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Norovirus infection in immunocompromised hosts

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Abstract

Acute gastroenteritis caused by noroviruses often has a duration of 2–3 days and is characteristically self-limiting. In contrast, chronic infection caused by noroviruses in immunocompromised individuals can last from weeks to years, making clinical management difficult. The mechanisms by which noroviruses establish persistent infection, and the role of immunocompromised hosts as a reservoir for noroviruses in the general human population, are not known. However, study of this patient cohort may lead to new insights into norovirus biology and approaches to treatment.

Keywords

Acquired immunodeficiency; chronic infection; immunocompromised; immunosuppressed; norovirus

Introduction

Noroviruses belong to the genus *Norovirus*, a large and diverse genus in the positive-strand RNA virus family *Caliciviridae*. The association of noroviruses with acute gastroenteritis is well established. The disease burden in the USA alone is an estimated 19–21 million episodes of gastroenteritis annually, with *c.* 400 000 emergency department visits, 56 000–71 000 hospitalizations, and as many as 570–800 deaths [1,2]. Noroviruses have been reported as the leading cause of severe diarrhoea in infants and young children requiring medical intervention in the USA, now that rotavirus vaccines have been successfully deployed [3,4]. Vaccines for noroviruses are not yet available, but recombinant virus-like particle vaccines have shown promise in clinical trials [5].

Noroviruses can establish a persistent infection in immunocompromised hosts, resulting in prolonged virus shedding and gastrointestinal disease that, over time, can become increasingly debilitating and life-threatening [6-8]. In a review of 123 deaths attributed to noroviruses, a serious underlying condition was reported for 17 individuals at the time of death, with ten (58%) of the deaths occurring in patients who were immunocompromised by

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chemotherapy or transplantation [9]. There is presently no virus-specific drug available to treat norovirus infection, although the urgent need for such drugs in immunocompromised patients has gained recent attention [8]. This review will focus on the current understanding of chronic norovirus infection that characteristically occurs in immunocompromised individuals, and the prospects for prevention and treatment.

Immunocompromised Patient Groups at Risk

Children

In early studies of the genetic diversity of noroviruses, the Toronto virus (formerly called ‘minireovirus’ and now classified as a reference GII.3 norovirus strain) was identified as a genetically distinct ‘Norwalk-like virus’ in sick children receiving care at the Children’s Hospital in Toronto, Canada [10]. Four of the 11 paediatric patients studied at the Children’s Hospital shedding norovirus were designated as immunosuppressed, with underlying conditions of leukaemia, post-liver transplant status, or severe combined immunodeficiency. Since then, an increasing number of case study descriptions have linked norovirus infection to conditions in children that are characteristically associated with immunosuppression, such as inherited immune disorders [11-13], small-bowel transplantation [14], kidney transplantation [15], haematopoietic stem cell transplantation (HSCT) [16,17], and cancer or cancer treatment [17-19]. Noroviruses have also been detected in children experiencing complications that may arise from immunosuppression. Haemophagocytic lymphohistiocytosis was reported recently in association with chronic norovirus infection of duration 40 days following bone marrow transplantation for treatment of relapsed myelogenous leukaemia in a 24-month-old child [20]. In a study of 27 paediatric patients with pneumatosis intestinalis, 17 (63%) were immunocompromised, with noroviruses being the predominant pathogens detected (23.5% prevalence) following screening for bacterial and viral agents [21]. The first study to systematically examine the prevalence of noroviruses in children with inherited immune deficiencies reported that noroviruses were the most commonly detected pathogens in the 62 children studied, and that shedding was prolonged, with 57.1% of faecal samples still being positive after a median of 9.5 months of follow-up [13]. It is of interest that the investigators reported evidence of norovirus viraemia in 25% of these paediatric cases. A retrospective study of diarrhoea in 55 haematopoietic stem cell transplant recipients aged <21 years showed that 49 developed diarrhoea and eight (6.3%) were positive for the presence of norovirus in stool [22]. The overall cumulative incidence of norovirus infection in this cohort was 12.9%, and the median time for norovirus clearance was 145 days (range: 13–263 days). A survey of two paediatric hospitals in the metropolitan Atlanta area that examined the prevalence of noroviruses [23] reported the detection of noroviruses in 15 of 92 (16.3%) of the patient stools tested. It was noteworthy that 11 of 15 (73.3%) of the norovirus-positive stools were obtained from immunocompromised patients ($n = 47$), indicating an overall norovirus prevalence of 23.4% in this group.

Adults

Chronic norovirus infection has been documented in adults following HSCT [24-27], kidney transplantation [28-31], heart transplantation [32], human immunodeficiency virus infection

[33], and cancer or cancer treatment [18,34]. Elderly populations are at increased risk for a serious outcome from infectious diseases [35], including norovirus illness [36-38], with declining immune function thought to be a contributory factor.

Nosocomial Norovirus Infections

Risk factors in nosocomial outbreaks

Noroviruses constitute the leading cause of severe viral gastroenteritis prompting admission to a hospital emergency department [39]. A number of studies have also documented the important role of noroviruses in nosocomial infections. In a survey of 289 hospitals in the USA that had initiated outbreak investigations in the previous 12 months, noroviruses were the most frequently detected nosocomial pathogens, accounting for 53 of 291 (18.2%) of the investigated confirmed outbreaks and resulting in the highest rate of hospital unit closures (65%) [40]. An analysis of risk factors for norovirus disease in one university hospital found that immunocompromised patients were at increased risk for a severe clinical outcome following norovirus infection [38]. Prolonged shedding by immunocompromised individuals has been suggested as a source of virus strains for nosocomial infections [41]. A nosocomial outbreak of norovirus in a bone marrow transplant unit was attributed, in part, to the longer shedding periods and hospital stays of these patients [26]. An immunocompromised patient suffering from an acute norovirus infection was identified as an index case for the introduction of norovirus into a hospital transplantation care unit where the patient was admitted for treatment of complications resulting from graft-versus-host disease following HSCT [27].

Genetic diversity and evolution of noroviruses in nosocomial outbreaks

Persistent or chronic viral infections are known to be caused by many positive-strand RNA viruses, and they are well documented in members of the family *Caliciviridae*. Feline calicivirus (FCV), a member of the genus *Vesivirus* and an agent of upper respiratory illness in cats, can establish a chronic infection in cats, even in the presence of prior vaccination and an intact immune system [42]. The upper respiratory tract was proposed as a major site of FCV persistence [43]. Moreover, evidence was shown for the evolution of antigenic variation in FCV strains over time, suggesting the presence of selective pressure driven by an adaptive immune response [44]. Murine norovirus (MNV), which is more closely related to human noroviruses, can establish asymptomatic and persistent infection in mice, with both virus and mouse host differences being linked to chronic infection [45,46]. It has been proposed that the colon may be an important site of persistent MNV replication in mice [47,48], and it is of interest that lesions in the colon have been proposed as sites of virus replication in preterm babies with severe norovirus infection [49]. One study identified the presence of MNV antigen in the mesenteric lymph nodes of certain immunodeficient mice, suggesting lymphoid tissue as another site of persistent infection [50]. Possible adaptive changes during persistent MNV infection have been linked to the N-terminal open reading frame 1 protein (NS1/2) [48], the RNA-dependent RNA polymerase (NS7) [47], and the minor structural protein VP2 [47], but the mechanisms of norovirus persistence will require additional investigation.

Norovirus infection in immunocompromised patients can begin with an episode of acute gastroenteritis, but the inability to clear the virus can lead to chronic infection. There is presently no evidence for naturally occurring norovirus strains that have evolved to preferentially establish persistent infection in human hosts. The predominant norovirus genotypes reported in immunocompromised individuals belong to geno-group II, which is reflective of the predominance of this genotype as the cause of acute gastroenteritis in the general population. Table 1 summarizes representative studies, many in hospitals or transplant units, reporting the genotypes of strains associated with chronic infections in immunocompromised hosts.

A growing number of outbreak investigations in hospitals have employed molecular techniques to elucidate the source and spread of noroviruses in nosocomial outbreaks [17,51-53]. An investigation of three separate norovirus transmission events resulting in gastroenteritis outbreaks in a hospital linked the source to three immunocompromised individuals with probable chronic shedding [41]. Sequence analysis of noroviruses shed over time in chronically ill patients may allow an in-depth understanding of virus adaptation and spread in the presence of little or no host immune pressure [54,55]. There is evidence that noroviruses in chronically infected immunocompromised patients accrue amino acid substitutions on the outer surface of the viral capsid over time that may change their antigenic profile [32,55] (Fig. 1). An important area of future investigation will be to determine whether these mutations are meaningful for treatment and clinical management.

The infectivity and transmissibility of noroviruses shed by chronically infected individuals in comparison with those of noroviruses shed by individuals with acute infection has not been fully established. One model proposes that norovirus transmission is most efficient in the early phase of an acute norovirus infection [56], when virus titres in stools have been shown to be highest [57]. A detailed analysis of three nosocomial outbreaks in different facilities found that norovirus gastroenteritis cases were most often linked to transmission events involving symptomatic patients or healthcare workers, with asymptomatic individuals being less likely to transmit virus [58]. In healthy adult volunteers challenged with Norwalk virus, the peak of virus shedding (median concentration reported as 95×10^9 genomic copies per gram of faeces), occurred at a median of day 4 after inoculation, whether infection was symptomatic or asymptomatic, and the median duration of shedding was 28 days, well after symptoms had resolved [59]. The prevalence of asymptomatic infection in immunocompetent hosts has been estimated to be as high as 12% [60], indicating that it will be challenging to determine whether chronic shedders serve as a reservoir for the general population without intense epidemiological surveillance and viral genome sequencing. Immunocompromised children with norovirus infection were reported to shed median viral concentrations of 3.6×10^8 cDNA copies per gram of stool collected between 2 days and 14 days post-onset [19]. In another study that examined norovirus viral loads in highly immunosuppressed patients and children, the median viral load was reported to be 2.9×10^7 genomic copies per milliliter of stool [61]. Further study of viral load and evolution in immunocompromised individuals will be needed to correlate virus titre with symptoms, severity of disease, and efficiency of transmission [62].

Treatment and Control of Norovirus Infection in Immunocompromised Hosts

Treatment

There is currently no specific antiviral drug for the treatment of norovirus gastroenteritis. Supportive fluid replacement therapy can be used to prevent dehydration, and nutritional supplementation may be required [6]. Nausea and diarrhoea, which are hallmarks of norovirus disease, are common in immunocompromised patients, making laboratory confirmation of norovirus infection an important diagnostic tool in patient management. For example, diarrhoea occurred in 79% of adult allogeneic stem cell transplant recipients in one study, but the aetiology could not be linked to any known aetiological infectious agent [63]. Conditioning therapy prior to transplantation and complications following transplantation, such as graft-versus-host disease, may cause diarrhoea [6,27]. A number of treatment strategies have been reported to improve chronic norovirus infection in immunocompromised individuals, including adjustment of immunosuppressive therapy (IST) drug types and dose levels [14,24,25,29,30], drugs approved for other pathogens [34], and passive γ-globulin therapy [31,33,64]. The recovery of normal intestinal morphology following reduction of IST in a norovirus-infected child who had undergone a small-bowel transplant is shown in Fig. 2. In mice, it was possible to clear persistent MNV infection in immunocompromised animals [59] with neutralizing antibodies, showing the potential benefit of passive immunotherapy [65]. However, there are also reports of treatment failure with breast milk, γ-globulin and IST adjustment in one immunocompromised patient [32].

Infection control

Noroviruses are highly infectious and stable in the environment. A review of transmission routes in 54 nosocomial outbreaks identified person-to-person spread (18.5%) and foodborne sources (3.7%) as the major known routes, but a clear route of transmission could not be identified in the majority (77.8%) of the outbreaks [66]. Infection control has remained the first line of defence in reducing norovirus exposure and spread [67], and is especially important in the immunocompromised population [7]. Hospitals and long-term-care facilities caring for immunocompromised patients should adhere strictly to rigorous infection control practices, to limit exposure of patients, staff and visitors to noroviruses [68]. Immunocompromised individuals should follow food safety guidelines that minimize exposure to contaminated food and water, and avoid contact with individuals who might be ill. The US CDC has published online guidelines for the prevention of norovirus infection, including management in healthcare settings www.cdc.gov/norovirus/index.html and resources on effective disinfectants. Infection control strategies with the most positive outcomes have been reviewed in the nosocomial setting [66], and include restricting movement of patients and staff, enhanced environmental cleaning, and attention to hand-washing. The practice of ‘presenteesim’ (a term for working while sick) should be avoided by healthcare workers managing immunocompromised patients: this practice has been linked to norovirus outbreaks in settings such as a bone marrow transplantation unit [26].

Vaccines

Norovirus vaccine development and evaluation is underway [69], but it will probably be several more years before licensed vaccines are available [70]. Immune correlates are not fully understood, but it is presumed that the adaptive immune system, including antibodies, CD4 lymphocytes, and CD8 lymphocytes, is critical in protection [46,71]. This is supported by data from a norovirus vaccine study that showed a correlation between the presence of serum antibodies with a histo-blood group antigen blocking titre of at least 200 and a reduced frequency of viral illness and infection upon virus challenge [69]. A norovirus vaccine may be of limited use in the general immunocompromised population with debilitated T-cell and B-cell function, with the exception of patients who would be eligible for incorporation of norovirus vaccination (when available) into the panel of recommended vaccines administered prior to or following organ or stem cell transplantation and IST [72]. Effective norovirus vaccines that lower the overall disease prevalence in the general population or in healthcare workers could indirectly benefit immunodeficient individuals by lowering the risk of exposure and subsequent infection.

Antiviral drugs

Noroviruses associated with human disease do not grow in cell culture, so drug design and screening have relied primarily on recombinant DNA-based research tools (such as recombinant norovirus replicative enzymes) or cell culture-adapted calicivirus models, such as MNV or FCV. A number of compounds, inhibitors and therapeutic antibodies are under investigation in the basic research setting [8,73]. Promising candidate drugs for the noroviruses will require safety and efficacy testing in adult volunteer challenge studies, and a proposed design of clinical drug trials in immunocompromised patients has recently been described [8].

Future Perspectives

Noroviruses are increasingly being recognized to constitute a major risk factor for debilitating diarrhoea and chronic gastroenteritis in immunocompromised patients. It is not known whether these individuals play a major role in the epidemiology of the virus, or are responsible for only sporadic and occasional transmission. There is a need for effective treatment in this special at-risk population to clear chronic norovirus infection and restore normal intestinal function. Such treatment may also offer benefits to patient groups who are at risk from acute life-threatening diarrhoea, including infants, young children, and the elderly.

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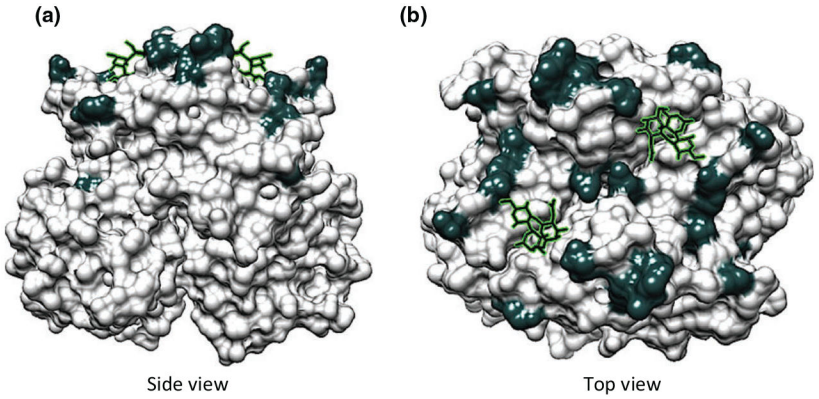

FIG. 1.

Modelling of amino acid changes on the surface of a GII.4 norovirus capsid following chronic infection over a period of almost 1 year in an immunocompromised patient (adapted from reference [55]). (a) Side view of VP1 dimer. (b) Top view of VP1 dimer. Amino acids that differ over time are indicated in dark grey, and histo-blood group antigen-binding sites are shown as stick models. It is noteworthy that the majority of mutations are predicted to occur on the exposed surface of the viral capsid. A number of mutations correspond to antigenic changes as described in the cited article.

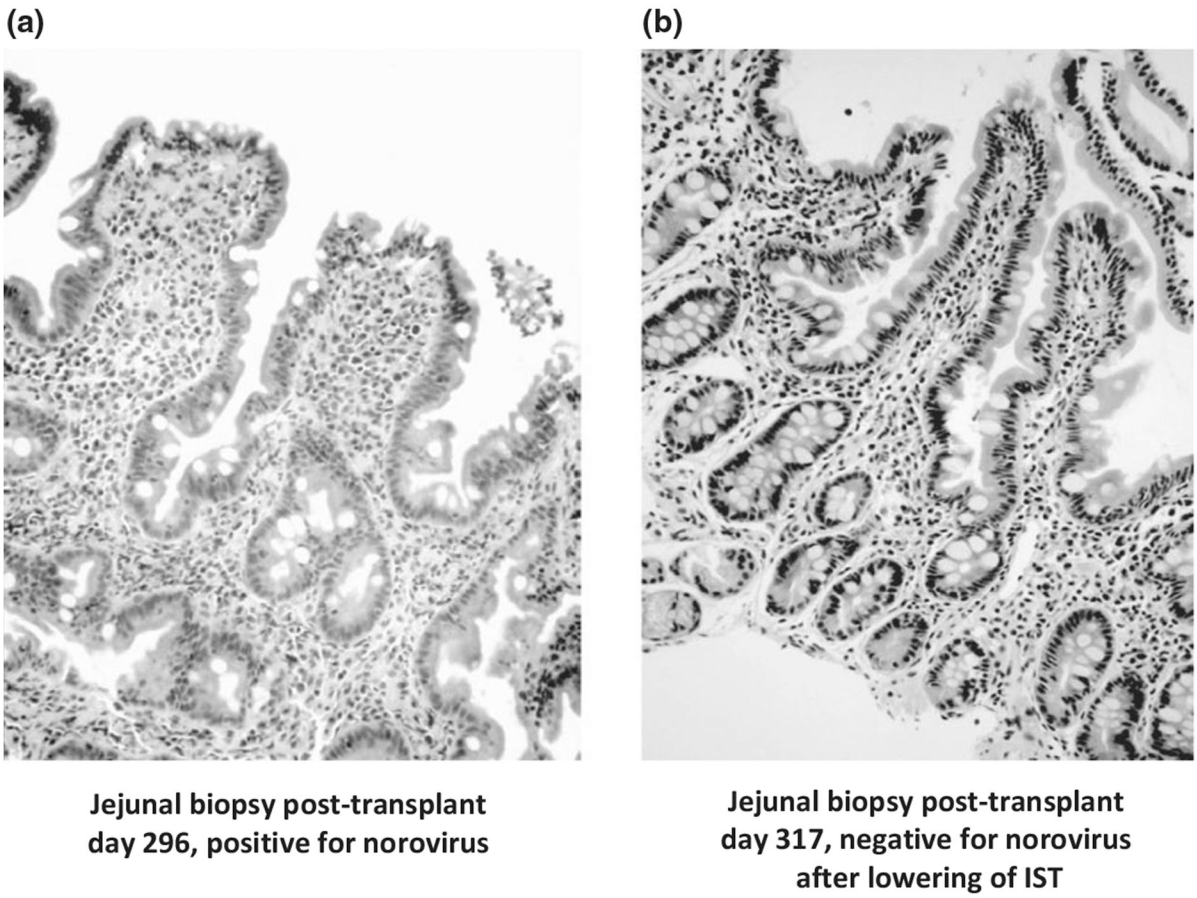

FIG. 2.

Intestinal biopsy of a paediatric small-intestine transplant patient. (a) During acute norovirus infection at day 296 post-transplant. (b) After resolution of symptoms at day 317 post-transplant following reduction of immunosuppressive therapy (IST), which allowed virus clearance. Note the severe blunting of intestinal villi during acute infection, and the regeneration of normal intestinal morphology after virus clearance. Adapted from reference [14].

TABLE 1.

Norovirus genotypes detected in immunocompromised patients

Setting (country)	Underlying condition or treatment	Genotypes	Reference
Children's hospital (Canada)	Cancer, liver transplantation, SCIDs	GII.3	[10]
Hospital (UK)	Bone marrow transplantation	GII.4	[52]
Hospital (UK)	HSCT	GII.3, GII.4, GII.7	[24]
Hospital (Switzerland)	HSCT, lung transplantation	GII.4	[25]
Hospital (The Netherlands)	Cancer, leukopenia, HSCT	GII.3, GII.4	[17]
Hospital (Germany)	Cancer	GII.3, GII.4	[19]
Individual patient (Sweden)	Heart transplantation	GII.3	[32]
Hospital (USA)	Intestinal transplantation	GII.4	[14]

HSCT, haematopoietic stem cell transplantation; SCID, severe combined immunodeficiency.