Secretors of HBGA and Susceptibility to Norovirus and Rotavirus Diarrhea

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Abstract: Histo-blood group antigen contains oligosaccharides that serve as receptors for norovirus (NoV) and rotavirus (RV). The receptors are only present on the surface of intestinal mucosal epithelial cells of secretors; therefore, secretors are susceptible to NoV and RV diarrhea and nonsecretors are resistant. The prevalence of secretors in different countries varies between 50% and 90%. Secretor rates evolved in response to environmental pressures such as infectious diseases.

Key Words: histo-blood group antigens, secretor of HBGA, diarrhea, rotavirus, norovirus

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Blood group antigens, A, B and O are located on red blood cells (RBCs) and mucosal tissues. They, along with secretor and Lewis antigens, are collectively referred to as histo-blood group antigens (HBGAs).[1] The present report was written to remind physicians that although the term secretor refers to the presence of blood group antigens in saliva, more importantly, it identifies individuals who secrete oligosaccharide receptors in secretions and on mucosal surfaces. Secretor status has been closely linked to susceptibility and resistance to a large number of infectious agents.[2,3] Secretors are susceptible to and nonsecretors are resistant to norovirus (NoV), rotavirus (RV), influenza A virus, rhinovirus, echovirus, respiratory syncytial virus, human immunodeficiency virus and *Helicobacter pylori*.[3] Conversely, nonsecretors are susceptible to and secretors are resistant to *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Salmonella enterica*, *Citrobacter rodentium* and *Campylobacter jejuni*.[3] The dichotomy between susceptibility and resistance patterns of secretors and nonsecretors to viruses and bacteria appears to be very important in the co-evolution of infectious diseases and HBGAs among people in different geographic and ethnic groups.[4–7] The present report will focus on the attachment mechanisms between NoV and RV to their respective receptors on mucosal epithelial cells of the intestine. The aim of the review was to familiarize readers with the role that oligosaccharides play as receptors for infectious agents.

OLIGOSACCHARIDES AND THE SYNTHESIS OF HISTO-BLOOD GROUP ANTIGENS

Oligosaccharides are complex sugars comprised of 3–15 simple sugars with a lactose core consisting of galactose and glucose.[8] They are present on cells and may function as receptors for infectious agents and affect susceptibility to disease.[2,5,6] They are also present in secretions such as breast milk where they may function as decoy receptors for infectious agents and serve to reduce susceptibility to disease.[9–11]

Oligosaccharides can exist as naked molecules or with side chains of fucose and sialic acid.[8] Oligosaccharides with fucose side chains serve receptors for attachment of NoV and RV.[2,12,13] The addition of fucose to an oligosaccharide is controlled by a specific set of transferases. There are 9 fucose transferase genes, *FUT1-9*.[14] FUT genes *FUT1*, *FUT2* and *FUT3* are involved in the synthesis of A, B, O, secretor and Lewis antigens. FUT1 is responsible for the synthesis of HBGA on RBC and FUT2 is responsible for the synthesis of HBGA in tissues. *FUT3* gene is responsible for the synthesis of Lewis antigen in tissues.[15] Individuals with functional *FUT2* genes are classified as secretors.

The synthesis of HBGA is a complex biochemical process, beyond the scope of this review article. Briefly, HBGAs are synthesized by the addition of 5 specific monosaccharides of β-glucose (Glc), β-*N*-acetylglucosamine (GlcNAc), β-galactose (Gal), β-*N*-acetylgalactosamine (GalNAc) and α-fucose (Fuc) to a disaccharide backbone of galactose and *N*-acetylglucosamine.[16] Galactose and *N*-acetylglucosamine form the H antigen precursor which is the foundation for all HBGAs. There are 2 types of H antigen precursors: type 1 H antigen precursor is expressed on tissues and contains a β1, 3 linkage between Gal and GlcNAc (Fig. 1-1), and type 2 H antigen precursor expressed on RBC and contains a β1, 4 linkage. The following discussion will focus on type 1 H antigen (Fig. 1). Fucosyl transferase 2 attaches fucose to the galactose in the type 1 H antigen precursor at the α1, 2 positions to form type 1 H mature antigen, also referred to as the secretor molecule (Fig. 1-3). Blood group A and B antigens are formed in tissues when the A gene transferase adds *N*-acetylgalactosamine and/or the B gene transferase adds galactose to the mature type 1 H antigen in an α1, 3 linkage (Fig. 1-4, 1-6).[15,16] HBGA O is the absence of A or B antigens (Fig. 1-5) on a type 1 H molecule. When FUT3 transferase attaches fucose to GlcNAc at the α1, 4 precursor on type 1 H antigen, it forms Lewis a antigen (Fig. 1-2) and when it attaches fucose at the α1, 4 positions on the mature form of the type 1 H antigen, it forms Lewis b antigen. Lewis b antigen has 2 fucose residues due to the combined action of FUT2 and FUT3; therefore, Lewis b antigen is found only in secretors.

Mutations in the *FUT2* and *FUT3* genes may result in weakened or nonfunctional genes. Nonsecretors are homozygous for an enzyme-inactivating nonsense mutation in *FUT2* and they do not express blood group antigens on tissues or in secretions.[17] There are 29 null and partial FUT2 alleles; similar numbers of null polymorphisms exist in the *FUT3* gene.[15] The most common mutation resulting in a nonsecretor phenotype in the *FUT2* gene is due to guanine to alanine substitution at position 428.[14] The mutation is common among Caucasians and Africans but not among Asians and results in a nonsecretor. Among Asians, a mutation due to cysteine to threonine substitution at position 357 is silent and results in a secretor phenotype; however, a mutation due to alanine to threonine substitution at position 385 is more common and results in a nonsecretor phenotype.[18–20] The Se^{428} mutation found among Africans is extremely old and can be traced back almost 3 million years.[14,19] The evolution of mutations in the genes controlling the presence of oligosaccharide receptors on gastrointestinal mucosal epithelial cells and in

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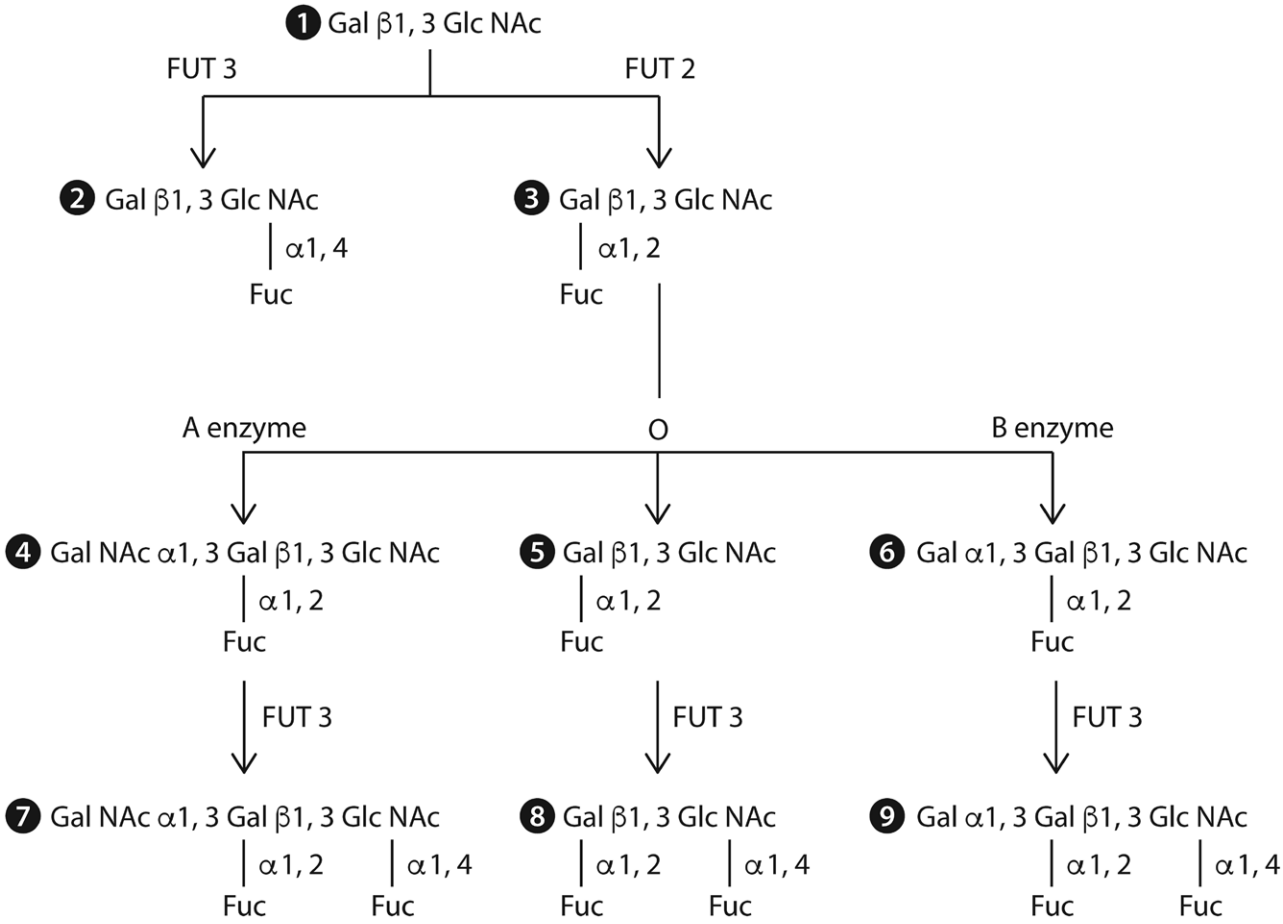

FIGURE 1. Synthesis of type 1 histo-blood group antigens (original drawing). Nonsecretors: (1) H type 1 precursor antigen, (2) Lewis an antigen. Secretors: (3) H type 1 mature antigen, (4) A antigen, (5) O antigen, (6) B antigen, (7) Lewis b A antigen, (8) Lewis b O antigen and (9) Lewis b B antigen. Glc indicates β-glucose; GlcNAc, β-*N*-acetylglucosamine; Gal, β-galactose; GalNAc, β-*N*-acetylgalactosamine; Fuc, α-fucose.

secretions may have resulted from selective pressure emanating from diverse environmental conditions and infectious diseases in various regions of the world as first suggested by Kudo in 1996[18] and subsequently investigated, supported and reviewed by others.[4,7,15,16,21,22]

NOROVIRUS

Virology

NoV is a nonenveloped, single-stranded RNA virus that belongs to the family *Caliciviridae*. It was first identified in fecal specimens from an outbreak of gastroenteritis in 1968 in Norwalk, OH.[23] It was visualized in fecal specimens in 1972 using immune electron microscopy because the virus could not be cultured in the laboratory.[24] It is a major cause of diarrhea in all age groups and currently the most common cause of pediatric diarrhea.[25] NoV has one species with 10 genogroups identified as G I-X.[26] Genogroups I and II are subdivided into 9 and 27 genotypes, respectively.[4,26] Genogroup II is the most common genogroup and II.4 is the most common genotype, accounting for 90% of cases and outbreaks.[12,22]

The viral capsid contains 2 structural proteins, VP1 and VP2. VP1 is the capsid protein.[27,28] VP2 is a smaller protein involved in stabilizing the capsid. VP1 has 2 domains: P (protruding) and S (shell) (Fig. 2). The P domain is subdivided into P1 and P2 subdomains, P2 being the most external domain that attaches to glycans on intestinal mucosa (Fig. 2). P1 and P2 exist as 90 dimers covering the surface of the viral particle.[12,29,30] The P2 subdomain is antigenically highly variable. Based on nucleotide diversity, NoVs can be divided into 60 P-types.[26] The variability in P2 explains a large number of different virus types in different regions of the world.[22,27,29]

Secretor Status and Susceptibility to Norovirus

In 1977, Parrino and others[31] challenged volunteers with NoV and made a prophetic observation. They noted that some volunteers seemed resistant to infection as evidenced by lack of illness, lack of an antibody response and absence of intestinal lesions on biopsy while other volunteers developed gastroenteritis, antibody response and intestinal lesions even when re-challenged months later. They assumed that nonsusceptible individuals possessed some form of innate immunity. Twenty-five years later, Lindesmith and colleagues[32] were able to explain the observations by Parrino et al[31] in another volunteer study. In their study, diarrhea developed in 62% of secretors and in none of the nonsecretors. They also noted that NoV is bound to the saliva of secretors and none of the nonsecretors. Thus, the presumed innate immunity was due to the presence of secreted HBGA in the saliva and presumably in the gut. Marionneau et al[21,33] proved that NoV bound to α1, 2 fucosylated oligosaccharides within HBGA on small intestinal epithelial cells.

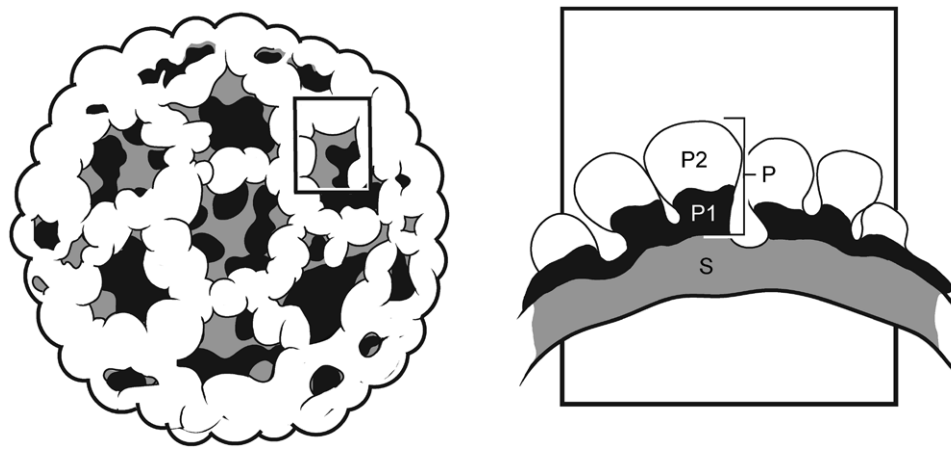

FIGURE 2. Schematic of NoV (original drawing). P is a protruding domain of VP1 in the viral capsid. P1 and P2 are subdomains of P. S is the shell domain of VP1 in the viral capsid. NoV indicates norovirus. VP1 is not designated.

Swedish investigators observed that during epidemics of G II NoV, secretors were susceptible to NoV diarrhea and nonsecretors were resistant.[34] None of the nonsecretors developed diarrhea despite representing 20% of the population. Individuals who were heterozygous for the secretor-gene developed diarrhea at the same rate as homozygous individuals, suggesting that the secretor gene was dominant. Haga and others[35] employed a sophisticated organoid model to prove that *FUT2* gene expression was both necessary and sufficient for binding to and infecting intestinal epithelial cells. They demonstrated the presence α1, 2 fucose within enterocytes of small intestinal organoids of both secretors and nonsecretors; however, α1, 2 fucose was only able to transit to the surface of the cells in organoids of secretors. Using a similar organoid model, Rimkute and others[36] very recently demonstrated that NoV attached to the HBGA embedded in abundant glycosphingolipids of intestinal enterocyte membranes in a secretor-dependent manner.

Specific Glycan Interactions With Norovirus

The target for binding of NoV to cells on the surface of the intestinal mucosa involves HBGA A, B, O, Lewis antigen and fucose. The fucose molecules must be attached to the HBGA at the α1, 2 positions as in secretors, or at the α1, 4 positions as in Lewis positive individuals (Fig. 1). In addition to fucose, binding of NoV also involves galactose.[37] Huang and associates[38] identified 7 binding patterns associated with blood groups A/B, O and Lewis antigens. The 7 binding patterns could be combined into either the A/B binding group or the Lewis group. The A/B group recognizes A and/or B and O antigens but not Lewis antigens. The Lewis group recognizes Lewis antigen and the O antigen.

The classification of NoV into genogroups clarified susceptibility patterns based on specific HBGA.[2] While early reports did not distinguish GI and GII viruses, later reports demonstrated that GI NoV preferentially attaches to antigens A and less so O; GII viruses fail to display a preference for specific blood groups as long as the individual is a secretor and Lewis antigen-positive, which may account for its greater frequency.[2,12,22] GI and GII NoV bind at different sugar moieties in the receptor. GI viruses are primarily galactose centric and GII viruses are primarily fucose centric.[2,12]

The binding sites in genogroups I and II are highly conserved.[2,12] In contrast, binding sites of genotypes are less conserved and account for diarrhea in diversely different populations. GII.4 infects secretors; however, GII.3, GII.6 and GII.7 are independent of secretor status and infect both secretors and nonsecretors.[39] Infection of nonsecretors indicates binding of the virus to the α1, 4 fucose in Lewis positive individuals.[4,12] Lindesmith et al[39] raised the possibility that bile acids may alter the binding site of NoV allowing the virus to attach and infect intestinal cells of nonsecretors.[39] Some of these factors may explain the high prevalence of NoV infections in Ugandan children with multiple genotypes beginning in the first year of life and recurring throughout childhood.[40]

ROTAVIRUS

Virology

RV is a nonenveloped, double-stranded RNA virus that belongs to the family *Reoviridae*,[41,42] and is a major cause of diarrhea in young children. It was discovered by Bishop and co-workers in 1973.[43] The genome is comprised of 11 segments that encode 6 structural proteins, VP 1-4, 6 and 7, and 6 nonstructural proteins.[41,42,44] The capsid is triple-layered (Fig. 3). VP2 is the inner layer of the capsid and it is lined with VP1 and VP3. VP6 is the middle layer. VP4 and VP7 constitute the outer layer. VP4 projects from the surface of the capsid and is comparable with the P domain of NoV (Figs. 2 and 3). VP4 is cleaved by a protease into VP8 and VP5. VP8 is the outermost portion of VP4 and functions in the initial attachment of RV to enterocytes.[12,13,42] It is hypervariable and is akin to P2 of NoV.[12] VP5 anchors VP4 into the middle of VP6 (Fig. 3). It participates in the penetration of the virus into the cell (Fig. 3). VP4 is designated as P for typing purposes and VP7 is designated G for typing purposes. There are 35 P types and 27 G types. P types P[4], P[6] and P[8] are most common and G types 1–4, G6 and G12 are the most common.[42,45] P11 and 14 types are notable for their proclivity to infect predominantly neonates.[13]

Secretor Status and Susceptibility to Rotavirus

The prevalence of P[4], P[6] and P[8] corresponds to the distribution of secretors, nonsecretors and Lewis antigens in various countries. Wherever secretory positive individuals are more common, as in Europe, North and Central America, and Asia, P4 and P8 predominate and wherever Lewis negative individuals are relatively more common, as in Sub-Saharan Africa, P6 predominates.[7] During 3 epidemics of P[8] in Nantes, France, all pediatric cases of diarrhea were among secretors even though nonsecretors represented 20% of the population.[46] Among Spanish children with diarrhea due to P[8], 99% were secretors and <1% were nonsecretors in a population where secretors comprise 70% and nonsecretors 30%.[47] In Taiwan, 99% of children with RV diarrhea were secretors even though nonsecretors represented 24% of the population.[48] In the

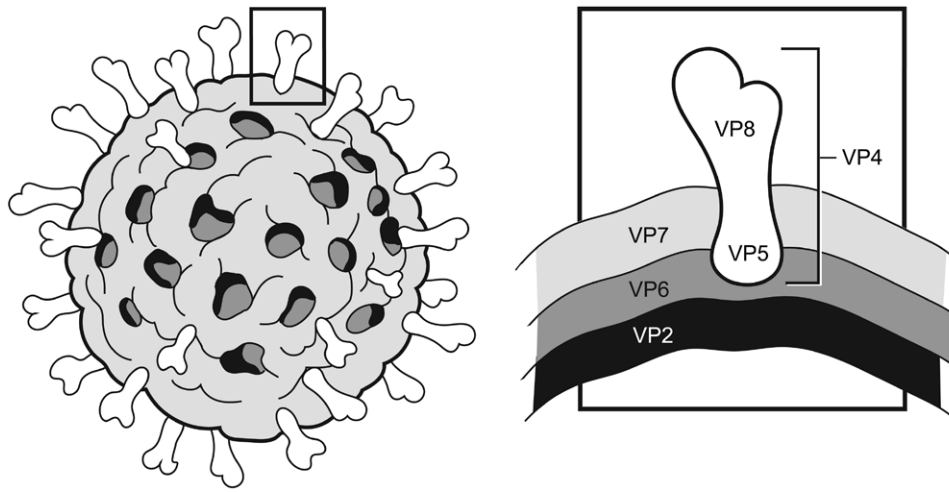

FIGURE 3. Schematic of RV (original drawing). VP4 is cleaved by a protease into VP8 and VP5. VP1 and VP3 are not shown. RV indicates rotavirus.

Taiwanese study, secretor status and Lewis positivity were independently associated with an increased risk for RV diarrhea. In Burkina Faso, Africa where Lewis negativity approaches 30% of the population, P[4] and P[8] infect secretor positive and Lewis positive individuals exclusively; in contrast, P[6] infect predominantly Lewis negative individuals irrespective of their secretor status.[49] Similar results have been observed in Malawi, Africa.[50] Variations in RV affinity for HBGA suggest possible genetic differences within P[4], P[6] and P[8] strains of virus.

Specific Glycan Interactions With Rotavirus

The target for binding of RV to cells on the surface of the intestinal mucosa is less well understood than the binding of NoV. The VP8 protein of VP4 binds to the glycans of HBGA in a specific manner according to P type.[2,7,12,13,41] P[4] and P[8], the most common strains of RV, bind to fucosylated glycans in Lewis positive secretors found prevalently in Europe and North America.[7] In contrast, P[6] binds to glycans in Lewis-negative individuals.[7] The ability of P[4] and P[8] to specifically bind to the fucose in the Lewis b antigen distinguishes them from P6.[51,52] Type P6 infects Lewis negative individuals irrespective of secretor status and that helps explain its prevalence in Sub-Saharan, Africa, where Lewis negativity rates are as high as 30%.[7,13,49] Hu et al[52] contend that P[4] and P[6] bind to the precursor of type 1 H antigen at a unique and conserved site that is consistent with their prevalence.[52] Overall, variations in RV affinity to HBGA suggest possible genetic differences in binding sites of P[4], [P6] and P[8] strains.[53,54]

Neonates handle RV very differently than older children. Although they get infected frequently, the infection is often mild or asymptomatic.[55,56] Pager et al[56] identified amino acid differences in the hypervariable region of VP8 between symptomatic and asymptomatic strains of neonatal RV and suggesting that these differences may be specific for P[6] RV. Ramani[13] suggested that P[6] actually recognizes both the precursor of type 1 H antigen and the type 1 H antigen itself as binding sites irrespective of Lewis antigen, which would ensure neonatal infection regardless of country or region. Hu and associates[52] provided further insight into the uniqueness of P[6] binding in neonates. Using strains common in neonates, they demonstrated structural changes in the virus that enabled binding to linear, unbranched glycans that are abundant in the neonatal gut but are rare in older children who possess branched intestinal glycans.

VACCINES

Rotavirus Vaccines

Two RV P[8] vaccines are currently available. Rotarix (GlaxoSmithKline, Brentford, United Kingdom) is attenuated human RV containing G1 P8 RV. RotaTeq (Merck, Kenilworth, NJ) is an attenuated bovine/human reassortant containing G1, G2, G3, G4 and P[8].[45,57] These vaccines have proven highly effective in the United States and Europe but less so in underdeveloped regions, especially in Africa, where P[6] RV is more common.[42,44] The vaccine data from less developed countries have been confusing, in part, due to the high rate of natural infection in young children. A study conducted in Malawi, Africa evaluated the effect of HBGA on the response to RV P[8] vaccine.[50] Shedding of the vaccine virus and vaccine seroconversion did not differ between secretors and nonsecretors nor between Lewis positive and negative individuals. Similarly, in the Taiwanese study, secretor status did not affect vaccine effectiveness.[48] A 2010–2017 study in Kenya documented more than 50% reduction in hospitalization rates for RV diarrhea since the introduction of Rotarix in 2014, thus demonstrating partial protection among African children.[58] In contrast to the studies conducted in Malawi and Taiwan, studies conducted in Pakistan and Ghana demonstrated reduced seroconversion rates to P[8] RV vaccine in nonsecretors compared with secretors.[59,60] A recently studied P[6] RV vaccine, RV2-BB, proved to be highly effective in African children irrespective of HBGA status.[61] The use of a vaccine containing P[6] may prove effective in further reducing RV diarrhea in regions such as Africa.

Norovirus Vaccine

NoV vaccine development has remained elusive until recently. The development of a vaccine had been hindered by the inability to readily grow the virus in common tissue culture and by a large number of genetically different virus types. The discovery of a murine NoV with similar VP1 and VP2 structures as human strains and its capacity to grow in tissue culture has contributed to the development of NoV vaccine.[62,63] Ettayebi et al had earlier shown that GII.4 NoV could grow in a human stem cell enteroid in 2016.[64] Now that the GII.4 genotype of NoV is acknowledged as the most common strain worldwide, it can be targeted as the vaccine candidate.[62,65] Vaccines are being developed but they are in preclinical stages of development. No licensed vaccine currently exists.

CONCLUSIONS

Secretor status has great consequences for a number of mucosal infections. In the case NoV and RV, the difference between secretors and nonsecretors could not be clearer; secretors are more susceptible to NoV and to RV diarrhea than are nonsecretors. The difference in susceptibility to RV infection between secretors and nonsecretors has also impacted RV vaccine effectiveness. We speculate that the difference in susceptibility to NoV between secretors and nonsecretors will be replicated in vaccine effectiveness once a NoV vaccine becomes available.

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