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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.

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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 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 mesen-