HUMAN ASTROVIRUSES: A BRIEF REVIEW

Martin Zang Pam¹ & Victor Omote²

 Department of Animal Health, Federal College of Animal Health and Production Technology, Vom, Nigeria (pamartinz80@gmail.com)
Department of Laboratory Services, Central Hospital Warri, Nigeria (<u>boyoo4pre@gmail.com</u>)

Abstract

Astroviruses belonging to the family Astroviridae are cosmopolitan and infect a wide range of mammalian and avian hosts. Human Astroviruses (classic HAstV) under the genera Mamastrovirus within eight (8) different serogroups are responsible for 2-9% of all acute nonbacterial gastroenteritis in children worldwide. Although its pathogenicity and pathogenesis are still poorly understood, attachment of the viral spike and capsid protein to intestinal epithelial cells activates a process which results in mal-absorption, loss of secretory functions, and reduced permeability. The possibility for cross-species transmission has raised alarm about possible zoonotic transmission. Thus, its biology, epidemiology, pathology, immunology, diagnosis and management are briefly reviewed.

Keywords: Human Astroviruses, epidemiology, pathology, immunology, diagnosis, management, interspecies transmission, zoonosis

Introduction

Astroviruses (AstVs) are a diverse family of viruses that infect a wide range of mammalian and avian hosts. Named after their distinct five-pointed six-pointed or star-like appearance when visualized under an Electron microscope (EM); astrovirus is derived from the Greek word astron meaning "star" (Risco et al., 1995). Although there were some undocumented reports about earlier outbreaks in China, the first reported cases of Human Astrovirus associated outbreak was recorded in 1975 following the identification of the starlike virion particles in the stool and vomitus of children from a maternity ward (Appleton and Higgins, 1975). Belonging to the family Astroviridae, astroviruses are small, positivesense, single stranded, and non-enveloped RNA viruses measuring ~28 to 35 nm in length and enclosed in a nucleocapsid coat (D'Souza, 2015). The genome contains three open reading frames (ORFs), named from the 5' end to the 3' end ORF1a, ORF1b, and ORF2. ORF1a and ORF1b encode the

nonstructural proteins (nsPs) involved in RNA transcription and replication, while ORF2 encodes the structural proteins, which are expressed from a subgenomic RNA (Monroe et al., 1993). The HAstV replication cycle shares many common features with the replication cycle of members of the Caliciviridae family. After cell entry and uncoating, the two main nonstructural polyproteins are translated from the VPglinked genomic RNA. Cleavage of these results polyproteins in the individual nonstructural proteins required for genome replication, which takes place in replication complexes assembled in close association with intracellular membranes. This process results in the formation of both genomic and subgenomic RNAs, which are produced in large quantities to ensure the production of high yields of structural proteins. After encapsulation and maturation, virions are released from the cell (Marczinke et al., 1994). HAstV infection is cosmopolitan and is believed to be responsible for 5-9% of the

cases of gastroenteritis in young children (Monroe et al., 2001). Humans of all ages are susceptible to astrovirus infection. However, children, the elderly, and those that are immunocompromised are more susceptible. Viral transmission peak seems to be season dependent. In temperate regions, transmission peak occurs during the winter months while the raining season accounts for bulk of transmission for tropical regions (Glass et al., 1996; Abad et al., 2001). Fecal-oral route account for bulk of HAstV transmission with few cases of zoonotic transmission reported (Meliopoulos et al., 2014). Although disease formation process (pathogenesis) is still poorly understood, it is believed that attachment of viral particle via its spikes to epithelial cells of the intestine produces a complex that disrupts normal epithelial cells functionality and results in mal-absorption, loss of secretory functions, and reduced permeability (Nighot et al., 2010; Meliopoulos et al., 2016). Unlike other gastrointestinal viruses, the virulence factors of astroviruses remain poorly understood. However, studies on avian model have implicated the capsid protein to serve as an enterotoxin responsible for the associated diarrhoea (Meliopoulos et al., 2016). Data emanating from studies on human viruses have demonstrated that the capsid protein of HAstV acts as an inhibitor of the complement system, which constitutes an important innate response against bacterial and viral infections (Bosch et al., 2014). HAstV infections are usually asymptomatic with few symptomatic immune-compromised cases among individuals. However, symptomatic cases are usually characterized by a mild, watery diarrhoea that lasts 2 to 3 days, associated with vomiting, fever, anorexia, and abdominal pain. Few cases of systemic invasion resulting in disseminated lethal infections among highly immune-compromised children have also been reported (Wunderli et al., 2011). Although the mechanism is still poorly understood, adaptive

immunity is believed to play a role in the initiation and severity of HAstV infection. Human studies among healthy volunteers revealed individuals with circulating antibodies against the virus were either asymptomatic or displayed mild symptoms when compared to those without circulating antibodies (Midthun et al., 1993). Cell culture propagation of some classic HAstVs is possible with the aid of trypsin (Willcocks et al., 1994) but electron microscopy and immunological assays are the commonly used diagnostic methodology before the advent of molecular detection techniques. The usage of these techniques is dependent on availability of equipment, skilled-man power, number of samples to assay, and purpose of analysis (diagnosis or research). HAstV infections are usually self-limiting and resolves within 2-6 days. However, serious gastroenteritis may require oral or intravenous fluid replacement to avoid dehydration. There are reports proposing the use of probiotics, flavonoids and intravenous treatment with IgG for immunecompromised hosts with severe or persistent diarrhea (Britton and Versalovic 2008; Superti et al., 1990; Björkholm et al., 1995). Prevention and control strategies employed against HAstV may be transmission route or/and host targeted. Since most transmission occurs via the fecal-oral route, improved proper fruits and vegetable sanitation, handling as well as adequate cooking of seafood are measures proposed to target the transmission route. Host dependent control strategies revolve around prompt diagnosis and management pending the availability of commercial vaccines. With the eminent threat posed by zoonotic diseases and the possibility of zoonotic transmission of Astroviruses, this review presents existing knowledge, highlights recent findings escalates research and gaps/limitations.

Historical perspective

Although there were some undocumented reports about earlier outbreaks of human Astrovirus infection in China, it was in 1975 that Appleton and Higgins reported the presence of a 28 to 30nm particle in stools of children vomiting and suffering from mild diarrhea in a maternity ward (Appleton and Higgins 1975). That same year, Madeley and Cosgrove described a distinct five-pointed or six-pointed star-like particle under an electron microscope when they viewed stool samples from infants suffering from diarrhea and named it Astro meaning "star-like" (Risco et al., 1995) In 1981, Lee and Kurtz were able to propagate Astroviruses in cell culture (primary human embryonic kidney cells) This giant stride resulted in the differentiation of Astroviruses from other agents, such as the Norwalk agent, which cannot be grown in culture. The same pair of researchers identified five serotypes of Astrovirus in 1984 using antisera (Kurtz and Lee 1984). In 1988, Hermann and co-workers developed monoclonal antibodies against Human Astroviruses which resulted in their diagnosis using enzyme immune-assay. The production of monoclonal antibodies paved the way for several modifications that resulted in the identification of two extra serotypes bringing the total to seven serotypes in 1991. The first complete Human Astrovirus genome sequence occurred in 1994. Improved knowledge of its genomic and subgenomic organization in combination with findings from the processing of its polyprotein resulted in the clamour for a re-classification of the Astroviruses and their separation from the families Picornaviridae and Caliciviridae which was eventually adapted by the International Committee for the Taxonomy of Viruses (ICTV) in 1995 (Monroe et al., 1995). The classification of theses viral particles into their own family (Astroviridae) and subsequent modification in technologies used for their diagnosis led to increased epidemiological studies which

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implicated Astroviruses to be a leading cause of gastroenteritis among children and immunecompromised adults by the year 1998. From early 2000 till date, lots of metagenomic surveillance studies have led to the identification of a new serotype bringing the number of classic Human Astroviruses to eight serotypes and another two groups of novel Astroviruses referred to as the Nonclassic which are commonly referred to as HAstV-MLB and HAstV-VA/HMO (Finkbeiner et al., 2008; Finkbeiner et al., 2008; Finkbeiner et al., 2009)

Taxonomy and classification

Viruses belonging to the Astroviridae family were initially grouped into one genus (Astrovirus) based on their morphology (Bosch et al., 2014). This classification was adopted by the International Committee for Taxonomy of Viruses (ICTV) in 1995, but has undergone several modifications over the years (Krishnan, 2004). In 2004, two genera Mamastrovirus (MAstV) and Avastrovirus (AAstV) were created from the Astrovirus genus based on origin of host. Astroviruses with mammalian host were grouped under the genus "Mamastrovirus" while astroviruses that infects avian species were categorized into the Avastrovirus genus (Donato and Vijaykrishna, 2017). Taxonomy of Astroviruses from the Realm to Genera level is summarized below:

Realm Riboviria

Kingdom Orthornavirae

- **Phylum** Pisuviricota **Class** Stelpaviricetes
- Class Stelpavincetes
- Order Stellavirales
- Family Astroviridae

Genera Avastrovirus and Mamastrovirus

The advent of genome sequencing and extensive epidemiological studies has rendered the species-based classification inadequate. Interspecies transmission of viruses and diversity of viruses within one host prompted the ICTV in 2010 to propose the classification of astroviruses based on the amino acid sequence of the ORF2 genome region, recommending that different strains of the same astrovirus species should share >75% identity in the capsid proteins (Bosch et al.,2012).

Astroviruses of the same genotypes are further classified into different serotypes based on their antigenicity. While all eight classic HAstVs clearly correspond to different serotypes, non-classic Astroviruses still requires series of investigation to determine their antigenic variations (Bosch et al., 2014).

Structure and Genome

Human Astroviruses (HAstV) are single stranded, positive-sense, non-enveloped RNA viruses of icosahedral particle symmetry that cause a variety of clinical diseases ranging from diarrhea to encephalitis, or asymptomatic infection in children, the elderly and immunecompromised individuals (Bosch et al., 2014). Measuring 38-41nm, all 8 serotypes consists of three capsid proteins and possesses a distinctive star-like appearance when observed under an electron microscope (Risco et al., 1995). Surface projections are small and surface appears rough with spikes protruding from the 30 vertices (Bosch et al., 2014). With a buoyant density ranging from 1.35 and 1.37 g/ml in CsCl, their capsid precursor protein (180 copies per particle) is primarily involved in viral maturation.

AstV genome is a positive-sense ssRNA molecule of around 6.8 (6.2 to 7.8) kb containing three open reading frames (ORFs), named from the 5' end to the 3' end ORF1a, ORF1b, and ORF2. ORF1a and ORF1b encode the nonstructural proteins (nsPs) involved in RNA transcription and replication, while ORF2 encodes the structural proteins, which are expressed from a subgenomic RNA (Willcocks and Carter, 1993). Regarding genome organization, two untranslated regions (UTR's), the 5' UTR and the 3' UTR, of 11 to 85 and 80 to 85 bases, respectively, are located at the ends of the AstV genome (Bosch et al., 2014). No Internal ribosome entry site (IRES) has so far been described in AstV (a feature it shares with viruses grouped in Caliciviridae family but not with other positive sense single-stranded RNA viruses (Racaniello V, 2007; Lindenbach and Rice 2007; Green 2007). In addition to the poly (A) tail consisting of around 30 adenines, a highly conserved secondary element is present at the 3' end of the AstV genome. This secondary structure is also present in the genome of some members of coronaviruses, noroviruses, and rhinoviruses but its function is yet to be determined (Robertson et al., 2005; Jonassen et al., 1998).

The lengths of ORF1a, ORF1b, and ORF2 vary depending on the AstV strain. This variation is largely dependent on the insertions and deletions present at the 3' end of ORF1a (Guix et al., 2005). ORF1a encodes a putative helicase domain (HEL), several transmembrane (TM) and coiled-coil (CC) domains, the protease domain (PRO), a VPg, a hypervariable region (HVR), a nuclear localization signal (NLS), and a putative death domain (DD). ORF1b encodes the RNA dependent-RNA polymerase (RdRp). ORF2 contains the region coding for the shell proteins, a P1 domain of unknown function, a variable region containing the P2 domain which includes the spike proteins, and an additional acidic domain at the C terminus (Bosch et al., 2014).

Replication cycle

The HAstV replication cycle shares many common features with the replication cycle of members of the Caliciviridae family (Bosch et al., 2014). Below is a step by step presentation of events of the replication cycle of Human Astroviruses as described by Schultz-Cherry (2013).

Attachement to host receptors probably results in clathrin-dependent endocytosis of the virus into the host cell. Entrance of the virus into the cell causes reduction in pH which leads to uncoating, and release of the viral genomic RNA into the cytoplasm.

The genome is then translated, giving rise to nsP1a1b and nsP1a polyproteins, which are then cleaved by the viral serine protease (in nsP1a) as well as some cellular proteases, resulting in the individual nonstructural protein.

Proteolytic processing of polyproteins nsP1a1b (around 160 kDa) produces the nsP1b protein (RdRp) (around 57 kDa) and the nsP1a protein (around 102 kDa), which is subsequently cleaved to yield several mature products.

Replication occurs in viral factories made of membrane vesicles derived from the ER.

A full-length negative-sense genomic RNA is synthesized and used as a template for the production of both positive-sense genomic RNA and positive-sense subgenomic RNA.

Subgenomic RNA translation gives rise to the capsid protein precursor VP90.

VP90 polyprotein initially assembles into immature virions in association with intracellular membranes through its C terminus. Several cellular caspases further cleave these VP90 polyproteins close to their C termini once they have dissociated from membranes. resulting in viral capsids composed of 70-kDa polyproteins (VP70).

Finally, VP70-containing viral particles would be released from cells and proteolytically processed by trypsin to enhance infectivity.

Virus release by cell lysis and maturation of the capsid by proteolytic cleavages Antibody induction / Inhibition of complement



Epidemiology

HAstVs are distributed all over the world and are associated with 2 to 9% of cases of acute,

nonbacterial diarrhea in children (De Benedictis et al., 2011). The mean incidence worldwide is 11%, with 7% and 23% incidences in urban and rural areas, respectively (Bosch et al., 2013). HAstV incidence is usually higher in developing countries, although paradoxically, a low incidence of infection is observed in sub-Saharan Africa (Kiulia et al., 2007).

Known as the second most common virus found in children with diarrhea, Human Astroviral infection is prevalent among pediatric population (Shastri et al., 1998), but the elderly and immunocompromised are also susceptible (Björkholm et al., 1995). Although less common among the healthy population, the typical age range for Human Astrovirus infection is from 0-5years of age, with up to 90% of children age five years have circulating antibodies specific for Astroviruses (Mustafa et al., 2000).

The classic HAstV distribution follows a seasonal pattern with a higher incidence of infection in temperate regions in the cold-weather period and rainy season for tropical regions (Steele et al., 1998). The cold temperature favours the stability of the virus, while rainy season encourages poor hygiene practices that embolden the distribution of the virus.

The primary route of transmission for Human Astroviruses is fecal-oral. Viruses released with feaces finds its way into water bodies where it contaminates food and drinking water (Le Cann et al., 2004). Common foods susceptible to become contaminated with HAstV at the preharvest stage are bivalve mollusks grown in polluted waters (Le Guyader et al., 2000) and fresh produce irrigated with contaminated water, such as lettuce, green onion, and other greens, as well as soft fruits such as raspberries and strawberries (Pintó and Bosch, 2008). These products are usually consumed with little or no cooking and hence are susceptible to act as vehicles for human enteric virus transmission. Most institutional outbreaks have been linked to fomites (Cubitt et al., 1999). Poor disinfecting practices as well as inadequate hygiene particularly in high-risk settings such as hospitals, institutions for the elderly, day care centers, or restaurants, accounts for most Human Astrovirus cases after Fecal-oral transmission.

Although astroviruses were initially considered to be so species specific that it led to their classification based on the host species, concern about the potential zoonotic transmission of astroviruses to humans has recently arisen. In comparison to individuals who had no contact with turkey, turkey abattoir workers were three times more likely to test positive for antibodies against turkey astroviruses (Meliopoulos et al., 2014).

Pathogenicity and pathogenesis

The lack of suitable cell culture systems for the majority of the genotypes, coupled with the absence of adequate animal model to study the disease progression of Astroviruses has complete understanding of hamper its pathogenesis. However, studies from turkey model have implicated the viral spikes and protein capsids as its key virulent factors (Toh et al., 2016; Bogdanoff et al., 2016). While it is been postulated that both the spikes and capsid protein functions in the recognition and binding to a carbohydrate receptor still unidentified, the capsid protein has been reported to act as an entero-toxin as well as function in inactivating host immune responses (complement cascade) (Meliopoulos et al., 2016).

Reports of Astrovirus studies using human colon carcinoma cells type 2 (Caco-2) revealed that binding of viral particle to susceptible cell line results in the disruption of tight junctions. Tight junctions are highly regulated cell–cell associations that help maintain cell polarity and prevent the free passage of macromolecules and microorganisms from one side of the epithelium to the other (Torres-Flores and Arias, 2015). Junctions are multi-protein domains composed of trans-membrane proteins, such as occludin and claudins, which interact with cytosolic adapter proteins, like Zonula occludens (ZO-1). These interactions connect the cell membrane with the actin cytoskeleton. Disruptions of the tight junction can result in altered ion and/or solute exchange, increasing fluid to the lumen of secretory functions, and decrease in epithelial permeability in the intestines are hallmarks of gastroenteritis caused by Astroviruses (Moser et al., 2007). It is worthy to note that diarrhea associated with Astroviruses had little or nothing to do with epithelial damage or inflammation of infected cells (Bosch et al., 2014).

Clinical manifestation

The clinical manifestation of human Astroviral infection has been reported to be dependent on a number of factors (age, immune status, previous exposure, co-infection with other entero-viruses and geographical location) (Jeong et al., 2012). However, HAstVs, are gastrointestinal pathogens associated with diarrhea after about 4-5 days of incubation (Lee et al., 2013). Mostly asymptomatic, few cases are characterized by a mild and watery diarrhea, vomiting, fever, anorexia, and abdominal pain (Bosch et al., 2014). Vomiting is less prevalent in astrovirus infection than in rotavirus or calicivirus infection. In general, HAstV diarrhea is milder than those caused by rotaviruses or noroviruses, and it resolves spontaneously, although in some cases HAstV infections have required hospitalization (Bosch et al., 2014).

Although HAstV are believed to be associated with gastro-intestinal infection, there are reports of systemic spread resulting to severe disseminated lethal infections in highly immune-compromised children (Wunderli et al., 2011). Finally, the relationship of HAstV infection to the etiology of intussusception in children has also been studied. Although with less frequency than rotavirus, norovirus, and adenovirus infection, HAstV infection has also been identified as a potential risk factor for intussusception in infected children (Aminu et al., 2009).

Host Immune Responses

The observation that AstV infection is age dependent led to the assumption that immune protection is acquired after an initial infection. However, the specific immune responses activated upon AstV infections are not yet completely understood (Bosch et al., 2014). There are epidemiological and clinical studies that have demonstrated that humoral immune response plays a role in restraining infection and disease in humans. Two clinical studies carried out among human volunteers revealed a negative correlation between infection severity and the presence of circulating HAstV antibodies prior to being challenged by the viral particle (Midthun et al., 1993).

Molberg and co-workers in 1998 demonstrated the presence of HAstV-specific CD4+ and CD8+ T cells residing in the normal tissue of small intestinal biopsy specimens from healthy adults in an organ culture system when it was challenged with inactivated HAstVs. Thus, it is clear that both humoral and cell mediated adaptive immune responses are involved in protecting normal healthy adults from reinfections.

Laboratory diagnosis

The diagnosis of Astroviruses started with electron microscopy of negatively stained stool samples, but has evolved to more sophisticated molecular methods with sensitivity and specificity as high as 90-95%. The usage of these techniques is dependent on availability of equipment, skilled-man power, number of samples to assay, and purpose of analysis (diagnosis or research). Each of these techniques is discussed briefly below.

Electron microscopy

HAstVs were routinely detected by direct transmission electron microscopy (EM) in

negatively stained stool samples (Cubitt et al., 1999). This method was the pioneer diagnostic method but a push for several alternatives was born out of the numerous limitations associated with its use. This procedure is laborious, time-consuming, and entails the services of experienced personnel. Secondly, its sensitivity has been questioned since only 10% of the viral particle present in stool retains the characteristic star-like shape necessary for its diagnosis (Madeley, 1979). Several techniques have been employed to increase the sensitivity of electron These methods microscopy. include concentration of viral particles in stool sample as well as the use of immune cells (Berthiaume et al., 1981).

Virus isolation

Astroviruses, like other enteric viruses, can be difficult to propagate in conventional cell cultures. The first propagation of HAstVs was made possible by Lee and Kurtz in Human embryo kidney (HEK) cells through the use of serum medium supplemented in trypsin (Lee and Kurtz, 1981). Several cell culture platforms have been studied with a bid to isolate and gain insight into the pathology of Human Astroviruses, but very few have been able to support the growth of Human Astroviruses. Presently, adenocarcinoma cell lines, colonic carcinoma cells and human hepatoma cell line are the commonly used platform used to propagate the growth of Human Astroviruses (Brinker et al., 2000). While virus isolation can serve as a useful tool to investigate astrovirus biology, it is still not an ideal diagnostic tool for detection of astrovirus in diagnostic laboratories, due to slow turnaround times and difficulty of isolation (Pérot et al., 2017).

Serology

The ability to grow astroviruses has simplified the production of antisera in experimental animals, allowing the characterization of serotypes and the development of a radioimmune assay for detection of anti-MAstV 1 (serotypes HAstV 1-8) antibodies Cubitt. 1988). (Wilson and Several modifications made possible via the development of monoclonal antibodies has resulted in the development of Enzyme-linked immunosorbent assays and Rapid immunochromatography tests with good sensitivity and specificity. These test kits have been commercialized by several companies, easy to use, but their usage has been hampered by the advent of molecular techniques (Pérot et al., 2017).

Molecular assays

The advent of molecular detection techniques, based initially on probe hybridization and later genome amplification, opened on the possibility to develop assays with exquisite sensitivity and specificity for the diagnosis of AstVs in stool (Glass et al., 1996). While the sensitivity of probe hybridization has been described to be on the same level as that of Enzyme ImmunoAssay (EIA), Reverse transcriptase PCR (RT-PCR) offers thresholds of detection as low as 10 to 100 genome copies per gram of stool (Glass et al., 1996). Nevertheless, the sensitivity of these molecular assays relies greatly on several variables, such as primer/probe selection, enzymatic amplification reaction conditions, and last but not least, the efficiency of the target nucleic acid extraction (Bosch et al., 2014). In any case, studies employing EIA and RT-PCR in parallel reported a higher number of positive samples scored by the latter technique as well as a longer period of viral shedding that extended beyond the resolution of symptoms (Mitchell et al., 1995).

Management, prevention and control

There is no anti-viral treatment for astrovirus infection, because the viral disease rarely required hospitalization. But Bjorkholm et al., (1995) demonstrated in a study how a 78 years old patient diagnosed with Waldenstrom's macroglobulinemia was given 0.4 g/kg of astrovirus immunoglobulin for four days, and the symptoms resolved. This led to a full recovery from the viruses; though, additional testing is yet to be completed.

However, young children who are at risk due to preexistent malnutrition or illness are given Oral rehydration therapy (ORT) which is also used for managing Rotavirus infections and other diarrhoeal diseases like Cholera, to avoid diarrhoeal dehydration and the serious effects of gastroenteritis (Bosch et al., 2014).

The prevention of HAstV infections is essentially based on the control of the transmission routes and on the prevention and control of disease at the host level. The control of the transmission routes includes virus detection and inactivation in water and food, and disinfection of contaminated fomites (Bosch et al., 2014). Individuals infected should have their feaces properly disposed far away from water bodies.

Prevention of disease development in the host includes vaccination and potentiation of the natural defenses such as the gut microbiota. No vaccines have been developed for HAstVs despite several descriptions of virus-like particle (VLP) production in different systems (Mor et al., 2011). This lack of commercial interest in vaccine production may be due to the low clinical impact of astrovirus infection in healthy patients and to the need for a multivalent vaccine to cover all circulating serotypes and strains or at least the most prevalent ones, since apparently there is not heterologous protection (Bosch et al., 2014). Some authors have speculated that probiotics, which may interfere with the biological cycle of enteric virus at many different steps, may be used as a measure to prevent and/or treat intestinal viral infections (Colbère-Garapin et al., 2007) Additionally, the antiviral activity of some synthetic flavonoids on astrovirus replication has been described (Bosch et al., 2014).

Potential threat of Zoonotic transmission

There are several studies that have documented the existence of interspecies transmission. Genome similarities have been reported from several studies that assayed for the relationship between Astroviruses recovered from different species (Donato and Vijaykrishna, 2017). Ecotones (ecological transition areas such as small and medium sized farms which rear multiple species) have highlighted as a critical factor been responsible for the reported interspecies transmission. The co-rearing of poultry such as domestic ducks, chickens, turkey, and guinea fowl can facilitate transmission between these species but also transmission to wild birds (Donato and Vijaykrishna, 2017). Many other species have contact with livestock in a farming environment; in addition to wild species, companion animals such as cats and dogs and other peri-domestic animals have contact with livestock and their providing biological waste substantial opportunities for cross-species transmission. Farms and abattoirs have also been recognized environments facilitating transmission as between livestock species to farm and abattoir workers. The genome similarity between Human Astroviruses and other viruses (members of the corona family) implicated in highlights zoonotic transmission the possibility of Astroviruses zoonotic transmission.

Conclusion

Our understanding of the implication of astrovirus infection has greatly benefited from the evolution of technologies, from initial morphological identification to the most recent advanced high throughput molecular regarding especially techniques, Human Astroviruses. More attention should be channeled into a better understanding of its virulent factors, disease formation process and interspecies transmission with a bid to avert the danger of zoonotic transmission.

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References

- Abad, F.X., Villena C, Guix S, Caballero S, Pintó R.M, Bosch A. (2001) "Potential role of fomites in the vehicular transmission of human astroviruses". *Applied and Environmental Microbiology*, 67 (9): 3904–7. doi:10.1128/AEM.67.9.3904-3907.2001.
- Aminu, M., Ameh E.A., Geyer A, Esona M.D, Taylor M.B, Steele A.D. (2009) Role of astrovirus in intussusception in Nigerian infants. J. Trop. Pediatr., 55:192–194. doi:10.1093/tropej/fmn101

Appleton, H, Higgins P.G. (1975) Viruses and gastroenteritis in infants. *Lancet*, i:1297. (Letter)

- Berthiaume, L., Alain R., McLaughlin B., Payment P., Trépanier P. (1981) Rapid detection of human viruses in faeces by a simple and routine immune electron microscopy technique. *J. Gen. Virol.*, 55:223–227. doi: 10.1099/0022-1317-55-1-223.
- Björkholm, M., Celsing F, Runarsson G, Waldenström J. (1995) "Successful intravenous immunoglobulin therapy for persistent astrovirus severe and after fludarabine gastroenteritis patient treatment in with a Waldenström's macroglobulinemia". International Journal of Hematology, 62 doi:10.1016/0925-(2): 117-20. 5710(95)00396-A. PMID 8590772
- Bogdanoff, W.A., Campos J., Perez E.I., Yin L., Alexander D.L., DuBois R.M. (2016) Structure of a human astrovirus capsid— Antibody complex and mechanistic insights into virus neutralization. J.

Virol., 91:e01859-16. doi: 10.1128/JVI.01859-16

- Bosch, A., Guix S, Pintó R.M. (2013) Epidemiology of human astrovirus, p 1– 18. In Schultz-Cherry S (ed), Astrovirus research: essential ideas, everyday impacts, future directions. Springer, New York, NY.
- Bosch, A., Pintó R.M, Guix S. (2014) Human astroviruses. *Clin Microbiol Rev*iew,27(4):1048–74.
- Bosch, A., Guix S., Krishna N.K., Méndez E., Monroe S.S., Pantin-Jackwood M., Schultz-Cherry S. (2012) Family— Astroviridae. In: King A.M.Q., Lefkowitz E., Adams M.J., Carstens E.B., editors. Virus Taxonomy: Ninth Report of the International Committee on Taxonomy of Viruses. San Diego, CA: Elsevier.
- Brinker, J.P., Blacklow N.R., Herrmann J.E. (2000) Human astrovirus isolation and propagation in multiple cell lines. *Arch. Virol.*, 145:1847–1856. doi: 10.1007/s00705007006
- Britton, R.A., Versalovic J. (2008) Probiotics and gastrointestinal infections. Interdiscip. *Perspect. Infect. Dis.*, 10. doi:10.1155/2008/290769.
- Colbère-Garapin, F., Martin-Latil S, Blondel B, Mousson L, Pelletier I, Autret A, François A, Niborski V, Grompone G, Catonnet G, van de Moer A. (2007) Prevention and treatment of enteric viral infections: possible benefits of probiotic bacteria. *Microbes Infect.*, 9:1623–1631. doi:10.1016/j.micinf.2007.09.016.
- Cubitt, W.D., Mitchell D.K, Carter M.J, Willcocks M.M, Holzel H. (1999) Application of electronmicroscopy, enzyme immunoassay, and RT-PCR to monitor an outbreak of astrovirus type 1 in a paediatric bone marrow transplant unit. J. Med. Virol., 57:313–321. doi:10.1002/(SICI)1096-

9071(199903)57:3<313::AID-JMV16>3.0.CO;2-A.

- D'Souza. D.H. (2015) Update on food borne pathogens viruses: types, concentration and sampling methods. Advances in Microbial Food Safety, 2015. Woodhead Publishing Series in Food Science, Technology and Nutrition. <u>https://doi.org/10.1533/9781782421153.</u> <u>1.102</u>
- De Benedictis, P., Schultz-Cherry S, Burnham A, Cattoli G. (2011) Astrovirus infections in humans and animals molecular biology, genetic diversity, and interspecies transmissions. *Infect. Genet. Evol.*, 11:1529–1544. doi:10.1016/j.meegid.2011.07.024.
- Donato, C., and Vijaykrishna D. (2017) The Broad Host Range and Genetic Diversity of Mammalian and Avian Astroviruses. *Viruses*, 10;9(5):10. doi: 10.3390/v9050102.
- Finkbeiner, S.R., Allred A.F, Tarr P.I, Klein E.J, Kirkwood C.D, Wang D. (2008) Metagenomic analysis of human diarrhea: viral detection and discovery. *PLoS Pathog.*, 4:e1000011. doi:10.1371/journal.ppat.1000011.
- Finkbeiner, SR., Holtz L.R, Jiang Y, Rajendran P, Franz C.J,Zhao G, Kang G, Wang D. (2009) Human stool contains a previously unrecognized diversity of novel astroviruses. *Virol. J.*, 6:161. doi:10.1186/1743-422X-6-161.
- Finkbeiner, SR., Kirkwood C.D,Wang D. (2008) Complete genome sequence of a highly divergent astrovirus isolated from a child with acute diarrhea. *Virol. J.*, 5:117. doi:10.1186/1743-422X-5-117.
- Glass RI, Noel J, Mitchell D, Herrmann JE, Blacklow NR, Pickering LK, et al. (1996). "The changing epidemiology of astrovirus-associated gastroenteritis: a review". Archives of Virology.

Supplementum. *Archives of Virology*, 12: 287–300.

- Green, K. (2007) Caliciviridae: the noroviruses, p 949–979. In Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE (ed), *Fields virology*, 5th ed. Lippincott Williams & Wilkins, Philadelphia, PA
- Guix S, Caballero S, Bosch A, Pinto RM. (2005) Human astrovirus C-terminal nsP1a protein is involved in RNA replication. *Virology*, 333:124–131. doi:10.1016/j.virol.2004.12.023.
- Herrmann, J.E., Hudson, R.W. Perron-Henry, D.M.; Kurtz, J.B. Blacklow, N.R. (1988) Antigenic characterization of cellcultivated astrovirus serotypes and development of astrovirus-specific monoclonal antibodies. J. Infect. Dis., 158, 182–18
- Jeong, H.S., Jeong A, Cheon D.S. (2012) Epidemiology of astrovirus infection in children. Korean J. Pediatr., 55(3):77-82. doi:10.3345/kjp.2012.55.3.77
- Jonassen, C.M., Jonassen TO, Grinde B. (1998) A common RNA motif in the 3' end of the genomes of astroviruses, avian infectious bronchitis virus and an equine rhinovirus. J. Gen.Virol., 79:715–718.
- Kiulia, N.M., Mwenda J.M Nyachieo A, Nyaundi J.K, Steele AD, Taylor MB. (2007) Astrovirus infection in young Kenyan children with diarrhoea. J. Trop. Pediatr., 53:206–209. doi:10.1093/tropej/fml093
- Krishnan, T. (2004) Novel human astroviruses: Challenges for developing countries. *Virus Disease*, 25:208–214. doi: 10.1007/s13337-014-0202-3
- Kurtz, J.B., Lee, T.W. (1984) Human astrovirus serotypes. *Lancet*, 2, 1405.
- Le Cann, P., Ranarijaona S, Monpoeho S, Le Guyader F, Ferre V. (2004) Quantification of human astroviruses

in sewage using real-time RT-PCR. *Res. Microbiology*, 155:11–15. doi:10.1016/j.resmic.2003.09.013.

- Le Guyader, F., Haugarreau L, Miossec L, Dubois E, Pommepuy M. (2000) Threeyear study to assess human enteric viruses in shellfish. *Appl. Environ. Microbiology*, 66:3241–3248. doi:10.1128/AEM.66.8.3241-3248.2000
- Lee, R., Lessler J, Lee R, Rudolph K, Reich N, Perl T, Cummings D. (2013) Incubation periods of viral gastroenteritis: a systematic review. *BMC Infect. Dis.*, 13:446. doi:10.1186/1471-2334-13-446.
- Lee, T.W., Kurtz J.B. (1981) Serial Propagation of Astrovirus in Tissue Culture With the Aid of Trypsin. J. *Gen*, *Virol.*, 1981;57 (2):421-4.doi: 10.1099/0022-1317-57-2-421
- Lindenbach, B.D TH, Rice C.M. (2007) Flaviviridae: the viruses and their replication, p 1101–1152. In Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE (ed), *Fields virology*, 5th ed. Lippincott Williams & Wilkins, Philadelphia, PA
- Madeley, C.R (1979). Comparison of the features of astroviruses and caliciviruses seen in samples of feces by electron microscopy. *J. Infect. Dis.*, 139:519–523. doi: 10.1093/infdis/139.5.519.
- Marczinke, B., Bloys A.J, Brown T.D, Willcocks M.M, Carter M.J, Brierley I. (1994) The human astrovirus RNAdependent RNA polymerase coding region is expressed by ribosomal frameshifting. J. Virol., 68:5588–5595
- Meliopoulos, V.A., Marvin S.A., Freiden P., Moser L.A., Nighot P., Ali R., Blikslager A., Reddivari M., Heath R.J., Koci M.D., Schultz-Cherry S. (2016) Oral administration of astrovirus capsid protein is sufficient to induce acute

diarrhea in vivo. *mBio.*, 7:e01494-16. doi: 10.1128/mBio.01494-16

- Meliopoulos, V.A., Kayali G, Burnham A, Oshansky C.M, Thomas P.G, Gray G.C et al., Kapoor A (ed). (2014) "Detection of Antibodies against Turkey Astrovirus in Humans". *PloS One*, 9 (5): e96934. doi: 10.1371/journal.pone.0096934. PMC 4020816. PMID 25278582
- Midthun, K., Greenberg H.B,Kurtz J.B, Gary G.W, Lin F.Y, Kapikian A.Z. (1993) Characterization and seroepidemiology of a type 5 astrovirus associated with an outbreak of gastroenteritis in Marin County, California. J. Clin. Microbiol., 31:955–962.
- Mitchell, D.K., Monroe S.S, Jiang X, Matson D.O, Glass R.I, Pickering L.K. (1995) Virologic features of an astrovirus diarrhea outbreak in a day care center revealed by reverse transcriptasepolymerase chain reaction. J. Infect. Dis., 172:1437–1444. doi:10.1093/infdis/172.6.1437.
- Molberg, O., Nilsen E.M, Sollid L.M, Scott H, Brandtzaeg P, Thorsby E, Lundin K.E. (1998) CD4+ T cells with specific reactivity against astrovirus isolated from normal human small intestine. *Gastroenterology*, 114:115–122. doi:10.1016/S0016-5085(98)70639-0.
- Monroe, S.S., Carter M.J Herrmann J.E, Kurtz J.B, Matsui S.M. (1995) Astroviridae, p 364–384. In Murphy FA, Bishop DHL, Ghabrail SA, Jarvis AW, Martielli GP, Mayo MA, Summers MD (ed), Virus taxonomy: classification and nomenclature of viruses. Sixth report of the International Committee on Taxonomy of Viruses. Springer-Verlag, Vienna, Austria.
- Monroe, S.S., Holmes J.L, Belliot GM (2001). "Molecular epidemiology of human astroviruses". Novartis Foundation

Symposia. 238: 237–45, discussion 245– 9. doi:10.1002/0470846534.

- Monroe, S.S., Jiang B, Stine S.E, Koopmans M, Glass R.I. (1993) Subgenomic RNA sequence of human astrovirus supports classification of Astroviridae as a new family of RNA viruses. *J. Virol.*, 67:3611–3614.
- Mor, S.K., Abin M, Costa G, Durrani A, Jindal N, Goyal S.M, Patnayak D.P. (2011) The role of type-2 turkey astrovirus in poult enteritis syndrome. *Poult.* Sci., 90:2747–2752. doi:10.3382/ps.2011-01617.
- Moser, L.A., Carter M., Schultz-Cherry S. (2007) Astrovirus increases epithelial barrier permeability independently of viral replication. *J. Virol.*, 81:11937– 11945. doi: 10.1128/JVI.00942-07
- Mustafa, H., Palombo E.A, Bishop R.F.(2000) Epidemiology of astrovirus infection in young children hospitalized with acute gastroenteritis in Melbourne, Australia, over a period of four consecutive years, 1995 to 1998. J. Clin. Microbiol., 38:1058–1062
- Nighot, P.K., Moeser A., Ali R.A., Blikslager A.T., Koci M.D.(2010) Astrovirus infection induces sodium malabsorption and redistributes sodium hydrogen exchanger expression. *Virology*, 401:146–154.
- Pérot, P., Lecuit M, Eloit M. (2017) Astrovirus Diagnostics. *Viruses*, 9(1):10. doi:10.3390/v901001
- Pintó, R.M., Bosch A. (2008) Rethinking virus detection in food, p 171–188. In Koopmans M, Cliver DO, Bosch A (ed), *Foodborne viruses: progress and challenges.* Washington, DC : ASM Press,
- Racaniello, V. (2007) Picornaviridae: the viruses and their replication, p 795–838.In Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B,

Straus SE (ed), Fields virology, 5th ed. Lippincott Williams & Wilkins, Philadelphia, PA

- Risco, C., Carrascosa J.L., Pedregosa A.M., Humphrey C.D. Sanchez-Fauquier A (1995). Ultrastructure of human astrovirus serotype 2. J. Gen. Virol., 76:2075–2080. doi: 10.1099/0022-1317-76-8-2075.
- Robertson, M.P., Igel H, Baertsch R, Haussler D, Ares M Jr, Scott W.G. (2005). The structure of a rigorously conserved RNA element within the SARS virus genome. *PLoS Biol.*, 3:e5. doi:10.1371/journal.pbio.0030005.
- Schultz-Cherry, S. (2013). Astrovirus Research: Essential Ideas, Everyday Impacts, Future Directions. New York, NY: Springer.
- Shastri, S., Doane A.M, Gonzales J, Upadhyayula U, Bass D.M. (1998) Prevalence of astroviruses in a children's hospital. J. Clin. Microbiol., 36:2571– 2574.
- Steele, A.D., Basetse H.R, Blacklow N.R, Herrmann J.E. (1998) Astrovirus infection in South Africa: a pilot study. *Ann. Trop. Paediatr.*, 18:315–319.
- Superti, F., Seganti L, Orsi N, Desideri N, Stein M.L,Tinari A, Marziano M.L, Donelli G. (1990) In vitro effect of synthetic flavanoids on astrovirus infection. *Antiviral Res.*, 13:201–208. doi:10.1016/0166-3542(90)90038-9.
- Toh, Y., Harper J., Dryden K.A., Yeager M., Arias C.F., Méndez E., Tao Y.J. (2016) Crystal structure of the human astrovirus capsid protein. J. Virol., 90:9008–9017. doi: 10.1128/JVI.00694-16
- Torres-Flores, J.M., Arias C.F. (2015) Tight junctions go viral! *Viruses*, 7:5145– 5154. doi: 10.3390/v7092865
- Willcocks, M.M., Ashton N, Kurtz J.B, Cubitt W.D, Carter M.J. (1994) Cell culture

adaptation of astrovirus involves a deletion. *J. Virol.*, 68:6057–6058.

- Willcocks, M.M., Carter M.J. (1993) Identification and sequence determination of the capsid protein gene of human astrovirus serotype 1. *FEMS Microbiol. Lett.*, 114:1–7. doi:10.1111/j.1574-6968.1993.tb06542.
- Wilson, S.A., Cubitt W.D. (1988) The development and evaluation of radioimmune assays for the detection of immune globulins M and G against astrovirus. J. Virol. Methods., 19:151–159. doi: 10.1016/0166-0934(88)90158-9.
- Wunderli, W., Meerbach A, Gungor T, Berger C, Greiner O, Caduff R, Trkola A, Bossart W,Gerlach D, Schibler M, Cordey S, McKee TA, Van Belle S, Kaiser L, Tapparel C. (2011) Astrovirus infection in hospitalized infants with severe combined immunodeficiency after allogeneic hematopoietic stem cell transplantation. *PLoS One*, 6:e27483. doi:10.1371/journal.pone.0027483.