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Developments in understanding acquired immunity and innate susceptibility to norovirus and rotavirus gastroenteritis in children

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Abstract

Purpose of review—We discuss recent advances in the understanding of acquired immunity and susceptibility to the two major pediatric enteric viral pathogens, norovirus and rotavirus.

Recent findings—The prominent decline in severe rotavirus gastroenteritis in areas with mature rotavirus vaccination programmes has correspondingly unmasked the significant burden of disease associated with norovirus gastroenteritis among children. As epidemiologists and vaccinologists set their sights on this next vaccine target, we provide an update on norovirus vaccine development.

In addition to these developments regarding acquired immunity, refinements to our understanding of innate susceptibility to norovirus has advanced. Significant recent advances now describe similar immunologic mechanisms in understanding susceptibility for both norovirus and rotavirus, involving histo-blood group antigenic associations, which may also prove to be genotype specific.

Summary—This information can potentially be used to tailor both applied and developmental efforts to public health interventions against these important pediatric enteric viral pathogens.

Keywords

acquired; *FUT2*; histo-blood group antigen; immunity; innate; norovirus; rotavirus; vaccine

INTRODUCTION

In some regions with successful rotavirus vaccination programmes, a fundamental shift has occurred in the epidemiology of acute gastroenteritis in pediatric populations and norovirus has overtaken rotavirus to become the predominant cause of severe gastroenteritis in young children. In light of this development, efforts have increasingly been directed toward understanding the epidemiology of noroviruses with the ultimate aim of preventing the large

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burden of disease due to this pathogen. Rapid advancements in molecular and genetic technologies have reduced the cost and increased the resolution of previously undetected host–pathogen relationships for enteric viral pathogens. This review encompasses the recent scientific progress in understanding both immunity and innate susceptibility to these important pediatric enteric viral diseases.

NOROVIRUS GASTROENTERITIS DISEASE BURDEN

Before rotavirus vaccines were licensed and recommended by the US Advisory Committee on Immunization Practices for routine use in 2006, rotavirus was the leading agent of severe pediatric gastroenteritis in US children, causing approximately half of all winter acute gastroenteritis hospitalizations in the US. As a result of the marked decline in severe rotavirus disease because of vaccination [1▪], noroviruses have now become the leading cause of pediatric gastroenteritis in US children [2▪]. An evaluation involving active surveillance among children under 5 years old in three US counties showed that laboratory-confirmed norovirus infection accounted for 21% of gastroenteritis requiring medical attention, compared with 12% for rotavirus. Extrapolating from incidence rates in this population, nearly 1 million medically attended norovirus infections are estimated to occur annually in US children younger than 5 years old, incurring substantial costs upon the US healthcare system. In that study, norovirus hospitalization and emergency department rates were highest among children between the ages 6 and 23 months. Modeling studies now underscore the key role that young children play in norovirus transmission to all age groups [3▪], consistent with earlier findings suggesting that contact with a symptomatic child is a major determinant in norovirus infection risk.

With increasing use of molecular detection assays, noroviruses are also now recognized to be the cause of approximately half of all foodborne disease outbreaks in the US [4]. They are a key healthcare-acquired infection, a common cause of travel-associated diarrhea, and can blight any close congregation of humans, including long-term care facilities, daycare centers, cruise ships, and dormitories [5]. Worldwide, norovirus is associated with 18% of acute gastroenteritis cases among children (17% of inpatient cases and 24% of community episodes), according to a recent systematic review [6].

NATURAL IMMUNITY TO NOROVIRUS

The understanding of natural immunity to norovirus is far from complete, although it is clear that immunity is not permanently sustained and reinfections can occur throughout life. Early volunteer studies suggested that protection against rechallenge with the same norovirus strain lasted for at least 6 months to 2 years [7,8]. However, both the dose and strain used in these challenge studies may not represent typical natural exposures. Estimates from a recently published transmission modeling study indicate that the duration of homotypic immunity may last longer than originally believed: 4.1 (95% confidence interval [CI] 3.2–5.1) to 8.7 (95% CI 6.8–11.3) years [3▪]. These models, which were fit to age-specific incidence data from England and Wales, also found that children younger than 5 years old were more infectious than older children and adults.

A second feature of norovirus immunity is that protection against one norovirus strain does not necessarily provide protection against other strains from the diverse collection of noroviruses, which comprise five genogroups and approximately 30 more specific genotypes known to infect humans. Rechallenged volunteers have been observed to be susceptible to heterologous strains, indicating a lack of cross-protection between genogroup I (GI) and genogroup II (GII) noroviruses. Results from a Peruvian birth cohort demonstrated that childhood norovirus infection risk is highest during childhood, followed by serial infections throughout life [9]. Repeat infections by noroviruses having the same genogroup were common in this cohort, but repeat infections from noroviruses having the same specific genotype were rarely observed.

Third, the predominant norovirus genotype, GII.4, undergoes a process of epochal evolution, whereby every 2–4 years a new variant emerges. Novel GII.4 variants have altered antigenicity and they, to some degree, escape immunity in the human population [10]. Further, GII.4 is believed to have advantageous characteristics such as being shed in higher numbers and perhaps having greater transmissibility than other genotypes [11,12]. The continuing evolution of new strains suggests that, as with influenza viruses, continued epidemiologic surveillance with periodic reformulations of norovirus vaccines may be necessary to keep pace with antigenic changes [13].

Finally, although norovirus is frequently detected in stool samples from patients with diarrhea, it is also frequently detected from stools collected from healthy individuals. Norovirus detection in the absence of symptoms may be the result of a lengthy period of postdisease shedding detectable by PCR or true asymptomatic infection. Overall, detection rates in many developed countries are approximately 4–8% among young healthy controls [6], but have been observed as high as 30% [14]. Asymptomatic norovirus detections occur consistently more frequently among children from lower income countries, however [10], perhaps driven by higher rates of infection (and, therefore, increased levels of postinfection shedding). This variation complicates the interpretation of diagnostic results and the etiologic attribution of gastro-enteritis by comparing detection rates of various pathogens in gastroenteritis cases and healthy controls, such as the Global Enterics Multi-Center Study (GEMS), the largest systematic assessment for understanding the cause of moderate-to-severe childhood diarrhea in developing countries [15].

DEVELOPMENT OF A PROSPECTIVE NOROVIRUS VACCINE

As no small animal model or cell culture system is currently able to represent human norovirus infection, norovirus vaccine research has been conducted using inactive, nonreplicating norovirus capsids that lack the viral genome and are expressed as virus-like particles (VLP). These VLPs are morphologically indistinguishable from naturally occurring virus capsids and, since they were first engineered over 20 years ago, have been proposed as vaccine candidates. In preclinical trials, VLP delivered intra-nasally, intramuscularly and orally have all led to measureable serological responses. An adjuvanted intranasal formulation was tested in a proof-of-concept efficacy trial, in which participants were intranasally administered two doses of adjuvanted norovirus VLP vaccine or placebo intranasally 3 weeks apart, then challenged with live virus, homotypic to the vaccine strain

[16]. This trial demonstrated greater than four-fold immunoglobulin A antibody rises in 70% of vaccinated individuals, who were less likely to become ill (37 vs. 69%, respectively; $P = 0.006$) or infected (61 vs. 82%, respectively, $P = 0.05$) than individuals who received placebo. This vaccine has since been further developed as an adjuvanted bivalent formulation, including both a GI.1 (Norwalk) and GII.4 (consensus) VLP.

The vaccine was recently assessed in a randomized, double-blind, placebo-controlled trial of 18–50 year old adults who received two injections of placebo or the norovirus GI.1/GII.4 bivalent VLP vaccine, and were then challenged with a GII.4 virus [17]. Fewer self-reported severe or moderate gastroenteritis symptoms occurred among vaccinated individuals compared with placebo recipients. An important outcome of these trials is the identification of a promising correlate of protection. Individuals with histo-blood group antigen (HBGA) blocking antibodies against norovirus VLPs at titers of 200 or more had a 72% (95% CI 21–90) reduced risk of norovirus gastroenteritis compared with individuals with titers less than 200. Further studies will be needed to determine if HBGA-blocking activity can serve as a correlate of immunogenicity and protection. If so, this would be an important development in the ability to accurately gauge the clinical performance of norovirus vaccines.

Nonetheless, substantial challenges remain to developing a norovirus vaccine that would be a useful public health tool. Natural norovirus immunity appears to be of relatively short duration with limited cross-protection. Noroviruses are highly diverse viruses so a broadly effective vaccine would require bivalency and contain both GI and GII VLPs. With GII.4 viruses periodically shifting their antigenicity, a vaccine may need to be regularly updated or engineered to protect against future strains. Finally, in order to realize the public health potential of a norovirus vaccine, it will be critical to demonstrate efficacy in the vulnerable groups (e.g., young children and the elderly) who may be the least likely to mount a protective vaccine response.

NOROVIRUS INNATE SUSCEPTIBILITY

In addition to acquired immunity from infection or vaccination, a genetic, innate component exists to norovirus susceptibility. Revelations first reported in the past decade regarding the association between norovirus infection and genetic indicators of HBGA expression have been recently refined.

HBGAs are a diverse family of carbohydrates expressed on the mucosal epithelia of the respiratory, genitourinary, and digestive tracts, that are recognized as receptors allowing norovirus attachment and cellular entry. HBGA production is coded by three gene families expressing the ABO (A/B enzymes), secretor (*FUT2*), and Lewis-type (*FUT3*) antigens. Single-nucleotide polymorphisms can inactivate the expression of these products, breaking a link in the norovirus binding and infection process. Recent research indicates that *FUT2* genotype is a major factor determining pediatric norovirus infection risk, particularly with the GII.4 norovirus type that predominates worldwide [18].

These genetic characteristics affecting HBGA expression, and thus norovirus infection risk, appear to be highly variable by ethnicity. Those without a functional *FUT2* secretor gene (i.e., nonsecretors) comprise 20–25% of North American/European Caucasian populations,

but just 2% of US individuals of Meso-American/Hispanic ancestry. This intimates possibly higher natural susceptibility to norovirus infections among Hispanic populations in the United States [18]. In South East and East Asians, a different secretor mutation (A385T) is common. Twelve percent of Chinese children held the mutation, conferring to them a lower risk of GII.4 and GII.3 infections [19]. And, in Vietnam, of the studied children having a nonsecretor *FUT3* mutation, all were resistant to norovirus variant GII.4 [20▪▪].

It has become increasingly clear that innate human variations in HBGA binding sites on the mucosal epithelium affect the risk of norovirus infection. Such findings are relevant to understanding variations in norovirus risk within and between populations and may help guide the design and interpretation of norovirus vaccine research. Indeed, norovirus vaccine challenge studies have typically excluded nonsecretor individuals to ensure susceptibility among the challenged individuals. Although this approach maximizes the chance of vaccine trials showing a protective effect, it limits the real-world representativeness of the study populations.

DOES ROTAVIRUS INNATE SUSCEPTIBILITY EXIST TOO?

Recent studies have reported for the first time evidence of innate susceptibility to rotavirus through mechanisms also involving host HBGAs. Laboratory observations reveal that the viral protein-8 distal region of human rotavirus spike proteins specifically recognize HBGAs [21], illustrating the biological plausibility of this association. Epidemiologic observational evidence now supports this molecular finding. Trang *et al.* [20▪▪], analyzed paired stool-saliva specimens from Vietnamese children hospitalized with acute gastroenteritis, finding a significant relationship between rotavirus gastroenteritis and HBGA status, similar to a host–pathogen association with norovirus seen in the same population. This 100% correlation between rotavirus infections and secretor status was also reported by Imbert-Marcille *et al.* [22▪▪] in a French pediatric sample, and by Payne *et al.* [23] in an ethnically and regionally diverse sample of US pediatric inpatient and emergency department admissions for acute gastroenteritis in 2011–2012. Nordgren *et al.* [24] studied children with rotavirus from both Burkina Faso and Nicaragua, finding that rotaviruses having a P[8]-type (viral protein, viral protein-4) exclusively infected children having Lewis and secretor positive HBGA phenotypes, also suggesting the importance of both *FUT2* and *FUT3* upon rotavirus susceptibility.

The P[8] type is the sole viral protein-4 component of both live, attenuated rotavirus vaccines, RotaTeq (Merck and Co., Whitehouse Station, New Jersey, USA) and Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), and is the predominant viral protein-4 type circulating globally. African populations have a high frequency of Lewis-negative HBGA phenotypes, therefore, leading Nordgren *et al.* [24] to surmise that a greater proportion of African children are possibly unable to mount an adequate immunologic response to the viral protein-4 vaccine component, thereby reducing rotavirus vaccine efficacy in clinical trials in African populations. However, this conclusion requires further validation and consideration of factors including the broadly heterotypic response recognized to be derived from these vaccines in the clinical trial data considered during vaccine licensure. These recent HBGA studies, all having relatively small sample sizes,

nonetheless provide highly consistent findings that innate susceptibility to rotavirus gastroenteritis exists among pediatric populations on four continents, in a mix of socioeconomic and environmental conditions.

SUMMARY

Genetic human variations in HBGA expression on the mucosal epithelium strongly affect the risk of norovirus infection, and indications of a similar relationship with rotavirus have recently been elucidated in diverse populations. This natural resistance to norovirus and rotavirus is perhaps associated with ethnicity and specific to particular viral genotypes. As stimulating as is the prospect for similar, innate protective mechanisms for both of these viral pathogens, many questions await further investigation. Well powered, diverse epidemiological assessments are needed, including healthy controls, as are further elucidations into the structural mechanisms of HBGA and norovirus/rotavirus interfaces, their evolution, and their genotypic differences. This information can potentially be used to gain insights into the mechanisms of enteric virus infection and immunity processes, facilitate the development of vaccines, and help to target public health interventions, perhaps including infection control and vaccine strategies.

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▪▪ of outstanding interest

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KEY POINTS

- Progress has occurred in the development and testing of candidate norovirus vaccines, including the identification of a possible correlate of protection.
- Innate susceptibility to norovirus, now widely acknowledged to occur through host histo-blood group antigen mechanisms, may differ between population groups and by norovirus genotype.
- A similar, innate protective mechanism may affect susceptibility to rotavirus.