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

F. Mattner[1], D. Sohr[2], A. Heim[3], P. Gastmeier[1], H. Vennema[4] and M. Koopmans[4]

Medizinsche Hochschule Hannover, [1]Institut für medizinische Mikrobiologie und Krankenhaushygiene and [3]Institut für Virologie, Hannover, [2]Institut für Hygiene und Umweltmedizin, Charité-Universitätsmedizin, Berlin, Germany and [4]Diagnostic Laboratory for Infectious Diseases, National Institute of Public Health and the Environment, Bilthoven, The Netherlands

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.

Keywords Cardiovascular disease, clinical complications, elderly patients, immunocompromised patient, norovirus infections, renal transplant

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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

Correspondence: F. Mattner, Medizinsche Hochschule Hannover, Institut für medizinische Mikrobiologie und Krankenhaushygiene, Carl-Neubergstraße 1, D-30625 Hannover, Germany
E-mail: mattner.frauke@mh-hannover.de

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.