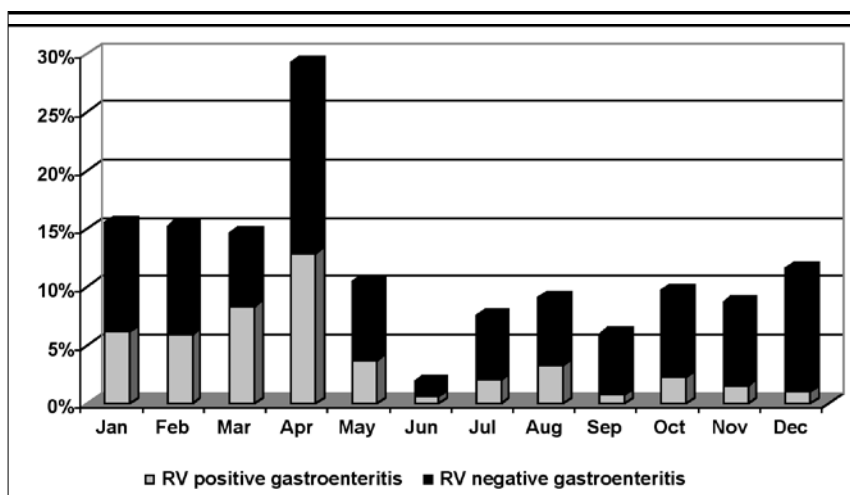
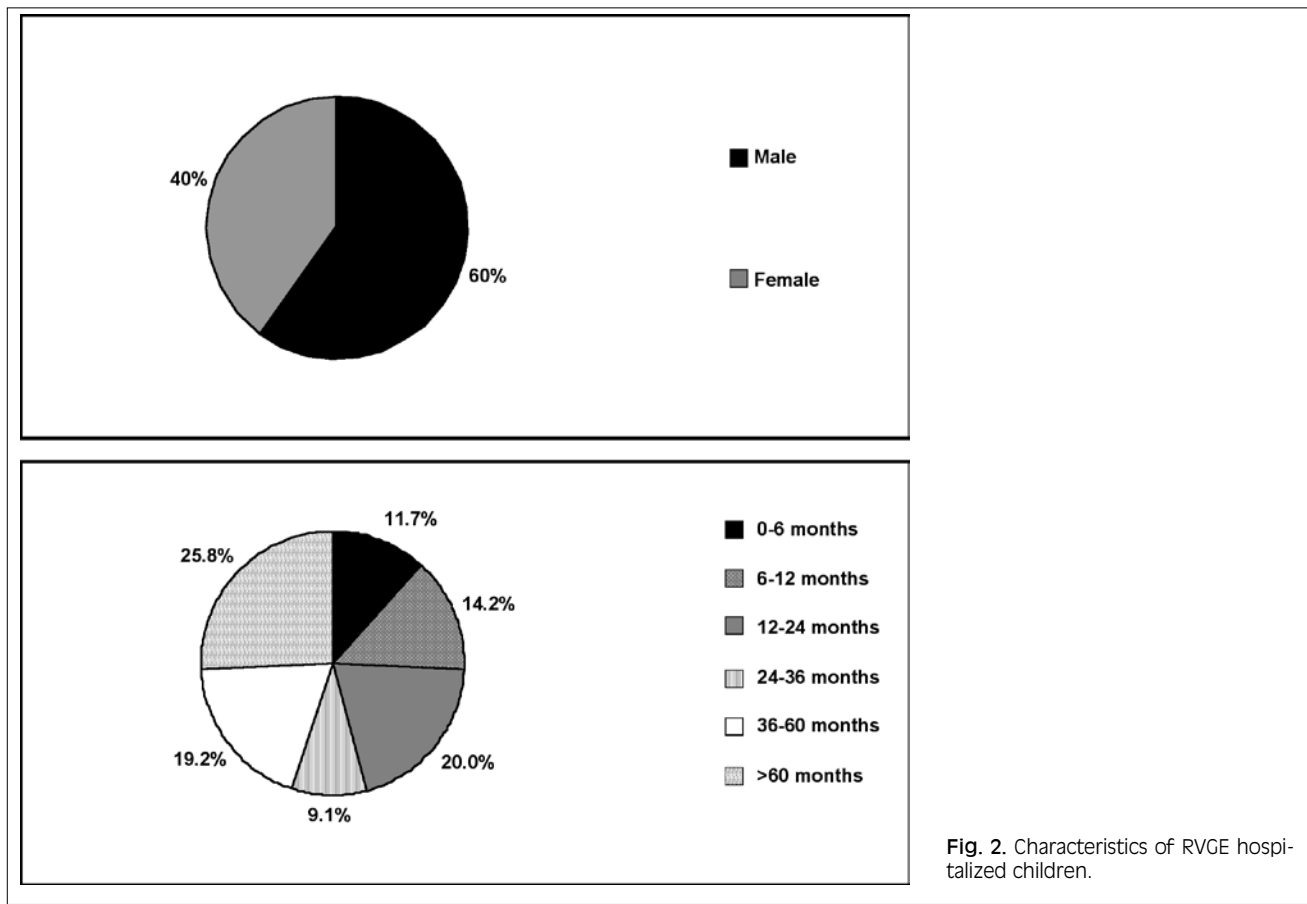


Fig. 1. Temporal pattern of GE-associated hospitalizations in the Pediatric Department of Ferrara, 2001-2005.



In the 25 countries of the European Union, a median of 40% of hospitalizations for acute gastroenteritis in children < 5 years of age are attributable to rotavirus infections. In this age group it is estimated that the median incidence rate is equal to 3/1000 children per year and that 1 child out of 67 is hospitalized for RVGE [4]. These rates are similar to the ones registered in this study (2.6/1000 and 1 in 74 children < 5 years of age, respectively).

As reported in literature [7, 19], even in Ferrara the existence of a seasonal pattern for RVGE was confirmed, with a higher incidence in winter and early spring. As described by other Authors [4, 7, 20-23], the highest incidence was found in children between 6 and 24 months of age with a prevalence in males.

Rotavirus infections have actually been described in all age groups, including adults. As in the present study, cases of RVGE have been observed by other Authors in children over 5 years old, with an incidence rate ranging from 16% to 25% [14, 24, 25].

The average length of hospital stay in Italy is 4 days [13], about 1.5 days shorter than the stay registered in Ferrara. However, analyzing the population by symptoms, we found that cases of RVGE with dehydration, vomiting and/or fever had an average length-of-stay of 4.4 days; the median length of stay rose to 7.4 days for patients with co-morbidities.

The data collected in this study refers to community-acquired infections. However, the importance of noso-

comial rotavirus infections is well known; these involve younger children (0-5 months) and determine a longer hospital stay. Even nosocomial rotavirus infections are highly seasonal, occurring mainly in winter; this coincides with the peak of other viral infections (especially respiratory infections) and contributes to overloading and overcrowding hospital wards [19, 26].

In industrialized countries, like Italy, rotavirus infections generate significant costs for health care systems, families and society. Hospitalization costs relate to hospital stay, professional services, laboratory exams and treatments [8]. In Europe the average cost of each hospitalized case ranges, according to the country, from 691 € in Poland to 1773 € in Spain (median: 1417 €) [4]. Similarly, in the present research the average cost reimbursed for each hospitalized case ranged between 1417 and 1595 €. According to a recent study, in Italy the total estimated cost of hospitalized cases ranges from 6 to 8 million €/year, bearing in mind the limit of the absence of a specific DRG for RVGE and the underestimation of the etiologically ill-defined cases [13]. To these we must add the costs for families and society of outpatient cases, which according to a recent study, could be estimated between 27 and 68 million € [27].

If the burden of RVGE is considered both in epidemiological and economic terms, as shown by the most recent data available in literature and confirmed by this study, it is understandable why the World Health

Organization emphasizes the importance of preventing this disease.

Considering the insufficient impact of the hygienic-sanitary measures usually adopted to limit diffusion of fecal-oral diseases [13, 19, 26], the development of safe and effective vaccines which prevent the moderate or severe complications of rotaviral infections, especially dehydration, is considered a priority.

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Received on July 27, 2006. Accepted on January 29, 2007.

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