Risk groups for clinical complications of norovirus infections: an outbreak investigation

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ABSTRACT

Norovirus infections have been described as self-limiting diseases of short duration. An investigation of a norovirus outbreak in a university hospital provided evidence for severe clinical features in patients with several underlying diseases. Clinical outcomes of norovirus infection were defined. Risk-factor analysis targeting underlying diseases and medication was performed using multivariate analyses. In five outbreak wards, 84 patients and 60 nurses were infected (an overall attack rate of 32% in patients, and 76% in nurses). The causative agent was the new variant Grimsby virus. Severe clinical features, including acute renal failure, arrhythmia and signs of acute graft organ rejection in renal transplant patients, were observed in seven (8.3%) patients. In multivariate analyses, cardiovascular disease (OR 17.1, 95% CI 2.17–403) and renal transplant (OR 13.0, 95% CI 1.63–281) were risk-factors for a potassium decrease of >20%. Age >65 years (OR 11.6, 95% CI 1.89–224) was a risk-factor for diarrhoea lasting >2 days. Immunosuppression (OR 5.7, 95% CI 1.78–20.1) was a risk-factor for a creatinine increase of >10%. Norovirus infections in patients with underlying conditions such as cardiovascular disease, renal transplant and immunosuppressive therapy may lead to severe consequences typified by decreased potassium levels, increased levels of C-reactive protein and creatine phosphokinase. In the elderly, norovirus infection may lead to an increased duration of diarrhoea. Therefore patients at risk should be hospitalised early and monitored frequently. Strict preventional measures should be implemented as early as possible to minimise the risk of nosocomial outbreaks.

INTRODUCTION

Norovirus (former Norwalk-like virus) infection, well-known as 'winter vomiting disease', has been described as a short self-limiting disease characterised by sudden onset of nausea, vomiting and diarrhoea. In adult volunteer studies and investigations of previously healthy individuals [1–6], clinical symptoms such as abdominal pain, nausea, vomiting, headache and chills have been reported. In many outbreak investigations, the mild self-limiting character of the illness associated with norovirus infection has been emphasised.

In 2002, unusually high numbers of norovirus infections were reported in Germany [7] and elsewhere [8,9]. Compared with 2001, the incidence of norovirus infection in Germany increased five-fold from 11 cases/100 000 population to 57 cases/100 000 population. The peak incidence was attributed to outbreaks occurring during the winter (weeks 41–53). During this period, outbreaks affected wards at a university hospital in northern Germany. The first outbreak occurred in a closed psychiatric ward in November, but the epidemic subsequently reached four other sections of the hospital, with particularly severe problems in the departments of cardiology and nephrology. This report describes the impact of norovirus infection in these settings, which was much greater than was anticipated on the basis of information published previously.

MATERIALS AND METHODS

Case definition

Between 1 November 2002 and 31 January 2003, all patients and staff members from one of the five studied outbreak wards who were affected with a sudden onset of diarrhoea (three or more episodes of loose stools in a 24-h period and/or vomiting [10]), were included as cases. Cases were considered to be norovirus-positive if samples from at least two patients from the same ward were positive by norovirus-specific RT-PCR tests. As all the included patients and staff members came from five wards, they were regarded as epidemiologically linked to each other within each ward. Patients admitted with clinical signs were regarded as index cases, and patients admitted ≥48 h before developing clinical signs were regarded as nosocomial cases.

Data collection

Data were collected prospectively during the outbreaks. The attack rate of the patients or staff members of each ward was calculated by dividing the number of cases in each group by the total number of patients or staff members potentially at risk. The population at risk was defined as all individuals working in or admitted to the ward in the period from the onset of clinical symptoms of the first patient until 2 days after the last patient became symptom-free. For the calculation of nosocomial incidence, index cases (patients) were ignored.

Staff members were interviewed and patient charts were reviewed to assess patient history (underlying disease) and clinical signs such as diarrhoea and vomiting. Data were also

collected concerning potassium, creatinine and C-reactive protein (CRP) levels, radiological examinations (abdominal X-rays), histology (renal biopsy), other invasive procedures, therapeutic measures taken (rehydration therapy, immunosuppressive therapy, use of metoclopramide and loperamide) and indicators of complications (haemodialysis, death, renal biopsy). For one patient, clinical data were not available.

Risk-factor analysis

The following potential risk-factors were analysed: age >65 years; gender; underlying disease (cardiovascular disorders, pulmonary disorders, gastroenterological disorders, autoimmune disease, malignancy, trauma, psychiatric disorder, renal disorder, renal transplant, haemodialysis); immunosuppression (steroids, methotrexate, cyclosporine A, tacrolimus, etc.); and symptomatic treatment (metoclopramide and loperamide). Nosocomial acquisition of the infection was also included in the analysis. Relapses were defined as a new period of either diarrhoea or vomiting after a symptom-free interval of ≥48 h. Three norovirus-positive patients were excluded from risk-factor analyses because they were also positive for other gastroenteric pathogens (two were positive for *Clostridium difficile* toxin; one was positive for adenovirus). Only those patients with complete data for tested outcomes were included in the analysis. Patients who were norovirus-negative were also included because norovirus was the most likely pathogen according to their epidemiological setting (in place and time) and because no other pathogens were detected despite careful diagnostic procedures. Furthermore, as most of the 'negative' stool specimens were sent to the laboratory when symptoms had already resolved, it was concluded that these patients were probably no longer shedding norovirus.

Laboratory diagnostics

Stool specimens were assayed for the presence of noroviruses by nested RT-PCR as described previously [11]. For confirmation and strain characterisation, samples were sent to the National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands. Samples were assayed for virus RNA, and PCR products were sequenced as described previously [12]. Sequences were aligned using the database of the Foodborne Viruses in Europe project [13]. In addition, all stool specimens were cultured for enteropathogenic bacteria, assayed for *C. difficile* toxin, and investigated for viral pathogens by electron-microscopy.

Statistical analysis

Categorical variables were compared using chi-square or Fisher's exact test; ORs and 95% CIs were calculated using Epi Info v.6.04c (CDC, Atlanta, GA, USA). All variables were evaluated by multiple logistic regression analysis with stepwise variable selection for inclusion in the final logistic regression model. SAS software was used for all multivariate analyses (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Epidemiology

The five wards involved in the outbreak belonged to the psychiatry, nephrology, gastroenterology, cardiology and trauma departments. In total, 84 patients met the clinical and epidemiological case definition of norovirus infection, and 72 patients acquired their infection nosocomially. Analysis of the outbreaks in each ward showed patterns characteristic of person-to-person transmission, except for the trauma ward, in which there were many cases apparent on the first day, followed by a pattern characteristic of person-to-person transmission on subsequent days. Food- or water-borne transmission were ruled out because all other unaffected wards of the hospital received food and water from the same sources. Thirteen patients were admitted with the disease from the community.

Stool specimens from 41 patients were assayed by norovirus RT-PCR. Most ($n = 27$; 66%) were positive, but 14 (34%) were negative. Each case patient from whom no stool specimen was available, or who had a negative norovirus PCR, was linked epidemiologically to confirmed cases. Four samples were referred to RIVM for confirmatory testing and sequencing. All sequences were identical, and clustered with the new variant Grimsby virus [14]. Bacterial cultures of all stool specimens failed to yield enteropathogenic bacteria. Apart from three patients who were excluded from risk-factor analysis, all other stool specimens tested were negative for *C. difficile* toxin and other viruses.

In total, 79 staff members were involved (60 nurses, 19 other staff members). The attack rate in nurses was twice as high as the attack rate in the patient group (Table 1) ($p < 0.001$). Because this was unusual, staff were interviewed to assess possible common sources of exposure. There were no meetings in or outside the clinic with the potential for common food consumption. Attack rates in other staff members could not be determined because they were responsible for several wards and therefore the denominator population was variable.

Clinical symptoms and complications

Staff members had self-limiting vomiting or diarrhoea, or both, for episodes lasting <48 h. Only one nurse required admittance to the hospital for symptomatic treatment with intravenous saline.

The main clinical feature with patients was diarrhoea, which affected 94% of patients. Only 68% of the patients developed vomiting (Table 2). The median duration of clinical symptoms was 1 day (range 1–7 days). In total, 38 (45%) patients were treated with intravenous saline infusions. The severity of dehydration in two patients led to somnolence; they had been drowsy, but were arousable to normal level at admission. Of 22 patients with increased serum creatinine levels, three required haemodialysis. Creatinine levels in the outbreak population increased by a mean of 35% (SD ± 25.7%). The median increase in serum creatine was 23 μmol/L during the infection episode. Diarrhoea and vomiting also led to potassium loss,

with potassium decreases of >10% in 18 patients, and >20% in seven patients. CRP levels were available for 57 patients (mean CRP level of 68.5 mg/L; SD ± 55 mg/L; median 58 mg/L; normal <5 mg/L).

One patient, suffering from ventricular tachycardias, developed three episodes of ventricular tachycardias and needed a cardioversion. Another patient could not reach the bathroom in time, slipped while vomiting and fell, suffering bruises. In two renal transplant patients, immunosuppressive therapy with sirolimus and mycophenolate mofetil hydrochloride had to be stopped because diarrhoea led to fever and severe dehydration, with instability of the cardiovascular system. No patient died while clinical signs of norovirus infection were apparent, but three patients died during the following 2 weeks. The underlying diseases of these patients were Klatskin-cancer (renal failure developed in this patient), active lupus erythaematodes with ulcerations of both legs (renal failure developed while norovirus symptoms were present), and heart failure in an elderly patient who died with severe nosocomial pneumonia; the prognosis had been poor for all three cases before norovirus infection. In total, 14 patients relapsed after being symptom-free for ≥48 h (range 3–9 days; mean 4.3 days, SD ± 2.5 days).

Table 3 summarises the univariate and multivariate risk-factor analyses. Relapses or medication with metoclopramide or loperamide were not significant risk-factors for any defined outcomes (data not shown).

DISCUSSION

Lopman *et al.*[15] questioned the assumption that norovirus gastroenteritis is a trivial disease after analysing data from norovirus outbreaks in England and Wales during 1992–2000. It has been suggested that norovirus infection could become an important factor contributing to the poor outcome of patients already weakened by other conditions [16]. Moreover, Lopman *et al.*[17] suggested that 'sick patients get sicker', referring to the length of diarrhoeal episodes for hospitalised patients compared with those in nursing homes. However, no details of the burden of disease in at-risk populations have been published previously.

The starting point for the present investigation was the observation of severe complications of norovirus infection in a few patients during a large hospital outbreak. It was noted that more patients developed diarrhoea rather than vomiting, which is in contrast to published findings [4]. However, norovirus includes a diverse group of viruses that segregate into lineages termed genogroups (GG) and genotypes. Most outbreak strains in closed settings (hospitals, nursing homes) have been characterised as GG II, with genotype II/4 (Grimsby) predominating [18]. In 2002, a new variant Grimsby virus emerged across Europe and the USA. In Europe, the emergence was associated with a steep increase in the total number of outbreaks reported in almost all countries involved in the Foodborne Virus in Europe network [13,14]. The outbreak in the present study was also caused by this new variant GGII/4

(unpublished data). Therefore, the pattern of illness that was observed may not be typical of other noroviruses.

In the present study, symptomatic norovirus infection lasted longer than expected (1–7 days) and relapses occurred. Protective factors against a longer duration were underlying diseases with a low degree of immunosuppression, such as trauma, gastrointestinal disorders and malignancies. Prolonged shedding over a period of 120 days has been described previously [19] in an intestinal transplant recipient; it was shown that a chronic norovirus infection (GG II, genotype Miami Beach) was the cause, and only a reduction in immunosuppressive therapy ended the episodes of diarrhoea and enteritis. Unfortunately, follow-up stool samples could not be obtained in the present study. Therefore, it is unknown whether any of the immunocompromised patients developed a chronic infection.

An intriguing novel feature was the occurrence of relapses of norovirus infections in 14 patients. It is not clear whether these cases represented true relapses, or a rebound of symptoms following rehydration. However, the interval between relapses ranged from 3 to 9 days. In one patient, a follow-up sample was positive by RT-PCR, but most patients were not sampled later in the course of the disease. There was no significant risk-factor associated with relapses, so this effect may be attributed to the new variant virus.

The need for haemodialysis and cardioversion in three patients focused attention on serum creatinine and potassium levels [20]. Surprisingly, the effect of illness on potassium levels, serum creatinine levels and CRP levels appeared high for a 'trivial' viral infection, so these parameters were included as outcome measures. Gendrel *et al.*[21] found elevated CRP levels (>20 mg/L) in 61 (26%) of 236 children suffering from viral gastroenteritis, whereas in the present study, 42 (73%) of 57 patients had elevated CRP levels.

Recently published data [15] suggest that complications of norovirus infection arise predominantly in the elderly. In the present study, individuals aged >65 years were associated significantly with longer diarrhoeal episodes. Cardiovascular disease and renal transplant were risk-factors for potassium loss; immunosuppressive therapy was a risk-factor for raised creatinine; and immunosuppressive therapy was a risk-factor for high CRP levels. Trauma was protective for longer diarrhoeal episodes, reflecting the fact that these patients belonged to the healthy population. Thus, this population may be considered as a small internal control group; indeed, OR were <1 for all outcomes except 'vomiting for >1 day', thereby providing evidence that healthy individuals develop predominantly mild symptoms.

In the present study, only 27 of 84 patients tested positive for norovirus. During an ongoing outbreak, it is not possible to obtain stool specimens from all patients involved; patients caring for themselves often forget to obtain specimens, and the wards involved were advised to discharge patients as early as possible. Hence, patients with a short course of infection might not have had the opportunity to provide specimens. Furthermore, norovirus-negative patients often submitted specimens after the symptoms had resolved, indicating that norovirus did not

persist for long periods in these patients. Nevertheless, the possibility cannot be discounted that either a small group of norovirus-negative patients might have been included in the study, or that norovirus-positive patients without symptoms were missed.

Another limitation concerns the patient groups investigated. The outbreak was confined to only five wards from five different departments. Consequently, only patients from these departments were investigated. Thus, data are lacking for other patient groups, particularly haematological, pneumological, surgical and paediatric patients.

There were marked differences in attack rate, perhaps depending on factors associated with the ward and staff group. For example, dementia patients, for whom isolation procedures are difficult to establish, were treated on the psychiatric ward. In contrast to attack rates reported by the CDC [9], nursing staff were at higher risk of infection compared with patients, perhaps because the present study only included staff members who had been working on the ward during the outbreak period in the denominator population. In cardiology, educational interventions concerning the prevention of transmission of noroviruses were started at an early stage, which may have resulted in the lowest attack rate.

The outbreak investigation demonstrated that 'sick patients got sicker' when acquiring a norovirus infection. Furthermore, at-risk populations were identified for several clinical outcomes. Patients with cardiovascular disease, those receiving immunosuppressive therapy, the elderly and organ transplant recipients were at higher risk of a severe clinical outcome. These patients should be monitored frequently when suffering from norovirus infection.

Although many recommendations exist for preventing transmission of noroviruses [22], the potentially severe impact of norovirus outbreaks in frail hospital populations has been underestimated. An important recommendation should focus on prevention of such outbreaks in hospitals, especially when immunocompromised patients are treated. Immunocompromised patients should be educated about possible severe courses of 'trivial' gastrointestinal infections, and should be instructed to consult a physician as early as possible to allow monitoring for possible complications. The present findings underline the importance of applying stringent infection control measures when dealing with norovirus infections.

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