

Viral Intestinal Infection - Viral Gastroenteritis

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Received: January 17, 2020; **Published:** April 29, 2020

Abstract

Virus intestinal infections (acute gastroenteritis - AGE) are the most common cause of infectious diseases after respiratory infections worldwide. Specific prevention of vaccination is available only in rotaviruses, the therapy is mainly symptomatic. The development of molecular biological diagnostics, which includes all major viral agents of gastroenteritis, leads to more accurate monitoring and subsequent reporting of these infections.

Keywords: *Viral Gastroenteritis; Adenoviruses; Rotaviruses; Noroviruses; Prevention*

Introduction

Acute gastroenteritis (AGE) is one of the most common causes of infectious diseases in addition to respiratory infections, with an estimated 5 billion cases a year worldwide. In areas of warmer climates and less accessible health care, AGE's share of total mortality is as high as 30% [1,2]. Acute gastroenteritis can be induced by these bacteria (e.g. *Campylobacter* spp., *Clostridium difficile*, enteropathogenic *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Vibrio cholerae*, *Yersinia enterocolitica*), as well as viruses (e.g. adenoviruses, astroviruses, noroviruses, rota-viruses, sapoviruses) and parasites (e.g. *Cryptosporidium* spp., *Entamoeba histolytica*, *Giardia* spp.) [1]. In this article we want to focus on the issue of gastroenteritis of viral origin.

Clinical and epidemiological characteristics of the disease.

Virus gastroenteritis usually begins with nausea, vomiting and increased temperature. Diarrhea is often watery, with mucus, but also with blood. The term „intestinal virosis“ or, less accurately, „intestinal flu“ is also used for this infection.

In particular, rotaviruses, adenoviruses, noroviruses, sapoviruses or astroviruses are the causative agents of viral gastroenteritis and coronaviruses may also be involved. Infants and children around the world are still rotaviruses, but in vaccinated populations [3], for example, in the US, the incidence of rotavirus gastroenteritis is gradually decreasing. Noroviruses are the most common causes of AGE by adults. The AGE epidemic usually affects groups of people who spend time in close physical proximity, for example in schools, hostels or restaurants, in hospitals, on ships etc. The virus spreads among susceptible persons in both direct and indirect ways - vomit, excrement or contaminated skin of the infected person, but also through contaminated areas, ingestion of contaminated food or liquids, or even by aerosol from vomit. As such, viral gastroenteritis is very contagious; a relatively small infectious dose is sufficient for infection - already tens of viral particles. Sick persons should avoid contact with others until the symptoms of the disease have subsided. If the infected person is in the same household, other family members should not - if possible - share kitchen or tableware, toiletries and bedding. Frequent hand washing is recommended as a precaution for all types of gastroenteritis, especially after using the toilet and before preparing food. It is also important to thoroughly wash fruits, vegetables and not eat raw or poorly cooked food. Travelers should use bottled water and avoid ice cubes or ice cream without the original packaging. Viral gastroenteritis usually subsides by itself, and intervention by a physician

is generally not necessary. However, adults should consult a physician if they are unable to hold fluids for more than 24 hours, if they vomit for more than 2 days, vomit or faeces show blood or body temperature rises above 40°C, as well as symptoms of dehydration. This is manifested by excessive thirst, dry mouth, deep yellow urine or a small amount of urine, weakness, vertigo, dizziness. Children should be referred to a doctor if the child has a temperature above 39°C for 1 to 2 days, if they are apathetic or very irritated, have pain, bloody diarrhea or is dehydrated. If the child is somnolent, you should contact your doctor immediately. If diarrhea with blood or a child is constantly vomiting, hospitalization is required. During hospitalization, it is necessary to examine/monitor the patient's metabolic environment. Dehydration is monitored by comparing the amount of fluid received and urine excreted with the normal standard. Diarrhea and vomiting also lead to loss of electrolytes and possible acidosis. Therefore, the physician also corrects the metabolism of minerals, especially Na and K. It is also important to gradually restore the patient's nutrition. Suitable foods are bananas, apples, crackers, mashed potatoes, rice soups, lean meat or chicken broth. However, patients should avoid fatty, fried and spicy foods, alcohol, chocolate and flatulent vegetables for several days after the infection has resolved. For rotavirus and astrovirus infections, a lactose-free diet is appropriate, and especially low-lactose milk (e.g. Nutrilon low lactose, AL 110, Alidiar...) should be given to infants. Antibiotics are completely ineffective in the treatment of viral gastroenteritis. Conversely, they can aggravate the disease and prolong its duration by damaging the natural intestinal microflora. Lactobacilli, zinc or adsorbents (Calcium carbonicum, Smecta, Santax) may have some effect on disease reduction. In case of high fever, antipyretics may be given.

Characteristics of gastroenteritis inducing viruses (AGE)

Adenoviruses: The name of adenoviruses is derived from the fact that they were originally found in adenoid tissue; nasopharyngeal almonds. The presence of adenoviruses was manifested after ten days by degeneration of the nasopharynx of the surgically harvested cells. From a morphological point of view, adenoviruses have the shape of a twentyhedron having triangular walls with protuberances. It belongs to non-enveloped viruses. Virion has a size of 60 - 90 nm. Inside the virion is double stranded DNA. Human adenoviruses belong to the family Adenoviridae, genus Mastadenovirus C. They are divided into 7 groups (A-G) and more than 50 serotypes. The clinical picture of intestinal adenoviruses is similar to that of other viral pathogens causing intestinal problems. Typical symptoms include fever, vomiting and watery stools with no admixtures at a frequency of 3 - 15 daily. The incubation period is on average 10 days (2 - 15 days), the disease usually lasts 3 - 11 days and most patients do not need hospitalization. However, fatal cases have also been reported in immunodeficient patients, but this has been associated with the basic disease [4]. Adenoviruses infect different types of mucous membranes depending on the serotype. Serotypes 40, 41 and 51 have intestines as the target organ and cause the symptoms described above, caused by deposits of mucosal necrosis. Adenoviruses are among the typical causative agents of viral gastroenteritis. Respiratory serotypes 1-7 are also commonly found in the faeces, but they are not associated with intestinal disease. Except the intestine, adenoviruses most prefer the respiratory tract and eye. Serotypes 12, 18 and 31 infect the intestine asymptotically [5]. Adenoviruses are endemic throughout the world, but unlike respiratory adenoviruses, they do not show seasonality. In most cases, the transmission of infection is via the faecal-oral route, but a droplet infection is also possible. Faecal excretion lasts for 1 - 14 days, and the incidence of infectious episodes is influenced by population density and hygiene conditions. The most common virus capture is during the first week of the disease. From the diagnostic point of view, PCR (Polymerase Chain Reaction - the method of fast and easy DNA segment multiplication based on the principle of nucleic acid replication) and its modification has the highest yield. Other methods of direct virus detection include ELISA (Enzyme-Linked Immunosorbent Assay - method based on highly specific antigen-antibody interaction), latex agglutination (method of antigen detection based on precipitate), immunofluorescence (method based on the principle of coupling antigen and labeled antibodies) and immunochromatography (system-based method using the formation of an antigen-conjugate-monoclonal antibody complex bound to the membran). Further identification of adenoviruses is possible by sequencing ("reading" DNA - a method for determining the order of nucleobases (A, C, G, T) in DNA sequences). The virus can also be grown from clinical material on tissue cultures, where the cytopathic effect is manifested by the formation of larger, clumping cells, but it is a relatively lengthy procedure that is of little importance from a diagnostic point of view, as well as the detection of antibodies. Antiviral medicines are not available for the treatment of adenoviral infections. The treatment is only symptomatic, in particular a sufficient fluid supply must be ensured. Diet for at least five days is also important. Intestinal disinfectants

have a supporting effect. Prevention consists mainly in compliance with hygiene measures. An enteric adenovirus vaccine is not available; In the US, a live attenuated vaccine has been tested and used for some time in the military to prevent respiratory episodes caused by adenoviruses [6].

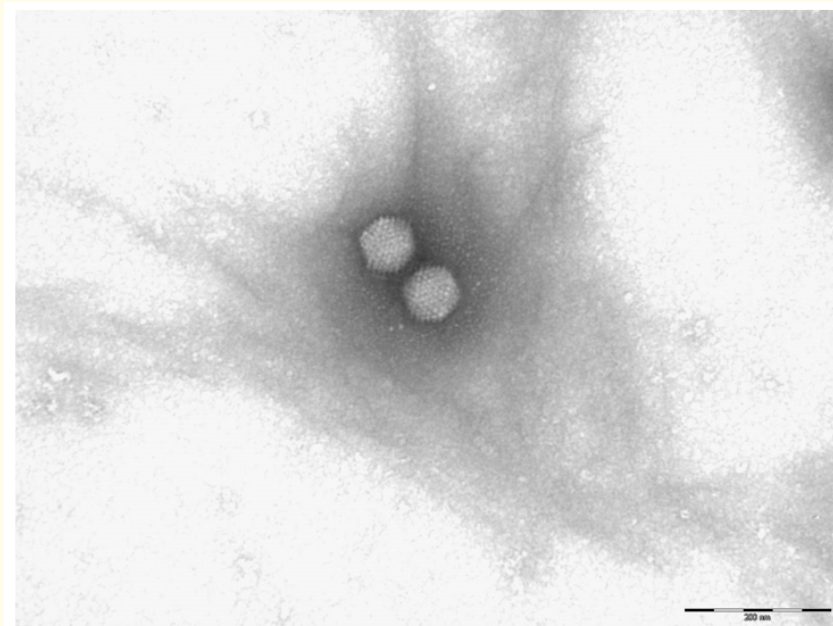


Figure 1: Adenovirus. Source: RNDr. D. Krsek.

Rotaviruses: The name of the rotaviruses is derived from the morphology of the electron microscope, as it resembles a spokes arranged around the center of the wheel (Latin = wheel). Rotaviruses are polyhedrons with a diameter of 70 - 75 nm with a characteristic sharply bounded bilayer capsid. The genome of rotaviruses consists of double stranded RNA. The genus Rotavirus belongs to the family Reoviridae and 8 different A-H groups are known to date; within a given group, viruses are subdivided into subgroups and serotypes. Rotaviruses from groups A, B, C and H are pathogenic to humans. Most human diseases are caused by group A. The incubation period of the rotavirus infection is 1 to 3 days. In adults, the disease usually occurs asymptotically or with a mild course, as well as in children under two months, the infection occurs more rarely, often asymptotically, probably due to colostrum and breast milk. Rotaviruses are particularly vulnerable to children from 4 months to three years of age. Repeated infection is markedly milder. In some cases, upper respiratory tract or anorexia first appears, but usually the first symptoms of rotavirus infection are fever and vomiting. After 1 to 3 days, rotaviruses attack the mucosa of the upper two thirds of the small intestine. This causes a decrease in the absorption of sugars, a deficiency of the lactase enzyme that breaks down the lactose and subsequently diarrhea, which persists for 5 to 8 days. Stool is very frequent and watery, usually without any mucus or blood. Flatulence and skin rash as well as respiratory symptoms may also occur. Complications may include parainfection hepatopathy, encephalopathy, meningoencephalitis or febrile convulsions. The treatment consists mainly in rehydration with a fluid containing electrolytes and glucose. Probiotics can reduce diarrhea by about 1 day if the infection is easier. The pathogenesis of rotavirus infections has several factors - lactose malabsorption, increased secretion in crypt cells by activation of the nervous system in the intestinal wall, and enterotoxin production. Rotaviruses multiply exclusively in the small intestinal epithelial cells. After virus multiplication, the cells die and a large amount of virus is released into the intestine that infects other cells. Rotavirus infections are widespread

worldwide. They are seasonal in nature and are most common in Europe in winter and early spring. Rotaviruses are transmitted via the faecal-oral route and are excreted in the faeces of an infected person for 7 to 10 days. Detection of rotaviruses is possible by latex agglutination, ELISA, immunofluorescence, immunochromatography, electronoptics and PCR. A more detailed determination of subgroups and serotypes is possible with ELISA with monoclonal antibodies, however sequencing methods are currently gaining importance. Isolation of rotaviruses on tissue cultures is possible, but it is very laborious and, like serological methods, is not suitable for routine diagnosis. Prevention of non-compliance with hygiene principles is vaccination. Two rotavirus vaccines are currently available - Rotarix and RotaTeq [7]. In some European countries (e.g. Finland, Austria) vaccination against rotaviruses is part of a vaccination schedule.

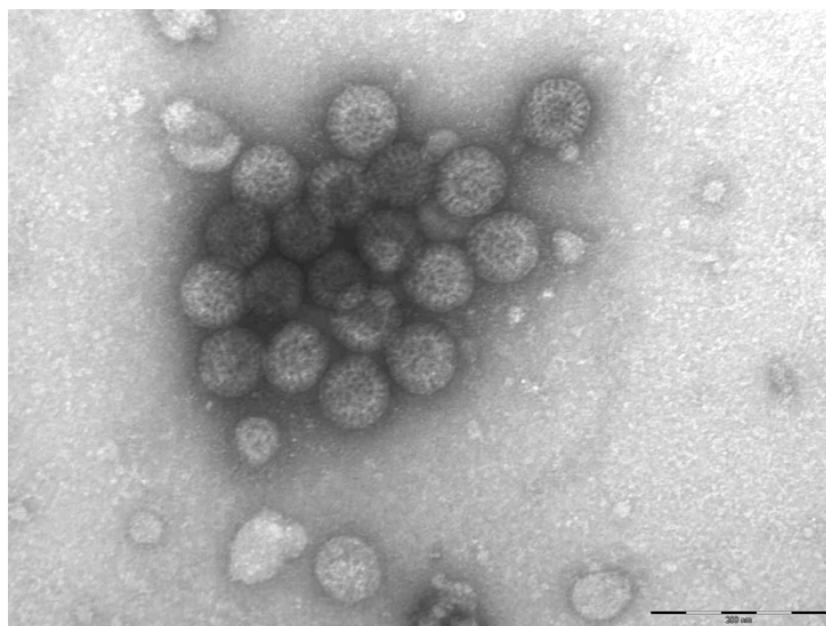


Figure 2: Rotavirus. Source: RNDr. D. Krsek.

Noroviruses: Noroviruses were discovered in 1972 during an epidemic at a primary school in Norwalk, USA [8], from which their name was derived. Noroviruses are small non-enveloped single-stranded RNA viruses of 26 - 35 nm in size. It belongs to the family Caliciviridae (from the Greek word calyx - cup) because the viruses have characteristic cups on the surface. Norovirus includes only one species of Norwalk virus. Noroviruses are divided into 5 groups (GI-GV), for humans are pathogenic noroviruses of the groups GI, II and IV. The incubation period of the disease is in the range of 18 - 72 hours, followed by painful abdominal cramps as the first symptoms of noroviral gastroenteritis, also called "winter vomiting disease". Nausea, vomiting and watery diarrhea develop without the presence of blood or mucus. Vomiting is the main, dominant symptom. If it occurs in the family, it is usually the first adults to get sick. The infection may or may not be accompanied by an elevated temperature. Other symptoms include abdominal pain, headache, anorexia, general weakness and seizure. Uncommon symptoms include myalgia, chills and sore throat. At uncomplicated course, symptoms resolve after 3 - 7 days. Asymptomatic infection may occur in up to one third of patients. Noroviruses infect the proximal part of the small intestine, causing a reduction in the enzymatic activity of the brush border. On the small intestine mucosa, micro-lesions arise, causing diarrhea, which can lead to dehydration and electrolyte loss. Noroviruses are currently considered to be year-round cause of gastroenteritis epidemics. However, the number of

diseases culminates in the winter months. The therapy is symptomatic and is primarily aimed at covering fluid loss. The way of transmission of noroviruses is via the faecal-oral route. It is possible to transfer aerosols from vomit of infected individuals, contaminated water can also cause infection. The disease is already caused by a very small infectious dose (10 - 100 virions), while the content of infectious particles in stool and vomiting is extremely high. Noroviruses are diagnosed by electron microscopy, immunochromatography, ELISA, molecular biological methods based on PCR. Further determination is possible by sequencing techniques. Noroviruses can be multiplied on tissue cultures, but this method is used only for scientific purposes. Serological methods have no relevance in clinical practice. Norovirus vaccine does not exist. It is important to observe hygiene habits, since immunity after a past infection is short-term.

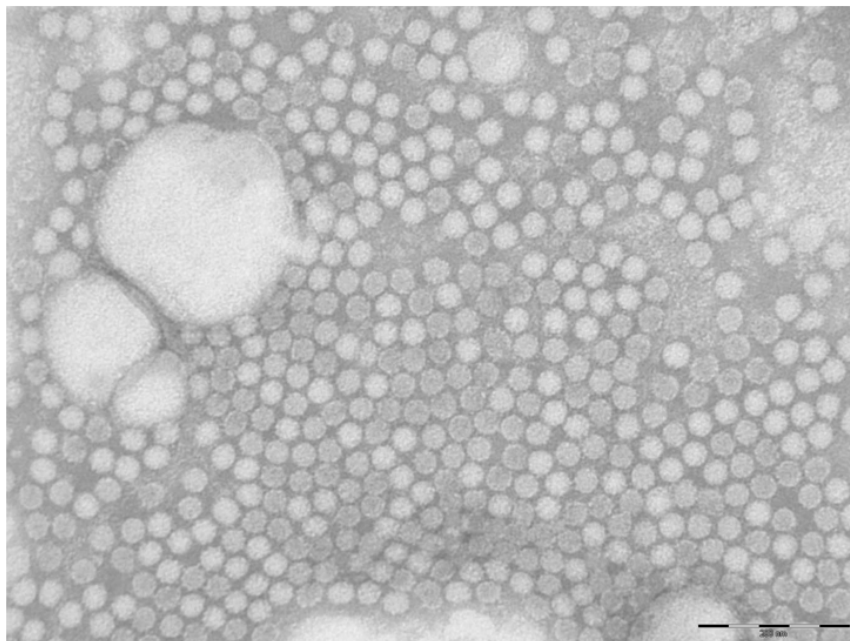


Figure 3: Norovirus. Source: RNDr. D. Krsek.

Astroviruses: The name of astroviruses is derived from the Greek word astron - stars. Astroviruses have a typical five- or six-pointed star appearance when viewed in an electron microscope. They are non-enveloped viruses with the size of 28 - 35 nm, their genome consists of positive single-stranded RNA. Human astroviruses belong to the family Astroviridae, genus Mamastrovirus and are further divided into individual groups and serotypes. Representatives of this relatively new astroviridae viral family - astroviruses - are now described as one of the causes of gastroenteritis in children and adults [9,10]. The incubation period for this infection is 1 - 4 days. The main symptoms are diarrhea, followed by nausea, vomiting, fever, anorexia and abdominal pain. The duration of symptoms is approximately three to four days. Treatment is only symptomatic. Astrovirus infections are usually not severe and only in some rare cases lead to dehydration. Prolonged course is extremely rare. Virus replication occurs in intestinal epithelial cells, and as with rotaviruses, as a result of astrovirus infection, deficiency of disaccharidases may occur. Astroviruses have a seasonal occurrence with geographical variation. In mild climates, the number of infections is highest in the winter months, unlike tropical areas where prevalence is highest during the rainy season. Transmission is also the faecal-oral route. Faecal excretion of the virus usually lasts approximately 2 weeks after the retreat of clinical symptoms but may last up to 3 months in immunodeficient patients. Diagnostic methods are electron microscopy, ELISA and immunochromatography. The most modern and sensitive method for the detection of astroviruses is PCR; Astroviruses can also be multiply on tissue cultures and virus replication can be verified by immunofluorescence, this approach is not routinely applied, as is serological detection of antibodies.

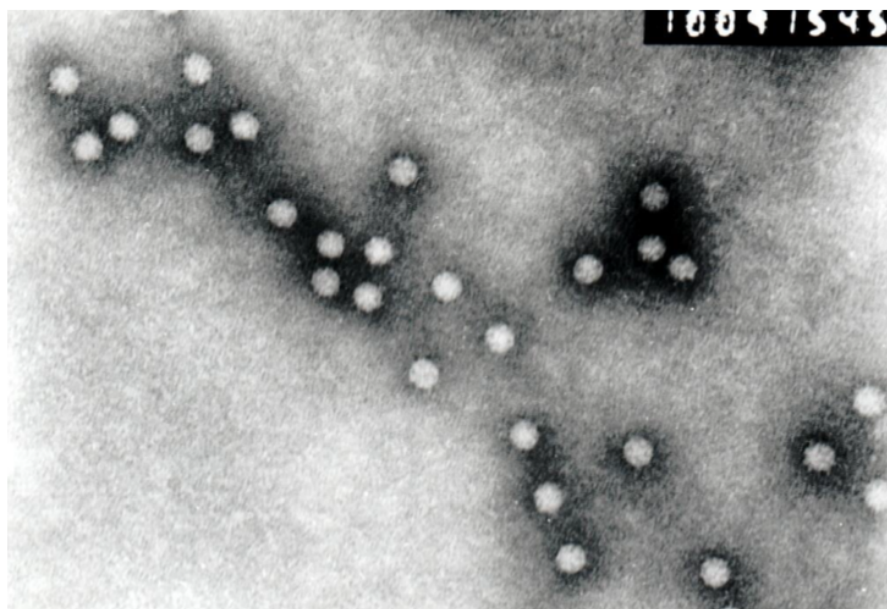


Figure 4: Astrovirus. Source: MUDr. J. Schramlová.

Sapovirus: The name of the virus is derived from the city of Sapporo in Japan, where the virus was first discovered after an outbreak of gastroenteritis in an orphanage [11]. Sapoviruses are non-enveloped viruses 27-40nm in size, whose genome contains single-stranded RNA with positive polarity. Only one virus species - *Sapporovirus* - is included in the genus *Sapovirus* of the Caliciviridae family. Sapoviruses are divided into 5 groups (GI-GV), for humans pathogenic GI, GII, GIV, GV. The incubation period of infection is 12 - 48 hours. Symptoms include abdominal pain, nausea, vomiting, diarrhea, chills, fever, muscle pain and dehydration. The cause of diarrhea is microlysis caused by damage to the brush border of the small intestinal mucosa. Treatment is symptomatic. Sapoviruses occur worldwide and year-round - with higher prevalence in autumn and winter. Transmission is faecal-oral. After the disease has resolved, viruses are excreted in the faeces for another 1-2 weeks. The most common diagnostic method used to identify sapoviruses is PCR. Other possible methods are ELISA and electron microscopy. Further determination is possible with the help of sequencing. Cultivation is possible but is not routinely used.

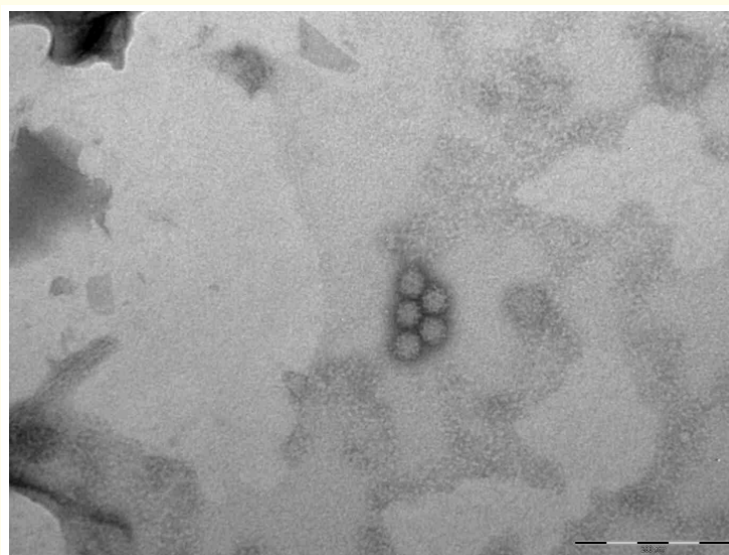


Figure 5: Sapovirus. Source: RNDr. D. Krsek.

Coronaviruses: Coronaviruses may also be considered as potential causal agents of viral gastroenteritis. The name of the viruses was derived from the appearance in an electron microscope, when the edge with surface mallet tips resembles a crown. These are large pleiomorphic RNA viruses 100 - 150 nm in size. Coronaviruses cause respiratory and intestinal diseases in both humans and animals. Infections mainly affect children under 1 year of age and often occur as haemorrhagic enterocolitis with fever and abdominal pain. Coronaviruses occur worldwide without typical seasonal occurrence. Diagnosis is performed by electron microscopy and PCR. Cultivation is possible on cultures of human fetal intestinal cells.

In day-to-day outpatient practice, faecal sampling should be performed in case of suspension for AGE viral etiology and the collected material should be sent for virological examination (Table 1-3). Viral particles are massively excreted most in the first days of faeces, but in smaller amounts much longer, often weeks. If the situation permits, it is advisable to investigate the full range of possible AGE agents available. The introduction of molecular biology methods has significantly increased the causality of pathogens in this group of diseases. Specific treatments cannot be applied to these infections [12-14] and should be treated symptomatically. In addition to therapy, it is of course necessary to consistently apply and follow appropriate anti-epidemic measures and coordinate them in cooperation with the Public Health Protection Authority.

Material	Stool	1 cm ³
	liquid stool	3 ml
Transport	Sterile test tube with cap or container with a scoop at temperature+4°C	
Storage	Within 48 hours: 2 - 8°C	
	Over 48 hours: -20°C	

Table 1: Collection and transport of material for virological examination in case of suspected AGE.

Viruses Required	Incubation Time	Duration	Duration Average Virus Excretion Time	Examination Methods
Noroviruses	18 - 72 hours	3 - 7 days	2 - 15 days	Electron microscopy, ELISA, Immunochromatography, PCR
Rotaviruses	24 - 72 hours	5 - 8 days	7 - 10 days	Electron microscopy, ELISA, Immunochromatography, Immunofluorescence, Latex agglutination, PCR
Adenoviruses	48 - 360 hours	3 - 11 days	1 - 14 days	Electron microscopy, ELISA, Immunochromatography, Immunofluorescence, Latex agglutination, PCR
Astroviruses	24 - 96 hours	3 - 4 days	14 - 21 days	Electron microscopy, ELISA, Immunochromatography, PCR
Sapoviruses	12 - 48 hours	3 - 7 days	7 - 21 days	Electron microscopy, ELISA, PCR

Table 2: Laboratory methods suitable for the examination of AGE - causing viruses.

Examination Methods	Speed	Specificity	Sensitivity	Price	Frequency usage in practice	Precision
Electron microscopy	+++	+	+++	+	+	+++
Latex agglutination	+++	+	+	+	++	+
Immunochromatography	+++	+	+	++	+++	+
ELISA	+++	+	+	++	++	+
Immunofluorescence	+++	+	+	++	++	+
PCR (+sequencing)	+++	+++	+++	+++	++	+++
Isolation on tissue cultures	+	+	+	+	+	+

Table 3: Advantages and disadvantages of available laboratory methods.

Conclusion

There are able to investigate samples using electron microscopy and PCR for presence of noroviruses, rotaviruses, adenoviruses, astroviruses, sapoviruses and coronaviruses in National Institute of Public Health of Czech Republic. The highest yields were found for these two methods. The speed of examination is high for other methods immunochromatography, latex agglutination, ELISA, immunofluorescence except isolation on tissue cultures, but their sensitivity and precision is not high. The fastest method is PCR, where we use a multiplex kit, in which we can examine more samples for the presence of GI, II noroviruses groups, adenoviruses, rotaviruses, astroviruses and sapoviruses in one reaction. Only molecular biological methods are suitable for closer determination. We combine PCR with the electron microscopy method because we are able to confirm the PCR result and also detect the presence of coronaviruses that are not present in the multiplex kit. The implementation of PCR for many laboratories is problematic due to the high cost of the kits and the need for instrumentation. This is why the most frequently used method for routine laboratories is poorly accurate immunochromatography.

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Volume 9 Issue 5 May 2020

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