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CHAPTER 63

Astroviruses, Enteric Adenoviruses, and Other Gastroenteritis Viral Infections

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INTRODUCTION

Diarrheal disease remains one of the most common causes of morbidity and mortality in developing countries. The problem is particularly acute among young children, who will have an estimated 10–15 episodes of diarrhea in the first 5 years of life[1] and among whom 1.5–2.5 million deaths will occur each year.[2,3] For up to half of all episodes, an etiologic agent cannot be found. The importance of viral agents as causes of diarrheal disease has been increasingly appreciated, beginning with the discovery of rotavirus[4] and caliciviruses[5] in the 1970s. More recently, advances in detection methods for some other viruses, such as astroviruses and enteric adenoviruses, have led us to appreciate their role as causes of diarrheal disease. In addition, a variety of other viruses, such as picobirnaviruses, coronaviruses, toroviruses, parechoviruses, bocaviruses, and even influenza (H1N1) have been associated with gastroenteritis, but their clinical and public health importance remains unclear (***Table 63.1***). Many of these viruses may be responsible for the fraction of illness for which a pathogen cannot be found. A better understanding of their epidemiology will have implications for programs to decrease morbidity and mortality in developing countries.

ASTROVIRUSES

THE AGENT

Astroviruses were first identified in 1975[5,6] and named based on a characteristic five- or six-pointed appearance noted by electron microscopy. Since 1990, improvements in diagnostic methods, including the adaptation of astrovirus to grow in continuous cell lines,[7] sequencing and elucidation of the structure of the genome,[8–10] and development of improved methods of detection such as enzyme immunoassays and reverse-transcription polymerase chain reaction,[11–14] have led to new insights into the role of astrovirus in human disease. It is now clear that astroviruses are a common cause of sporadic gastroenteritis among children and may be associated with large-scale outbreaks of diarrhea as well.

Astroviruses are 28–30 nm, spherical, nonenveloped viruses with a positive sense ssRNA genome and have been classified in their own family, *Astroviridae*.[15] Eight serotypes of human astroviruses have been identified.[16,17] Of these, type 1 is predominant in most studies, accounting for more than half of strains isolated;[16,18,19] types 2, 3, and 4 each account for 10–16% of astrovirus detections; and types 5, 6, 7, and 8 are less uncommonly detected.[16,17] The relative distribution of types seems to vary by geographic location and by year,[20] and more variability may be found in developing countries.[21,22]

EPIDEMIOLOGY

Gastroenteritis associated with astroviruses has been reported worldwide, both as sporadic disease and as outbreaks. Cases of astrovirus-associated gastroenteritis are most common among children less than 2 years of age,[19,21–32] and are less frequent among older children and adults.[33,34] In volunteer studies, most adults neither became infected nor developed diarrhea.[33,35] However, in large outbreaks among schoolchildren,[36,37] teachers became ill as well, perhaps as a result of a large dose of virus in this type of setting or a different mechanism of spread. In addition, outbreaks have been reported among elderly people, probably due to waning immunity with increasing age.[38–40]

Gastroenteritis associated with astrovirus, like rotavirus, occurs in both developed[19,23,24,27–30,41–43] and developing countries,[32,44–48] suggesting that improvements in water and sanitation are unlikely to decrease disease incidence. In temperate climates, astrovirus diarrhea cases peak in winter,[17,19,24,29,31] whereas the seasonality is less clear in tropical settings.[32,44,46] With improvements in detection methods, astrovirus represents an important cause of community-acquired and nosocomial illness and may be the most common viral cause of gastroenteritis in children after rotavirus and possibly Norwalk-like viruses.[19] In developing countries, astroviruses have generally been detected in less than 10% of young children treated for gastroenteritis in outpatient clinics or in hospitals, and the lower proportions reported from some studies (<1%–3%) may reflect insensitive detection methods rather than true prevalence.[19,21,42,45,47–50] Even so, one study in rural Mexico has found astrovirus to be the most common cause of diarrhea in the first 3 years of life, causing 26% of diarrheal episodes in a prospectively followed cohort.[32] Outbreaks of astrovirus gastroenteritis have been reported in schools,[36,37] day-care centers,[25,51,52] hospitals,[26,29,39,53,54] nursing homes,[38,40] and households.[32,55] Nosocomial spread of astroviruses may be common.[56] While the modes of transmission are still unknown, the primary mode of spread of virus is likely to be through fecal-oral contamination via person-to-person contact,[33,35,36,53] although the stability of the virus in water may indicate that waterborne spread is possible.[57]

THE DISEASE

Astroviruses cause gastroenteritis characterized by 2–5 days of watery diarrhea, often accompanied by vomiting and less often by high fever, abdominal pain, and other constitutional symptoms.[23,29,44,46] It is generally milder than rotavirus, less commonly resulting in dehydration,[19,23,26,39,44] and rarely associated with death.[45] Lactose intolerance[43,58] and poor weight gain[46] have been reported following astrovirus infection, and children with poor nutritional status may develop more severe disease[46] or

Table 63.1 Summary of Virologic and Epidemiologic Features of Certain Viruses Associated with Gastroenteritis

Virus	Family	Taxonomy	Detection	Epidemiology	Comment
Astrovirus	*Astroviridae*	28–30 nm, ssRNA, N-env; 10% have 5–6-point star appearance; 8 serotypes	EM, IEM, EIA, RT-PCR	Endemic, most disease in children <2 years; epidemic, children and adults, including elderly; daycare, schools, hospitals	No clear seasonality in tropical countries; fairly common cause of viral diarrhea in children; less severe than rotavirus
Enteric adenovirus	*Adenoviridae*	70–80 nm, dsRNA, icosahedral, N-env; 2 main serotypes	EIA, EM, IEM, RT-PCR, culture, DNA probes, hybridization	Endemic disease in children <2 years	No clear seasonality; disease as severe as rotavirus, but less common
Picobirnavirus	*Birnaviridae*	35 nm, dsRNA, bisegmented genome	EM, PAGE, RT-PCR	Associated with diarrhea in HIV-infected adults; no clear association with diarrhea in healthy persons	Possible association with *Cryptosporidium* infection
Coronavirus	*Coronaviridae*	60–200 nm, ssRNA, pleomorphic, env, with club-shaped projections give a halo appearance	EM	Not known	May cause diarrhea in children and adults; possible association with tropical sprue and necrotizing enterocolitis
Torovirus	*Coronaviridae*	100–150 nm, ssRNA pleomorphic, env, with club-shaped projections	EM	Not known	Possible cause of diarrhea in humans

EIA, enzyme immunoassay; EM, electron microscopy; env, enveloped; IEM, immune electron microscopy; N-env, nonenveloped; PAGE, polyacrylamide gel electrophoresis; RT-PCR, reverse transcription–polymerase chain reaction.

chronic diarrhea.[50] Illness among adults is generally mild and of short duration.[33,35,39] However, in studies of immunocompromised persons, astrovirus is often the most common virus detected in persons with diarrhea and associated with prolonged shedding of virus.[59–61] HIV infection was associated with more severe astrovirus disease in children with HIV in Malawi.[21] Indirect evidence suggests that immunity to astrovirus develops early in life.[25,33,35]

Astrovirus infects intestinal epithelial cells. The incubation period is 3–4 days,[33,35] but may be shorter in outbreak settings.[37] Children may shed virus 1–2 days prior to illness and for 4–5 days following illness,[25,29,51] but shedding for 3 weeks has been reported when more sensitive detection methods have been used. Since most illness with astroviruses is found in young children and elderly persons, it is assumed that protection from illness is conferred by infection, and that the protection is relatively durable. Like many other enteric viruses, the immunologic correlates of protection are poorly understood for astroviruses.

DIAGNOSIS

Astroviruses were first detected by electron microscopy but this method has proven relatively insensitive compared to newer assays.[9,24,26,31,36,37,40,47,53,58,62,63] Enzyme immunoassays are commercially available[11,42] which are more sensitive, easier, and less expensive to use.[23,25,30,36,42,44,46,64] Molecular diagnostic methods – reverse transcription–polymerase chain reaction (RT-PCR) and probes – are the most sensitive and can also be used to type virus. Finally, the virus can be grown in cell culture.[65]

TREATMENT, PROGNOSIS, AND PREVENTION

Therapy for astrovirus diarrhea includes rehydration with oral or intravenous fluids. Illness is generally mild and self-limited, but malabsorption and lactose intolerance have been reported following infection. Death associated with astroviruses is rare.[43,45,58]

In outbreaks, identification of the source of infection, such as food or contact with ill persons, may be helpful in preventing further illness. Sporadic cases are common in children and no methods of prevention have been identified. Since the infection may be spread through close personal contact, enteric precautions including appropriate hand-washing practices and isolation of ill persons may be advisable.

ENTERIC ADENOVIRUS

THE AGENT

When adenoviruses were first identified in fecal specimens of children with diarrhea, their etiologic role was questioned because adenoviruses are common causes of other illnesses (e.g., upper respiratory tract infections) in children and are excreted in the stool. But unlike the common respiratory adenoviruses, enteric adenoviruses were difficult to grow and were therefore distinguished as the fastidious enteric adenoviruses (FEAs). Eventually, these FEAs were placed in their own group and found to belong to two predominant serotypes, 40 and 41. Besides these serotypes, serotype 31 has occasionally been causally associated with gastroenteritis and newer serotypes 42–49 have been identified in HIV patients with chronic diarrhea. Like astroviruses, the development of rapid, sensitive diagnostic assays for the detection of EAs has increased our appreciation of their role as causes of diarrhea in children.

Adenoviruses are members of the family *Adenoviridae* and of the genus *Mastadenovirus*. The 49 defined serotypes are divided into six subgroups (A–F); serotypes 40–49 are members of subgroup F (called EAs because they have been associated with gastroenteritis in humans).[66,67] EAs are nonenveloped, icosahedral, double-stranded DNA viruses, and are 70–80 nm in size.

EPIDEMIOLOGY

Like rotavirus and astrovirus diarrhea, diarrhea associated with EAs occurs primarily among children less than 2 years of age. Infection is probably universal, and the age-specific incidence does not appear to differ between temperate and tropical countries, suggesting that improvements in water and sanitation will not decrease the incidence of disease.

Compared to other viral agents in developing countries, EAs appear to account for a smaller proportion of diarrheal disease than in developed countries. EAs generally have been detected in 1–4% of children with diarrhea in many studies,[19,49] although they have been detected commonly in some studies. EAs were more common than rotavirus in a rural outpatient setting in Guatemala (14% of children with diarrhea had EA

detected in stool compared to 5% with rotavirus), and were associated with 31% of hospital admissions for diarrhea.[68] In two South African studies, 6.5–13.2% of hospital admissions for diarrhea were associated with EAs;[69,70] in one study,[70] EAs were detected as often as rotaviruses. In the few studies that have examined the role of EAs in an adult population, they appear to be less important causes of gastroenteritis than in children. No seasonality of EA infections was apparent in studies in temperate[31,71–73] or tropical countries,[68,74] but few studies have reviewed multiple seasons.

THE DISEASE

Infections with EA can range from being mild or asymptomatic to producing profuse, nonbloody, watery diarrhea and vomiting.[71,72,75–79] Children often have 6–10 stools per day, and the mean duration of illness is 5–9 days.[68,71,72,75–78] Abdominal pain[71,76] and 2–3 days of low-grade fever (<38.5°C) are also frequently present, whereas temperatures greater than or equal to 39°C occur in less than 10–25% of children.[71,75] Mild isotonic dehydration may occur in 15–50% of children,[71,72,76] and only severe cases require hospitalization. Respiratory symptoms, including pneumonia, have been associated with EA infections but are present less commonly than with other adenoviruses.[72,75,77] Asymptomatic infections have been documented in 8% and 17% of children in day-care center studies.[23,68,71,72] Serum electrolytes are usually normal, and a slight leukocytosis may be present in a minority of children.[71]

Gastroenteritis associated with EAs has a similar presentation among patients in developed and developing countries. However, enteric adenoviruses may be associated with chronic diarrhea and less common serotypes in HIV-infected subjects.[59,80–84] Deaths from EA gastroenteritis are uncommon, but have been reported, particularly among immunocompromised children.[75,85,86] Long-term complications appear to be rare, but lactose intolerance[71] and malabsorption[87] have been reported and may exacerbate disease among children in developing countries where malnutrition is prevalent.

Differentiation of EA-associated gastroenteritis from other causes of viral gastroenteritis is difficult. EA-associated diarrhea may be more severe and prolonged than viral gastroenteritis caused by other agents[71,72,88] and is commonly associated with a high fever and dehydration similar to rotavirus.[71,88]

Like other viral agents of gastroenteritis, the exact mode of transmission is unknown. EAs are probably transmitted by fecal-oral spread, by person-to-person contact, or by respiratory droplets. No food- or waterborne outbreaks have been described.[89]

The incubation period of the disease is 3–10 days,[77,78,90] and viral shedding may persist for 10–14 days.[90] Mechanisms of diarrhea and immunity associated with EA are poorly understood. Type 40- and 41-specific antibodies develop following infection[71,91,92] and can be detected in the absence of recent diarrheal illness.[69,92] Children can become ill when reinfected with EA.[93] However, illness among adults is uncommon, even in outbreak settings where they have a high likelihood of exposure.

DIAGNOSIS

Electron microscopy (EM) was first used to detect EAs in fecal specimens when they are shed in large amounts (as many as 10^{11} particles/gram of feces). Since EM cannot distinguish EAs from non-enteric serotypes,[94] immune electron microscopy (IEM) can enhance sensitivity and specificity of EA detection.[95–98] Enzyme immunoassays using monoclonal antibodies to types 40 and 41 and to the adenovirus hexon common to all serotypes have been developed.[98–102] These are the easiest, most rapid methods for detection[103] and have proven to be highly sensitive and specific compared to IEM.[98] There are currently no commercial kits using DNA detection methods. EAs grow in Graham 293 cells, a cell line transformed by adenovirus type 5.[104] Viruses can then be identified using one of the preceding methods or by use of restriction enzyme analysis.

TREATMENT, PROGNOSIS, AND PREVENTION

No specific therapy is available for EA gastroenteritis, so therapy is directed towards treatment of dehydration. Oral rehydration solutions are effective in treating diarrhea with mild and moderate dehydration, and severe dehydration may require use of intravenous fluids.

Prevention of illness is currently not possible due to lack of understanding of risk factors for transmission. Attention to good handwashing when caring for ill persons seems reasonable.

NOVEL VIRUSES ASSOCIATED WITH GASTROENTERITIS

PICOBIRNAVIRUS

First identified in 1985,[105] picobirnaviruses (PBVs) have since been detected in a variety of animals,[106–111] as well as in human fecal specimens from patients with and without diarrhea.[59,112–115] It has been associated statistically with disease only in a study of HIV-infected adults in the United States[59] and Argentina.[116]

PBVs are small (pico), bisegmented (bi-RNA) viruses that are members of the family *Birnaviridae*. Atypical PBVs have been detected with three segments of RNA.[112] On electron microscopy, the virus is a 35 nm, discrete virus with no distinctive surface structure.

Little is known about the distribution or incidence of PBVs. In two studies, PBVs have been detected from diarrheic stools of adults with coexistent *Cryptosporidium* infection, and in one study, HIV-infected patients with chronic diarrhea excreted the virus for 7 months.[59,113] PBVs appear to have a global distribution and are relatively rare, with detection rates usually below 2% of children with diarrhea and less in immunocompromised adults.

No serologic immune response, measured by IEM, was detected in a group of adults with HIV,[59] although serum antibody has been detected by solid-phase IEM in infected rabbits.[110]

Although PBVs may be seen by EM, the virus has most often been identified by the distinct presence of two segments of RNA by polyacrylamide electrophoresis from a stool specimen.[59] The virus has been fully sequenced so RT-PCR has become a reliable method to detect and characterize the virus.

CORONAVIRUSES

Coronaviruses were first reported in association with diarrhea in adults[117] and tropical sprue among children and adults in India in 1975.[118] While subsequent reports documented detection of coronavirus-like particles (CVLPs) in stools of persons with diarrhea, they could not associate CVLPs with diarrhea.[119,120]

Coronaviruses are pleomorphic, 60–200 nm, ssRNA viruses that belong to the family *Coronaviridae*. Because of their pleomorphic appearance, misdiagnosis is problematic and no confirmatory test is available. Consequently, the prevalence of human enteric coronaviruses (HECVs) is unknown, and while they have been detected in studies in several countries,[16,24,45,62,121–129] they are not clearly associated with disease. In studies that have compared rates of HECV detection in stools from patients with diarrhea versus controls, the results are mixed. Because of the long duration of shedding and the possibility for asymptomatic infection, the pathogenicity of HECVs may be difficult to prove by comparing rates of detection between well and ill persons. Many studies have reported the majority of viral detections among young children and infants,[24,121,126–128,130] but detections among adults are common.[24,84,119,127,131] With some exceptions,[45,126,130] most studies have reported no differences in detection by time of year.[127] Mode of spread of HECVs is unknown.

Illness descriptions from outbreaks thought to be associated with coronaviruses have included the occurrence of vomiting and diarrhea of short

duration, often accompanied by fever.[117,130] Besides gastroenteritis, HECVs have been reported in association with other gastrointestinal diseases including necrotizing enterocolitis,[132,133] and neonatal diarrhea[122] in infants, and tropical sprue.[118,134] In several reports of clinical signs and symptoms associated with the new severe acute respiratory syndrome (SARS)-associated coronavirus, diarrhea has been a common symptom, reported in around a quarter of patients[135,136] It is not clear whether patients with the SARS coronavirus can have diarrhea without respiratory symptoms.

HECVs may be identified with EM by their distinctive 20 nm, clublike projections.[137] Enteric coronaviruses are distinct from respiratory coronaviruses and do not cross-react by enzyme-linked immunosorbent assay (ELISA) or immunoblots, although there is cross-reactivity on IEM.[129]

TOROVIRUSES

Toroviruses are members of the family *Coronaviridae* and the genus *Torovirus*. They are pleomorphic, 100–150 nm, ssRNA viruses with 20 nm, clublike projections extending from the capsid.[138–140]

The epidemiology of these infections remains unclear. Toroviruses have been detected in stools of children and adults with diarrhea in developed countries.[49,140–142] However, in these studies there was no epidemiologic association with illness, and the detections could not be confirmed using additional tests. In an EM survey of diarrhea among children in Toronto, torovirus-like particles were detected in 224 (8%) of 3800 stool specimens. The particles in some of these stools were later confirmed as torovirus by an ELISA incorporating bovine and human antibodies.[143]

A serum response to infection can be measured in infected cows, which develop IgM and IgG following gastrointestinal infection,[144] but no serum immune response has been reported in humans. Electron microscopists can identify torovirus-like particles in human specimens but cannot confirm the detection.[145] Several additional methods including ELISA,[144,146] cDNA probes for hybridization,[142] and RT-PCR[143] have been used successfully in animals and hold promise for detection of human disease.

OTHER VIRUSES

A variety of other viruses have been implicated in gastroenteritis to some degree, including parvoviruses, enteroviruses, reoviruses, and pestiviruses, and have been reviewed in detail elsewhere. Parvoviruses, reoviruses, and pestiviruses may cause diarrhea in nonhumans, and there are reports of human cases of gastrointestinal illnesses.[147–153] However, the data are inconclusive, and they are not currently thought to be causes of gastroenteritis in humans.

In 2004, echovirus types 22 and 23 were reclassified as human parechoviruses (HPeV) which are small, nonenveloped, positive-sense single-stranded RNA viruses in the family *Picornaviridae*.[154–158] In an investigation in Thai children with gastroenteritis in whom no other pathogen could be found, HPeV were found in 15% of fecal specimens examined. The full sequence of these viruses is known, which has facilitated detection and characterization by RT-PCR.

Early identification of parvoviruses as a putative cause of diarrhea in animals and humans led to the discovery in 2005 of two members of the parvovirus family, human bocavirus HBoV2 and HBoV3, to be newly recognized agents of diarrhea.[159–166] These DNA viruses have been detected from stool and respiratory samples from patients with acute diarrhea, and in one study were present in 37% of patients tested and were significantly associated with diarrhea. However, no controls were used and prolonged shedding might account for this high rate of detection. The virus has been found in a global distribution and has often been detected in the presence of other pathogens.

Finally, the recent epidemics of influenza (H1N1) have led to the recognition that up to one-third of these patients have diarrhea as part of their clinical presentation.[167,168] While we do not normally consider influenza virus to be a cause of diarrhea, the high prevalence of gastrointestinal symptoms should encourage clinicians to consider this possibility during the flu season when no other enteric pathogens can be found in a patient with a respiratory illness.

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