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Astrovirus

Victoria A. Meliopoulos, Virginia Hargest, and Valerie Cortez

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3.1 Introduction
Foodborne illnesses caused by viral contamination of food are a significant burden to public health. While foodborne illness is typically attributed to noroviruses, rotaviruses, and hepatitis A and E viruses\(^1\), astroviruses (AstVs) are now recognized as a leading contaminant of food and water sources. AstV infections are generally self-limiting, but can be associated with severe and systemic complications such as spread to extraintestinal sites (e.g., brain) in immunocompromised individuals. These adverse effects, as well as the extraordinary stability of the AstV particle, underscore the importance of understanding AstV pathogenesis and developing improved diagnostic techniques to prevent future outbreaks of foodborne gastroenteritis.

3.2 Astrovirus Classification
AstV is a positive-sense single-stranded RNA virus, and its genome consists of three open reading frames (ORFs). ORF1a and ORF1b encode the conserved RNA-dependent RNA polymerase, a viral protease, and various other uncharacterized nonstructural proteins, and ORF2 encodes the highly variable capsid protein.\(^2\) Madeley and Cosgrove first coined the term *astrovirus* in 1975 after noting its star-shaped morphology under an electron microscope.\(^5,6\) This characteristic appearance of AstV is due to protruding spikes of the capsid protein on the virion surface.\(^3\) Mature and immature human AstV (HAstV) particles are approximately 43 nm in diameter and have a continuous inner core layer surrounded by an outer layer of globular spikes,\(^7\) which likely harbors the receptor binding site.\(^8,9\) Cellular receptors for AstV have not yet been identified, but differences in the susceptibility of various cell lines to AstVs could indicate that they use multiple binding or receptor molecules.\(^10\)

3.3 Phylogeny
After the virus was first sequenced in 1993, it was proposed that these unique enteric pathogens be classified under a new family: Astroviridae.\(^11\) The International Committee on Taxonomy of Viruses divides Astroviridae into two genera according to species specificity: \(^{12\text{Avastrovirus}}\) infects avian species and \(^{12\text{Mamastrovirus}}\) infects mammalian species (Figure 3.1). Both genera are subdivided into two genogroups on the basis of their genetic relatedness within the ORF2 gene, which encodes the highly variable capsid protein. These genogroups are further classified into individual genotypes according to their mean amino acid distance.

Three distinct clades of HAstVs have been identified. The first clade includes the eight classical genotypes that were thought to be the sole causes of HAsTV infections until the late 2000s, when an additional eight genotypes were identified and named after the location where they were first discovered: Melbourne (MLB 1–3) and Virginia (VA 1–5).\(^13–19\) Phylogenetic analysis revealed that MLB and VA genotypes occupy two unique clades within *Mamastrovirus* that are distinct from the classical genotypes. The extent to which viruses from the three clades contribute to foodborne illnesses remains unclear, largely due to limited surveillance and screening of the food supply chain for these agents.
3.4 Zoonotic Potential

AstVs have been traditionally classified by the hosts from which they were first identified. However, several recent lines of evidence point to the possibility of cross-species transmission and challenge the dogma that AstVs are host restricted. First, avian, human-like, and novel AstVs were identified from fecal samples of synanthropic nonhuman primates in Bangladesh and Cambodia. Serum antibodies reactive against HAstVs were also identified in a subset of animals. Second, mink-like AstVs were sequenced in pigs and dogs. Third, there are reports of cross-genera transmission of avastroviruses in mink and mamastroviruses in European rollers (Coracias garrulus). A seroprevalence study on poultry workers also supports that avastroviruses can be transmitted in humans, because antibodies to turkey AstV type 2 were detected in a significant proportion of participants. However, it remains unclear whether such interspecies transmission events can cause overt disease. It is also unknown whether some of these molecular findings actually represent the identification of viruses with shared ancestry, as has been suggested for cattle and sea lions, which harbor viruses that cluster with HAstVs, and may also be confounded by the high propensity of AstVs to recombine. These findings suggest that cross-species transmission of AstVs is not only possible but probable. In the context of transmission of foodborne illness, these studies support the need for stringent screening for AstVs and recognition that the species specificity of AstVs is not a barrier limiting transmission from food sources.

3.5 Clinical Signs

While challenges in diagnosing cases of HAstV contribute to its underestimated prevalence, it is currently considered a leading cause of pediatric gastroenteritis, after rotaviruses and noroviruses. By the age of 5 years, 90% of children have detectable serum antibodies to at least one HAstV genotype. However, AstV infections are also underreported, because most of the infections are self-resolving and do not require hospitalization. A typical HAstV infection is characterized by mild watery diarrhea that lasts 1–4 days and is sometimes accompanied by vomiting, fever, loss of appetite, and abdominal pain. Many infections can be asymptomatic, meaning a carrier can unknowingly shed virus without taking proper infection control measures. Highly susceptible groups include young children and those immunocompromised by disease, immunosuppressant medications, or advanced age. An early study of immunocompromised children hospitalized for diarrheal illness reported a HAstV prevalence of 5%, with most infections being caused by adenovirus. However, advances in detection methods and the discovery of novel genotypes have facilitated the identification of HAstV infections. A recent study on pediatric oncology patients reported a HAstV prevalence as high as 22%. Virus shedding can last as long as 3–6 months in some children, and prolonged shedding could be associated with noncanonical strains. Thus, the high prevalence of HAstV in hospital settings is of particular concern and highlights the need to implement stringent infection control measures to
TABLE 3.1
Clinical Characteristics of Patients with Systemic Astrovirus Infections

<table>
<thead>
<tr>
<th>Gender/Age</th>
<th>Underlying Conditions</th>
<th>Type of Infection</th>
<th>Causative Agent</th>
<th>Site(s) of Detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/15 years</td>
<td>X-linked agammaglobulinemia</td>
<td>Encephalitis</td>
<td>HAstV-VA/HMO clade</td>
<td>Brain</td>
<td>Quan et al. 43</td>
</tr>
<tr>
<td>Male/3 months</td>
<td>SCID, gamma C deficient, postallogeneic</td>
<td>Encephalitis, disseminated</td>
<td>HAstV-4</td>
<td>Brain, heart, lung, spleen, bone</td>
<td>Wunderli et al. 45</td>
</tr>
<tr>
<td></td>
<td>HSCT</td>
<td></td>
<td></td>
<td>marrow, small intestine, stool, plasma</td>
<td></td>
</tr>
<tr>
<td>Male/7 months</td>
<td>SCID, postallogeneic</td>
<td>Gastrointestinal/ respiratory</td>
<td>HAstV-4</td>
<td>Stool, serum, nasopharyngeal and pharyngeal swabs</td>
<td>Wunderli et al. 45</td>
</tr>
<tr>
<td>Male/13 months</td>
<td>ZAP70 defect (T-cell deficiency)</td>
<td>Gastrointestinal/ respiratory</td>
<td>HAstV-4</td>
<td>Stool, nasopharyngeal and pharyngeal swabs</td>
<td>Wunderli et al. 45</td>
</tr>
<tr>
<td>Male/1.5 years</td>
<td>Postallocenic HSCT</td>
<td>Encephalitis</td>
<td>HAstV-VA1/HMO-C</td>
<td>Brain</td>
<td>Brown et al. 44</td>
</tr>
<tr>
<td>Male/42 years</td>
<td>CLL, postallocenic</td>
<td>Encephalitis</td>
<td>HAstV-VA1/HMO-C</td>
<td>Brain</td>
<td>Naccache et al. 46</td>
</tr>
<tr>
<td>Male/4 years</td>
<td>Congenital aplastic anemia, postallocenic</td>
<td>Encephalopathy</td>
<td>HAstV-MLB1</td>
<td>CSF, stool, urine, throat</td>
<td>Fremond et al. 42</td>
</tr>
<tr>
<td>Male/37 years</td>
<td>AML, postallocenic</td>
<td>Meningitis</td>
<td>HAstV-MLB2</td>
<td>CSF, plasma, stool</td>
<td>Cordey et al. 48</td>
</tr>
<tr>
<td>Female/21 years</td>
<td>None</td>
<td>Meningitis</td>
<td>HAstV-MLB2</td>
<td>CSF, anus, urine, plasma</td>
<td>Cordey et al. 48</td>
</tr>
<tr>
<td>Female/8 months</td>
<td>AML, postallocenic</td>
<td>Encephalitis</td>
<td>HAstV-VA1/HMO-C</td>
<td>Brain</td>
<td>Lum et al. 49</td>
</tr>
<tr>
<td>Male/20 months</td>
<td>Transient neutropenia</td>
<td>Viremia</td>
<td>HAstV-MLB2</td>
<td>Plasma</td>
<td>Holtz et al. 50</td>
</tr>
<tr>
<td>Female/13 months</td>
<td>None</td>
<td>Respiratory</td>
<td>HAstV-VA1</td>
<td>Nasopharyngeal swab</td>
<td>Lum et al. 49</td>
</tr>
<tr>
<td>Several/2–36 months</td>
<td>None mentioned</td>
<td>Unexplained fever</td>
<td>MLB2</td>
<td>Plasma, nasopharyngeal swab</td>
<td>Wylie et al. 51</td>
</tr>
<tr>
<td>Male/2 years</td>
<td>HSCT</td>
<td>Gastrointestinal</td>
<td>HAstV-8</td>
<td>Stool, plasma, gastrointestinal biopsy</td>
<td>van der Doef et al. 52</td>
</tr>
<tr>
<td>Female/2 years</td>
<td>HSCT</td>
<td>Gastrointestinal/ respiratory</td>
<td>HAstV-8</td>
<td>Stool, plasma, nasopharyngeal swab</td>
<td>van der Doef et al. 52</td>
</tr>
<tr>
<td>Male/5.2 years</td>
<td>HSCT</td>
<td>Gastrointestinal/ respiratory</td>
<td>HAstV-8</td>
<td>Stool, plasma</td>
<td>van der Doef et al. 52</td>
</tr>
</tbody>
</table>

Note: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CSF, cerebrospinal fluid; HAstV, human astrovirus; HSCT, hematopoietic stem cell transplant; SCID, severe combined immunodeficiency.

prevent transmission, especially among immunocompromised individuals of any age who are at risk of developing severe symptoms, including systemic spread of the infection.8

In fact, there are a growing number of case reports on systemic disease caused by both classical and nonclassical HAstV strains, including encephalitis, meningitis, and multiple organ failure, as summarized in Table 3.1. Most patients who experienced disseminated disease are immunocompromised due to the genetic disorder X-linked agammaglobulinemia42,43 or by hematopoietic stem cell transplant procedures.44–47 The only well-documented case of an immunocompetent patient who experienced extragastrointestinal disease was that of a previously healthy woman who was hospitalized at the University of Geneva Hospitals, Switzerland, in 2014 with acute meningitis.48 In this patient, cerebral spinal fluid, urine, and fecal samples collected at admission were positive for HAstV-MLB2. From these reports, we now have greater appreciation for the clinical spectrum of HAstV disease and parallels with animal AstV disease, as discussed later in this chapter.

Currently, there are no vaccine or treatment options for HAstV, in part due to the short duration and relatively mild symptoms caused by infection. The lack of focus in developing a HAstV vaccine might be because of its perceived low clinical impact or the need for a multivalent vaccine to cover all genotypes. If treatment is required, it generally involves the management of symptoms by oral or intravenous fluid replacement to combat dehydration caused by HAstV-induced diarrhea.

### 3.6 Epidemiology

Diagnostic techniques to identify HAstV infections have significantly improved in recent years. Initially, HAstV was detected by the presence of viral particles in stool samples by electron microscopy.5,6,53 However, this procedure is time consuming and cannot be scaled for high-throughput screening in most clinical settings.29 Conventional reverse-transcription (RT)-PCR and enzyme immunoassays were later used to determine the antigenic types of HAstV.54 For broad and rapid screening of HAstV, numerous real-time RT-PCR methods have been developed, many of which are multiplexed with primers that detect other enteric viruses.39 However, these molecular techniques do not detect HAstV infections by nonclassical VA or MLB genotypes, which require screening by additional molecular methods. To date, only one real-time RT-PCR multiplex method has been validated for detecting classical HAstV1-8, MLB1, and VA2 strains.36 The development of broad-spectrum methods that can detect the 16 known genotypes is impeded by the limited...
sequence information that is publically available, and thus remains an important goal for medical and research communities.

### 3.7 Modes of Transmission

Contaminated food, water, and fomites are the primary means for transmission of HAstV in humans. The virus is nonenveloped and its ability to resist inactivation in the gastrointestinal tract makes it highly stable. AstV can be detected in the stool for months from asymptomatic shedding and can persist up to 90 days on dry surfaces, such as food preparation tables. HAstV contamination of water is a major concern because of HAstV’s robust capsid structure; particles are stable in groundwater and at extreme temperatures. In fact, many wastewater treatment protocols are unable to remove HAstV, and it continues to be detected in both treated and untreated wastewater. Stringent methods are required by wastewater treatment plants to remove HAstV during the recycling process. AstV is resistant to standard chlorine concentrations (0.3–0.5 mg/L) (www.cdc.gov) used to disinfect water, and even treatment with 1000 mg/L of free chlorine for 2 hours resulted in only an approximately three-log decrease of AstV infectivity. Water parks and other recreational water supplies must also be monitored for AstV contamination. HAstV can be transmitted by consuming contaminated fresh or marine water, and by eating foods that are contaminated by these water sources, including leafy green vegetables and soft fruits. Therefore, environmental contamination of water used to irrigate crops can also pose a risk.

Surfaces contaminated with fomites must be disinfected with 90% ethanol, and this is required in most health-care settings. AstV can remain stable at pH 5 and is resistant to many detergents including nonionic, anionic, and zwitterionic detergents. Lipid and chlorine solvents are also ineffective; however, formaldehyde and peroxymonosulfate can fully inactivate the virus. Temperature modulation is also ineffective. Heating AstV for 10 minutes at 60°C is insufficient to inactivate the virus; refrigeration is ineffectual since AstV is also very stable at low temperatures, remaining infectious as long as 10 years; however, repeated freeze–thaw cycles can destroy AstV. Yet most studies on disinfection have focused on canonical HAstV strains, leaving the question of how infection from noncanonical strains can be prevented.

Bivalve mollusks such as clams, mussels, and oysters are also a common source of AstV contamination. Mollusks are filter feeders that continuously take up water, and due to the ability of AstV to remain stable in water, they can frequently become tainted. Although AstV typically spreads in colder months, most studies of AstV prevalence in shellfish (reviewed in Karlsson and Schultz-Cherry) were able to detect AstV at all times of the year. In epidemiological studies involving shellfish-related outbreaks of illness, AstV was detected in both stool samples and the suspected food; however, the presence of other viruses made it impossible to determine causality. Unfortunately, most food processing and disinfection techniques are ineffective against AstV.

Food preparation and handling can also be a source of contamination. Asymptomatic shedders of AstV may inadvertently contaminate both food preparation surfaces and foods that require handling, such as salads, sandwiches, and garnishes. Infection could also come directly from animals raised for human consumption. For example, AstV has been detected in the muscle tissue of turkeys, although it is unclear if turkey AstVs cause disease in humans. Further complicating matters, limited detection techniques make it hard to document AstV outbreaks. Compared with novel strains, more information is available about the classical HAstV strains, with numerous reports of food outbreaks and their detection in wastewater (reviewed by Bosch et al.). Three recent studies have reported both VA and MLB viruses in wastewater samples in the United States, Japan, and Uruguay, indicating that these novel strains also play an important role in causing foodborne illness.

### 3.8 Impact on the Agricultural Industry

Because of its stability and the threat of cross-species transmission, AstVs pose a major problem for the agricultural industry. Animals raised for human consumption, such as chickens, ducks, cows, sheep, lambs, and turkeys, can be infected by various AstV genotypes that manifest a spectrum of symptoms. In cattle, bovine AstV causes not only gastrointestinal disease but also encephalitis and meningitis. There are also several reports of mammastrovirus-related encephalitis in mink (known as shaking mink syndrome). Chicken AstV (CAstV) infections often occur in broiler chickens and are strongly linked with diseases in hatcheries and young birds. CAstV infections are associated with malabsorption diseases such as running-stunting syndrome, which is characterized by poor weight gain in young broiler flocks within the first few weeks to months after hatching. CAstV infect organs outside of the intestinal tract, including the liver and kidneys, and cause up to 40% mortality in commercial broiler chickens. CAstV can also induce “white chick” syndrome, which decreases the hatch rate, increases mortality and weakness, and leads to pale plumage in chickens.

Similarly, turkeys infected with AstV also exhibit stunted growth. In addition to diarrhea episodes, turkey AstV (TAstV) infections are associated with poult enteritis mortality syndrome (PEMS). PEMS affects turkey poult s at the age of 1–4 weeks and is characterized by diarrhea, dehydration, and increased mortality. Infected pouls can also experience thymic and bursal atrophy. The frequency of TAstV ranges from 40% to 80% in symptomatic poult s but is less than 50% in healthy flocks. Thus, the increased mortality and decreased growth and hatch rate associated with avian AstV infection pose a huge burden to the poultry industry. Also, the threat of contamination of human food sources underscores the importance of understanding AstV pathogenesis.

### 3.9 Pathogenesis

Most pathogenesis studies have focused on the mechanism by which AstV causes diarrhea. Intestinal epithelial cells, the primary replication site of AstV, form a tight barrier and carefully regulate the passage of nutrients, molecules, ions, other solutes, and water from the mucosal side to the
intestinal lumen. Tight junctions are held together by the tight junction complex, which comprises proteins such as occludin, claudins, ZO-1, and cadherins. Through these junctions, cells can regulate and maintain barrier permeability. Typically, intestinal pathogens disrupt the intestinal epithelium by causing cell death or overt inflammation. However, AstV-induced diarrhea usually occurs in the absence of cell death or inflammation,  

Although HAstV-8 can induce apoptosis in the human adenocarcinoma cell line Caco-2.  

Histological sections from turkey intestines showed no evidence of lesions, cell death, or inflammation, and were negative for TUNEL staining. Increased serum levels of the immunosuppressive cytokine TGF-β were found in infected turkeys for as long as 12 dpi, and intestinal homogenates from infected turkey embryos had increased TGF-β bioactivity.

Still, numerous studies report that AstV infection alters permeability of the intestinal barrier. In vitro, AstV infection caused a decrease in transepithelial resistance (TER) in Caco-2 monolayers and allowed the passage of fluorescein isothiocyanate (FITC–dextran through to the basolateral chamber.  

In vivo, TER or flux alterations began 16–20 hours postinfection (hpi), with maximum permeability by 36–48 hpi. In the later stages of infection, localization of claudins and ZO-1 proteins was also affected. Similar results were seen in vivo in a turkey poult model using TAstV, where compared with uninfected controls, infected poult s had increased mucosal-to-serosal flux and altered conductance levels of the small intestine, implying dysregulation of ionic transport. There is evidence that mice infected with murine AstV also showed increased intestinal permeability, as measured by the amount of orally administered FITC-dextran reaching the blood, although further study is needed. Increases in intestinal permeability are attributed to changes in localization of tight junction–stabilizing F-actin rings and the junctional protein occludin. In turkeys, the AstV nsP protein colocalized with F-actin fibers in infected intestinal epithelial cells, indicating there may be some direct interaction that is leading to disruption of tight junctions. Also, there was relocalization of the sodium transport protein NHE3 into the cytoplasm of intestinal epithelial cells and away from the plasma membrane, although overall levels of NHE3 were not affected, supporting that AstV interferes with ionic transport. Within 15–20 minutes of infection, AstV also activated extracellular signal–regulated kinase 1/2 (ERK1/2), and inhibition of ERK resulted in decreased viral replication. Therefore, AstV might cause targeted and sequential disruption of the tight junction structure that initiates a signaling cascade, resulting in dysregulation of ions and the inability to regulate water transport.

Interestingly, AstV-mediated disruption of barrier permeability does not require active replication. Moser et al. found that both ultraviolet-inactivated HAstV and recombinant capsid protein decreased barrier permeability in Caco-2 cells and activated extracellular signal-regulated kinases 1 and 2 (ERK1/2). Similarly, in the turkey poult model, administration of the recombinant TAstV-2 capsid protein caused transient diarrhea for less than 72 hours, and capsid-treated birds had loss of NHE3 expression at the plasma membrane, similar to pouls infected with virus. These observations highlight the need for increased vigilance with disinfection techniques, because it appears that even inactivated virus can cause disease symptoms.

Because AstV infection does not cause severe inflammation, the immune response to AstV is not well characterized. AstV can infect both intestinal epithelial cells and intestinal macrophages, but infection in macrophages is not productive. Although AstV can result in decreased macrophage function and viability, AstV-infected macrophages have increased levels of nitrogen oxide (NO) as a result of inducible NO synthase (iNOS), and NO can decrease AstV replication in vitro. AstV is also sensitive to type I interferon (IFN-β) response. IFN-β levels increase after AstV infection and contribute to preserving barrier integrity. Productive replication is required to induce IFN-β, because the capsid protein alone of UV-inactivated HAstV cannot increase IFN-β levels. IFNAR−/− mice, which are unable to respond to type I IFNs induced by AstV, continued to shed as long as 53 dpi and could not clear the virus after infection compared with C57Bl/6 controls. Figure 3.2 summarizes the current body of knowledge on AstV pathogenesis.

Studies on AstV pathogenesis in humans have been limited. Although initial studies on AstV were conducted in adult volunteers, the results may not necessarily be extrapolated to immunocompromised and/or immunologically naïve children. The Caco-2 cell line is most commonly used for in vitro studies on classical HAstV, which may not completely recapitulate the mechanisms that occur in vivo. Various other immortalized cell types can propagate HAstV; however, some cell lines can propagate specific genotypes but not others. Furthermore, the lack of a cell culture system for the MLB and VA strains in the research setting greatly limits our ability to characterize these novel viruses.

Translating AstV studies to an in vivo model is also challenging. Currently, most studies have been performed in a turkey poult model. Although the information gleaned from these experiments has been invaluable, the turkey model poses several problems. Although poult s develop clear, easy-to-discern clinical signs, TAstV-2 is an avastrovirus and is genetically distinct from mastroviruses; therefore, it is unclear how aspects of TAstV–induced disease translate to HAstV canonical and noncanonical strains. Studies on TAstV-2 have also been hampered by the lack of a cell culture system to propagate the virus, and researchers are limited to generating the virus in intestines of inoculated embryonated turkey eggs. Moreover, experiments on turkeys are difficult and costly to set up: turkey poult s are purchased as eggs and need to be incubated and hatched under specific conditions. The experimental setup is challenging because (1) the hatch rate is approximately 50%, which results in decreased sample sizes; and (2) AstV is a highly transmissible pathogen and uninfected controls must be housed in a separate room to avoid cross-contamination. Turkey eggs are made available to researchers through agricultural sources, and therefore researchers compete with agricultural needs to obtain eggs. Most importantly, turkey-specific reagents are not widely available, which hampers the ability to perform mechanistic studies. These limitations highlight the need to develop a small-animal model to make further progress in AstV research.

The recent discovery of murine AstV (MuAstV) offers promise in developing a conventional animal model for AstV. As with the turkey poult model, cross-contamination is a concern, and MuAstV has been detected in mice obtained from several laboratory vendors. Therefore, stringent husbandry practices...
are required to reduce cross-contamination. Fortunately, MuAstV is a mamastrovirus and many mouse-specific reagents are available for it, thereby making it an attractive model. However, care must be taken while defining this model, because mice do not develop clinical symptoms. Hence, further evaluation is necessary to develop an efficient mouse model for AstV.

3.10 Future Directions

AstV is a widespread and potentially dangerous enteric pathogen that cannot be ignored. Although the AstV field has expanded considerably in recent years, much work remains to effectively combat AstV-induced illness. From a clinical standpoint, it is crucial to develop sensitive diagnostic techniques to identify noncanonical genotypes as new strains are discovered. It is also vital to extend our knowledge of AstV pathogenesis to these new strains in order to examine their propensity for systemic virus spread and to develop prevention strategies. Identifying the viral receptor(s) and elucidating the mechanism of AstV-virus spread and to develop prevention strategies. Identifying new strains in order to examine their propensity for systemic infection is critical first steps in this direction, and cross-species transmission has serious implications. AstV surveillance efforts must be extended to food, water, and the environment to minimize transmission, and ascertain the threat of AstV to food safety. Recombination events and exposure to animal AstVs via food sources may pose a greater risk than previously thought, and stringent disinfection strategies must be optimized and fully executed. Future efforts need to focus on elucidating the drivers of these events and minimizing outbreaks of AstV infection.

REFERENCES

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