Paediatric Acute Gastroenteritis

Chapter 1: Epidemiology

Maria Naseer Malik

Surgical Resident Holy Family Hospital, Rawalpindi

Acute gastroenteritis is a rapid onset of diarrhea with or without other symptoms such as fever, nausea, vomiting, and abdominal pain. Globally young children are affected by 68% of diarrheal $diseases$.[4] It is not only a major cause of childhood mortality in the developing world but also a common and leading cause of morbidity in developed world e.g United States in pediatric age $group$[1]. Under five mortality due to diarrhea accounts for 19% of deaths. The burden of acute gastroenteritis is especially high in childhood in under developed countries, due to inadequate clean water availability, poor sanitation and nutritional risk $factors$[6]

The epidemiology of acute gastroenteritis depends on the specific causative agent and vary with the area, season, climate, and population under $studied$[3]. In a study by Hartman et al 75% to 90% of childhood acute infectious gastroenteritis is due to viruses. Bacteria account for 20% of cases and infectious diarrhea due to parasites account less than 5% of cases and usually persisting for at least two $weeks$[4].

According to a study Alexander et al acute viral gastroenteritis is most common in under 5 years of age. The gender ratio is almost equal. In developed countries average child under 5 year of age experiences two episodes of diarrhea per year. This rate being significantly higher in developing countries and accounts for over 200,000 mortalities per year $globally$[2].
Thorough epidemiological evaluation is necessary to assess the severity and type of disease, exposures and accurate diagnosis that will help in $management$[3].

Incidence in Pakistan:

Pakistan has high incidence of acute gastroenteritis and rank fifth among 15 developing countries that account for 73% of all under-five mortalities worldwide. Rota virus is the cause of majority of cases. Under-five mortality is 10.8% due to gastroenteritis and thus leading cause of death in this age $group$[6]

Epidemiological Determinants

Agent factors:

Acute gastroenteritis is caused by different infectious or inflammatory processes that directly affect enterocyte secretory and absorptive $functions$[5] A wide verity of organisms cause acute gastroentritis, and many of them have been discovered only in recent years such as campylobacters and rota $viruses$.[1]

Pathogens mostly identified in children with acute diarrhoea in developing countries are enlisted below in table 1.

Pathogen		% of cases
Viruses	Rota virus	15-25
Bacteria	Enterotoxigenic Escherichia coli	10-20
	Shigella	5-15
	Campylobacter jejuni	10-15
	Vibrio cholerae 01	5-10
	Salmonella (non typhoid)	1-5
	Enteropathogenic Escherichia coli	1-5
Protozoans	Cryptosporidium	5-15
No pathogen found		20-30

$Table\ 1$ [1] *(Courtesy: park textbook of preventive and social medicine* 23^{rd} *edition)*

Reservoir of infection:

Human and animals act as reservoir of infection. Human is the principal reservoir for some enteric pathogens e.g. Escherichia coli (enterotoxigenic strain), shigella., Vibreo cholerae, Giardia lamblia and Entameoba histolytica and thus most transmission occurs from human factors. For other enteric pathogens e.g. Campylobacter jejuni, Salmonella and Yersenia enterocolitica , animals are important reservoirs and transmission originates from both human and animal faeces.
The role of animal reservoirs in human disease is still uncertain for viral agents of $diarrhoea$.[1]

Host factors:

Diarrhea is most common disease specially in pediatric age group between 6 months and 2 years. Highest incidence is found in the age group between 6 to 11 months; i.e at the time of weaning. This is due to combined effects of **the deficiency of active immunity in the infant,** decrease in **maternally acquired antibodies,** ingestion of contaminated food, and direct contact with human or animal faeces when the infant starts to crawl. It is also common in infant under 6 months of age fed on formula milk or cow's $milk$[1].**Malnutrition** is major risk factor for acute gastroenteritis. It leads to infection and can cause severe diarrhoea , which is a well known vicious circle. **Immunodeficiency, decreased gastric acidity, incorrect feeding practices**, **poverty, prematurity, lack of personal hygiene and poor sanitation** are all contributory factors.

Environmental factors:

Environmental factors are responsible for the distribution pattern of the acute gastroenteritis. Different geographical areas have distinct seasonal patterns of acute gastroenteritis.
In temperature climates, bacterial diarrhea most frequently occurs during the warm season, whereas viral diarrhea, particularly caused by rota virus, has peak incidence during the winter season. In tropical areas, viral infectious diarrhea occurs throughout the year, with increase in

frequency during the drier, cool months, whereas bacterial diarrhea has higher incidence during the warmer, rainy season. The incidence of persistent diarrhea and acute watery diarrhea follows the same seasonal $patterns^{1,8}$.

Mode of transmission:

There are different mode of transmission of the causative agent but the most of the microorganisms responsible of acute gastroenteritis are transmitted primarily and exclusively by the **faecal-oral route.** Faecal-oral transmission may be water-borne; food-borne, or direct transmission such as via fingers, dirt or fomites which may be ingested by young $children^{1,7}$.

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Chapter 2: Pathophysiology

Muhammad Asad Asif

House Officer, Holy Family Hospital

Acute Gastroenteritis in children is a very serious condition that takes a significant number of lives every year. According to a recent study, millions of children fall prey to this disease[1]. It is a disease in which there is a rapid spell of diarrhea which may or may not be associated with vomiting, abdominal pain, and fever[2]. The inflammation of the lining of the digestive tract causes these symptoms.

Viral Gastroenteritis

Viruses are the most common cause of gastroenteritis in children[3]. Enteroviruses viruses like rotavirus and norovirus are one of the leading causes of this disease. Viral gastroenteritis is a very common disease that affects people of all age groups but it holds a particular significance in the pediatric group as it can produce severe complications[4,5]. Adenovirus, Calicivirus, and Astrovirus are the less common viral species causing acute gastroenteritis.

Rotavirus

The Rotavirus is a double-stranded DNA virus having an icosahedral shape with eleven segments. It belongs to the Reoviridae family. Rotavirus attacks the enterocytes present in the villi of the intestines[6]. Out of the several species identified for this virus Rotavirus A is by far the most common species to which human beings are susceptible.

Rotavirus has a secretary mechanism in which the nonstructural protein of the rotavirus releases calcium ions which increases the mobility of the intestine[7]. The non-structural protein 4 is not present in the mature virus so it has to be produced inside the infected enterocytes. The Lundgren and Svensson model paints a well-defined picture explaining how the NSP4 affects the enterocytes. This protein blocks the sodium transport channels, the most common of which is sodium-glucose co-transporter[8,9]. This mechanism combined with the loosening of the tight junctions of the epithelial cells causes an immense amount of fluid to be secreted into the lumen of the intestine.

Another mechanism by which rotavirus causes gastroenteritis is the malabsorptive process. Infectious diarrhea caused by this virus is typically a known inflammatory one[10]. According to several studies, this virus replicates along the tips of the villi. This virus affects the cells at the genetic level by down-regulating the production of absorptive enzymes resulting and male absorption and steatorrhea. This malabsorption results in the captivity of monosaccharides and

disaccharides in the intestinal lumen. These carbohydrates are osmotically active attracting the water inside the lumen resulting in significant water loss[11,12].

Norovirus

Norovirus is a naked, single-stranded RNA virus having an icosahedral shape[13] . It is estimated that they cause over one million hospitalizations

and 200,000 deaths in young **children** in developing countries annually [14]. It replicates inside the cytoplasm of the infected cells of the Gastrointestinal system. This virus like the rotavirus affects the enterocytes and spares the crypt cells[15]. The virus lessens the activity of the enzymes like disaccharidases present in the intestinal brush border resulting in inhibition in the absorption of carbohydrates and fats[16]. Other than the rotavirus and the norovirus, members of the Calicivirus family, Astrovirus, and the human enteric adenovirus of the adenoviral family are the less common viral causes of acute gastroenteritis in children[17].

Bacterial Gastroenteritis

After viruses, bacteria are the most common cause of acute gastroenteritis in children especially Campylobacter jejuni, Enteropathogenic Escherichia coli, Shigella, Salmonella, Vibrio cholera, etc. Almost 10 to 15% of dial episodes due to gastroenteritis are caused by bacteria[18].

Campylobacter Jejuni

Campylobacter jejuni is a Gram Negative flagellated bacteria having the shape of a curved rod. The flagellum present at one end of the bacteria helps it in motility. It can grow at 42-degree centigrade which makes it a highly thermophilic organism. The organism colonizes the epithelial cells of the distal ileum. It goes straight through the mucosal layer covering the enterocytes because of its polar flagellum. The pathogenesis of this bacteria involves the internalization of the infectious organism with the help of the microtubules and microfilaments present in the host cells[19]. The bacterium modifies the cytoskeleton of the epithelial cells resulting in its uptake. The process by which this bacterium causes inflammatory diarrhea has still yet to be discovered but a proposed mechanism suggests that the compiler vector releases a cytolethal distending toxin. This toxin renders the enterocytes to die by inhibiting the cell growth cycle. This ultimately leads to the death of the epithelial cells, ensuring inflammatory diarrhea. Several other complications are also associated with this organism including reactive Arthritis and Guillain-Barre syndrome. It is normally a self-limiting disease that is resolved by the end of the fifth day why electrolyte and fluid replacement[20].

Escherichia Coli

Escherichia Coli is also a gram-negative rod and belongs to the Enterobacteriaceae family it is a fermenter of lactose and it inhabits the colon of its human host. Out of the multiple strains that have been identified so far, The enteropathogenic and the enteroaggregative strain of E Coli Was found to be the most common when the stools of the affected children were tested. The mechanism

of action of this organism includes the production of a toxin that affects the intestine at the genetic level[21]. This toxin inhibits the functionality of the larger ribosomal subunit present in the cells which causes the inhibition of protein synthesis, resulting in the death of the cells.

Another strain of this bacteria is the enterohemorrhagic Escherichia Coli which can cause a hemolytic uremic syndrome in children. The glomerular membrane is lined with endothelial cells which are a part of the basement membrane barrier. The EHEC strain of E Coli attacks these endothelial cells rendering them as a thrombogenic material that attracts a large number of the platelet. Aggregation of these platelets causes the platelet count to drop significantly. This platelet count drop, along with the lysis of the red blood cells as they pass through the clump of platelets causes mechanical stress on the biconcave red blood cells ultimately leading to the hemolytic uremic syndrome[22].

Shigella

Shigella is a non-lactose fermenter and it is also so one of the most common bacteria found in the stools of children having acute gastroenteritis it spreads through the femoral route and is most commonly observed in daycare centers among children. Like EHEC, It produces a toxin called Shiga toxin which is neurotoxic and cytotoxic. Shigella gains its entry into human cells by modifying the cytoskeletal structure. The toxin is composed of two components; A and B component. The A component damages the brush border on enterocytes and the B component disrupts the cytoskeleton of the intestinal cells. It can also cause the humility new remix syndrome using the same mechanism as the enterohemorrhagic strain of Escherichia Coli described above[23].

Protozoal Gastroenteritis

Among Protozoans, the most common agents of disease are Cryptosporidium, Giardia, and Entamoeba[24]. All these protozoal infections are transmitted through water contaminated with the feces of an infected individual and the mode of transmission is through the fecal-oral route. Protozoans cause infection through direct cytotoxic effects.

Cryptosporidium, being the most common culprit of gastroenteritis in children, produces bouts of watery diarrhea that resolves by itself over time. The severity of infection depends on the protozoal load and the status of the immune system of the infected individual. After ingestion, Cryptosporidium colonizes the intestine in the form of oocytes that are released in the feces. This fecal infection with the oocysts when consumed by another host causes the oocysts to release multiple cysts[25]. They are the agents of destruction that disrupt the intestinal barrier increasing permeability, decreasing the absorption, and causing the secretion of fluids.

Giardia lamblia is the second most common protozoal agent of acute gastroenteritis in children after Cryptosporidium. It causes infection when the contaminated water containing mature cysts is ingested. The trophozoites attach themselves to the intestinal villi where it causes rapid multiplication and causes multiple episodes of diarrhea[25].

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Chapter 3: Presentation

Noor Us Saba , Zainab Idrees Ahmad

Acute gastroenteritis is one of the most common infectious diseases particularly in the paediatric population and a major health problem particularly in developing countries responsible for about 1.5 million doctor visits, affecting 3 to 5 billion children annually and 220,000 hospital admissions each year. It has also been the major cause of morbidity and mortality in less than 5 year old children.(1,2)

In Asia, the most common cause of AGE in children is Rotavirus accounting for 70–90% of cases of AGE. The prevalence of Rotavirus fatalities in four developed countries in the region is 49%, one of which is Pakistan with rotavirus infants mortality rate 67.6 per 100,000 children and among children to be 29 to 37% (10,11,12).

CAUSES:

The cause of AGE can be bacteria, fungi and parasites, however, viruses are the major etiological agent of AGE in younger children. Among viruses the major established causative agents are rotavirus (RV), norovirus (NoV), sapovirus (SaV), enteric adenovirus (AdV), and astrovirus.

But the leading cause of acute diarrhoea in children remains the A rotavirus (RVA) and the G1P, G2P, G3P, G4P, and G9P

being the commonest strains responsible for this (1).

CLINICAL PRESENTATION:

The clinical presentation of AGE depends on the etiological agent. Therefore, it is necessary to differentiate various clinical symptoms to correctly treat the condition. Most of the cases are self-limiting (2).

- Bacterial Gastroenteritis is more severe and presents with high-grade fever and vomiting as a common clinical presentation in most cases (2).
- Viral gastroenteritis is usually characterised by watery diarrhoea, low-grade fever, vomiting and abdominal pain. Additionally, tachycardia and tachypnea may be present due to fever and dehydration (2).

Moreover, Bloody, mucous diarrhoea and high fever tend to be associated with a bacterial cause, while acute viral gastroenteritis is more commonly accompanied by respiratory manifestations and longer-lasting vomiting (2).

The cause of worldwide morbidity and mortality due to gastroenteritis is Diarrhoea while Vomiting is known to be the most annoying clinical presentation which can be a cause of worry and distress leading to dehydration which is a complication of AGE (2,4,10).

SYMPTOMS UNIQUE TO COMMON VIRUSES:

1.ADENOVIRUS:

As for adenoviruses, group F strains of serotypes 40 and 41 are mainly detected in children with diarrhoea and fever, however, a major finding is the strong association between ***adenovirus infection*** and ***intussusception*** (2).

2.NOROVIRUS:

Constantly mutating Norovirus causes symptoms of diarrhoea, nausea and vomiting. Norovirus infections are typified by intense vomiting, sometimes without diarrhoea (3,4).

However, norovirus can cause serious clinical symptoms in children, the elderly and immunocompromised patients with a higher incidence of ***SEIZURES*** than other viruses(3,4).

3.ROTAVIRUS:

Rotavirus more commonly causes high fever, dehydration, and ***ELECTROLYTE DISTURBANCES***.

Complications include severe hyponatremia (<125 mmol/L), hypernatremia (>155 mmol/L), and encephalopathy and outcome can be fatal in some cases, however, universal immunisation is the key to achieving a significant reduction of rotavirus-associated diarrhea. (4,5)

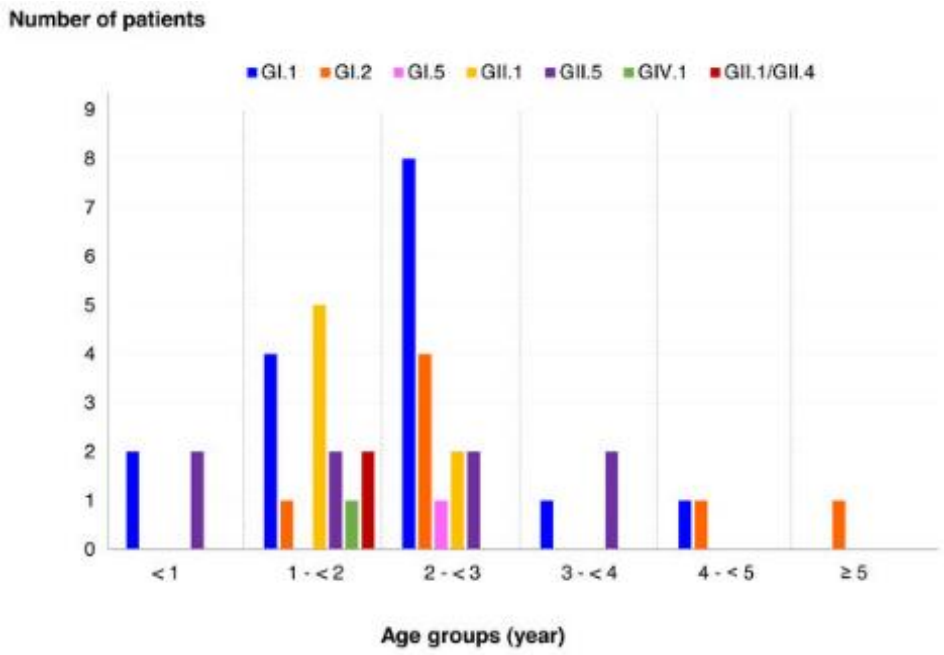
4.MER-COV:

Clinical symptoms include diarrhoea, vomiting, nausea and abdominal pain.

Human primary intestinal epithelial cells, small intestine explants and intestinal organoids, are highly susceptible to MERS-CoV, and the virus is able to maintain its replication robustly in small intestine cells. (6)

- The HAstV infection results in diseases ranging from asymptomatic to mild watery diarrhoea and systemic diseases. The novel strains HAstV-MLB and HAs-VA have been reported to be associated with **central nervous system** infection in immunocompromised children. (7)
- Aichi Virus has also been documented in stool samples of Iranian paediatric patients. (8)
- Sapovirus (SaV) is one of the important pathogens causing **sporadic cases** of acute gastroenteritis (AGE) in children (9).

Table 1



(9)

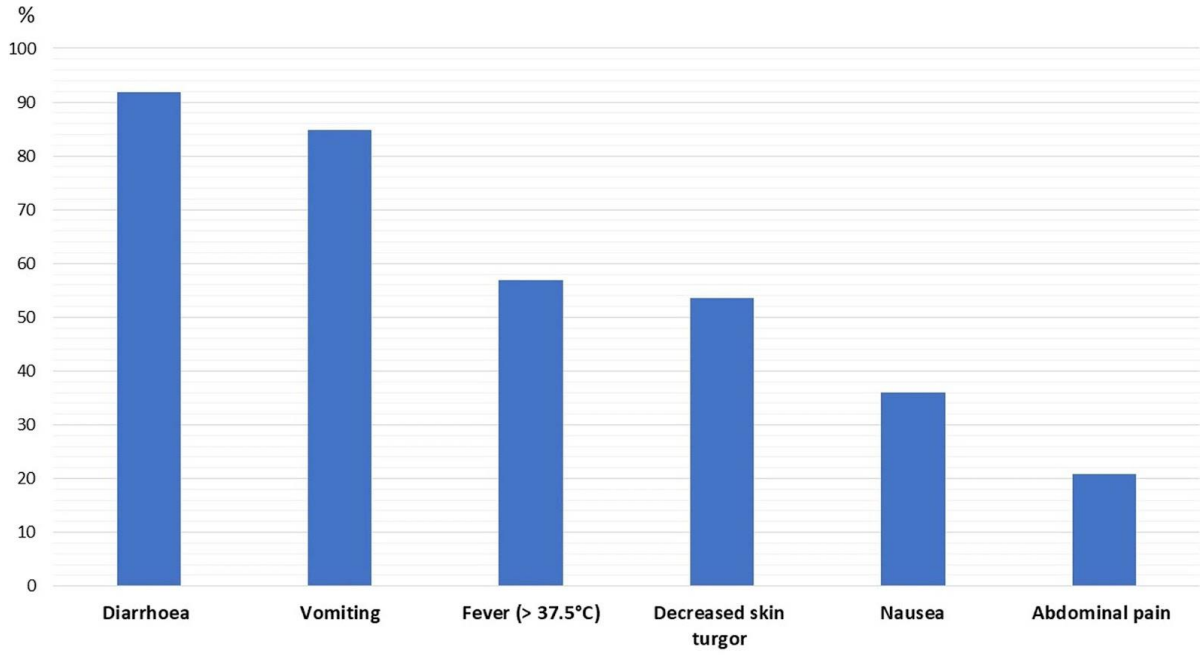
Clinical Presentation in Detail:

Patients with AGE typically present with decreased consistency of stools and an increase in the frequency of evacuations that can be greater than 3 times a day. This symptom can be associated with fever or/and vomiting, usually lasting less than a week and often not more than 2 weeks. Symptoms can be severe or prolonged that may require hospitalisation and microbiological investigations (13).

In a survey including children of age 5, the most common symptoms observed were

diarrhoea and vomiting (92% and 85%, respectively) however fever, nausea, and abdominal pain were less commonly found. In about half of the patients, decreased skin turgor was noted (13).

Table (2)



(13).

1. DIARRHOEA:

The American Academy of Pediatrics (AAP) defines acute gastroenteritis as a diarrheal disease of rapid onset, with or without additional symptoms and signs, such as nausea, vomiting, fever, or abdominal pain that can be classified as acute watery diarrhoea, acute bloody diarrhoea (dysentery), persistent diarrhoea, and diarrhoea with severe malnutrition caused by specific microorganisms such as rotavirus, norovirus, Salmonella, E. coli, and Campylobacter but viruses are the leading causes and have higher frequency rates in children from HIC than in those from LMIC (2).

PATHOGENESIS:

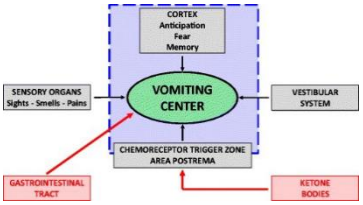
Watery diarrhoea caused by cytolytic organisms is secondary to impaired fluid and electrolytes absorption across the intestinal epithelium that produce epithelial inflammation, cytokine liberation and sometimes necrosis of the intestinal lining. Watery diarrhoea is caused by rotavirus that is the most common organism involved in AGE in children. In case of V. cholerae and ETEC infection, adenylate cyclase is activated and turns epithelial cells to an active secretion of chloride state while Shigella, Salmonella and Campylobacter produce inflammation and necrosis of epithelium and microabscesses. Bloody diarrhoea and dysentery is associated with high fever and toxicity (2).

In patients of prolonged illness identification of the involved organism is necessary for appropriate treatment and for this stool examination is done if the episode is not resolving on its own as in most of the cases AGE is self-limiting (13).

2. VOMITING:

Children with acute gastroenteritis habitually have vomiting preceded by nausea due to the activation of the vomiting centre located in medulla oblongata (14)

Table (3)



Pathophysiology of vomiting

The mechanism can be activated in two ways (14).

1. **Ketone bodies:**
   In children with moderate to severe acute gastroenteritis decreased availability of carbohydrates cause decreased levels of insulin and as a result elevated ketone bodies contribute to ongoing symptoms of nausea and vomiting.

2. **Afferent stimuli:**
   The second major pathways for the induction of vomiting are the afferent stimuli initiated by gut mucosa damage produced by the pathogens.

   These visceral pathways are the target of anti-emetic pathways used for the correction of severe vomiting when oral rehydration therapy fails.

TREATMENT for both DIARRHOEA and VOMITING:

Since AGE viral or bacterial usually lasts less than 1 week and no longer than 2 weeks so recommended management is supportive and includes repletion of ongoing fluid losses and the resumption of an age-appropriate diet as soon as rehydration is complete. Treatment with antidiarrheal agents, antimotility drugs, antisecretory drugs, absorbents, or antimicrobials is not advised and identifying the organism is not warranted except in severe cases (14).

- Mostly the debilitating symptoms of vomiting and diarrhoea causing complications like dehydration are associated with NAUSEA and VOMITING.

3. FEVER:

Fever is a normal response to infection and due to the release of high levels of cytokines body temperature may be raised. When the child's temperature is more than 38 °C, FS usually occurs.

Rotavirus gastroenteritis is associated with febrile seizures. Compared to CwG, febrile seizures develop earlier during the course of the illness and tend to last longer. However, despite these minor differences, both febrile seizures and CwG are considered to have a good prognosis(15,16).

INTUSSUSCEPTION:

Intussusception, cause of acute intestinal obstruction in children younger than 5 years is potentially lethal but the etiology of it is still not understood.

There is no prove that it is caused by rota virus but its temporal association with the first licensed rotavirus vaccine RotaShield, led to its withdrawal in 1999 (17).

SEIZURES:

Afebrile and febrile seizures and transient reduced consciousness are noted in a substantial proportion of children (87.5%) (15).

The term 'convulsions with mild gastroenteritis (CwG)' has been widely used to describe non-febrile seizures that are associated with gastroenteritis in the absence of clinical signs of dehydration or electrolyte imbalance. Seizures might be due to dehydration, metabolic acidosis, or fever more likely to require hospitalization.

HYPOTHESIS:

It has been proposed that viraemia occurs during the acute phase of disease and there is direct invasion of CSF by the virus. Other hypothesis suggests the association between rotavirus infection and seizures by the role of the rotavirus non-structural protein 4 (NSP4) which induce nitric oxide metabolites. Nitrites and nitrates are highly reactive metabolites raised in both serum and CSF in patients with rotavirus-associated seizures. It is also known that NSP4 plays a major role in mobilizing intracellular calcium that can induce seizures (15).

Table(4) (4)

Variable	Rotavirus Positive Gastroenteritis N = 50	Rotavirus Negative Gastroenteritis N = 66	P value
Acute GI complications; n (%)	1 (2%)	0 (0%)	0.43
Pathogens from the respiratory tract; n (%)	4 (27%) [n = 15] [a]	11 (69%) [n = 16] [b]	0.03
Pathogens from CSF[c]; n (%)	0 (0%) [n = 6]	0 (0%) [n = 5]	1.00
Neurological signs; n (%)	12 (24%)	10 (15%)	0.24
Seizures; n (%)	5 (10%)	8 (12%)	0.78
Reduced conscious level; n (%)	10 (20%)	5 (8%)	0.06
Encephalopathy; n (%)	3 (6%)	0 (0%)	0.08

GI: gastrointestinal; CSF: cerebrospinal fluid

n shown in square brackets where incomplete data

[a] RPG: Adenovirus (n = 1), Rhinovirus (n = 1), Parainfluenza (n = 1), *Staphylococcus aureus* (n = 1).

[b] RNG: Adenovirus (n = 4), Rhinovirus (n = 3), Metapneumovirus (n = 2), Enterovirus (n = 2), Respiratory syncytial virus (n = 1), Group G Streptococcus (n = 1).

[c] Viral studies performed in CSF sample included PCR for herpes simplex viruses 1+2, Varicella Zoster virus, Enterovirus, Cytomegalovirus, Epstein Barr virus. PCR for rotavirus was performed in one sample only.

https://doi.org/10.1371/journal.pone.0194009.t004

SUMMARY:

In short, AGE main symptoms include nausea, vomiting and diarrhoea sometimes associated with fever. Most of the times these are self-limiting but can lead to complications like severe dehydration, seizures(febrile or afebrile) or intsusessuption.

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Chapter 4: Investigation

Hiba Khalid, Jawad Basit, Mohammad Ebad ur Rehman

Young children typically recover from viral acute gastroenteritis in fewer than fourteen days, and severe infections are almost invariably the result of an infection caused by rotavirus. Rotavirus infections almost always produce severe illnesses. It is possible that one or more of the following diagnostic procedures may be carried out to arrive at a diagnosis for this acute pediatric disease.

CLINICAL ASSESSMENT:

- Diagnosis is often made clinically in instances with diarrhea with severity ranging from mild to moderate, and laboratory investigations are not typically necessary in the majority of these patients (1).
- Patients who are experiencing diarrhea should have a comprehensive medical history taken, which should include questions about any recent contact with another patient who is suffering from an infection that is similar to the patient's own infection, the frequency and consistency of the patient's stools, vomitus, and the patient's most recent use of antibiotics or antivirals. In addition, the patient should be asked about any recent contact with another patient who is suffering from an infection that is similar to the patient's own infection (2).
- Because chronic constipation is such a common issue among children, it is imperative that any danger of fecal incontinence brought on by chronic constipation be looked out for. This is because chronic constipation can lead to fecal incontinence. It is vital that this issue be investigated as soon as possible due to the high prevalence of persistent constipation in children.
- It is necessary to do a clinical examination in order to rule out the potential of an abdominal mass or of undergoing surgical treatment.
- If during the course of the physical examination any abnormality of the patient's vital signs is discovered, it is imperative that this be looked into further with a high degree of suspicion. It is not unusual for patients who have gastroenteritis caused by viruses to have a low-grade temperature; nevertheless, one should be wary of a non-viral source of the sickness if they have a high-degree fever.
- Tenderness, rebound, or guarding must trigger the suspicion for other causes of symptomatology (3)

Laboratory Investigations:

- Rarely, tests using rapid antigen detection may be carried out in order to identify viruses such as rotavirus, norovirus, or others.
- Even though stool cultures are not usually required, they must be performed in the event of an outbreak.
- It is necessary to culture the stool specimens for both bacteria and viruses.
- Stool cultures are also required in instances when there is a history of international travel, instances of bloody diarrhea, and in children who are immunocompromised.

- Other types of tests, such as immunofluorescence, antigen-detecting enzyme assays, and polymerase chain reaction PCR, might also be carried out. .

Assessment of degree of dehydration:

- Loss of weight is a reliable sign of the extent to which someone is dehydrated.
- However, in order for a patient to show clinical indications of weight loss, they must first have shed more than five percent of their body weight (2).
- Some of the clinical indications of extreme dehydration include aberrant and extended capillary refill, abnormal skin turgor, and the absence of tears (4).
- Additional symptoms include a sluggish or lethargic posture, sunken eyes, and a lack of interest in drinking.
- Dehydration can be monitored using the four-item scale that was developed for the purpose (5).

Monitoring of electrolyte imbalances:

- For the majority, there is no need for any serum or urine testing in order to monitor the acid-base balance of the blood.
- For the majority, there is no need for any serum or urine testing in order to monitor the acid-base balance of the blood (6)[1].
- When someone is only slightly dehydrated, serum electrolyte abnormalities are not typically observed. In severe circumstances, however, they need to be observed carefully.
- When administering intravenous fluids to a kid who has been diagnosed with severe dehydration, it is important to examine the child's baseline levels of electrolytes, bicarbonate, and urea/creatinine. Laboratory tests are required for patients who have only minor dehydration and whose medical history and physical examination do not fit the profile of simple gastroenteritis.

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Chapter 5: Management

Ruqia Arshad, Umbreen

FLUID REPLACEMENT

Mild to Moderate Dehydration

In mild to moderate dehydration, the goal of treatment is to restore the fluid deficit and maintain hydration. The usual ORS composition is 50 mEq per L of sodium, 25 g per L of dextrose, and 30 mEq per L of bicarbonate. Mild to moderate dehydration can be managed by replacing the fluid loss as 50 mL per kg. This can be accomplished at home by competent caregivers using a syringe to administer approximately 1 mL of ORS per kg of body weight every five minutes over three to four hours. If vomiting occurs, the ORS should be restarted after 10 minutes to one hour. An average of 10 mL per kg should be added for every loose stool or episode of vomiting. A syringe or calibrated measuring device is highly recommended for more accurate measurement

Moderate to Severe Dehydration

Moderate to severe dehydration usually requires hospitalization, although oral rehydration therapy can be attempted in the emergency department using a syringe or a nasogastric tube if the infant or child refuses to drink. Criteria for hospital admission include caregivers who are unable to adequately administer an ORS at home, intractable vomiting, poor ORS intake by mouth or nasogastric tube, profuse diarrhea, unusual irritability or drowsiness, or no symptom improvement after 24 hours of ORS administration at home. The child's regular diet should be continued during oral rehydration therapy, if possible, but may have to wait until after intravenous fluids are administered when the child is hospitalized.

An accelerated method of oral rehydration therapy for infants and children with severe diarrhea and/or vomiting entails administering 30 mL per hour of an ORS for infants, 60 mL per hour for toddlers, and 90 mL per hour for older children. An average of 10 mL per kg should be added for every loose stool or episode of vomiting. Ondansetron (Zofran), a 5-hydroxytryptamine-3 serotonin antagonist, can be used in the emergency department if vomiting is hindering oral rehydration therapy. A meta-analysis showed that ondansetron (0.15 or 0.3 mg per kg intravenously, or 2 to 8 mg orally [single dose] depending on body weight or 1.6 to 4 mg per kg orally [six divided doses] depending on age) significantly decreased vomiting in children with acute gastroenteritis soon after administration of the drug (number needed to treat = 5). [corrected] The risk of requiring rehydration with intravenous fluids was significantly reduced (relative risk = 0.4; 95% confidence interval, 0.3 to 0.7). Patients taking ondansetron also had a significantly

reduced risk of hospital admission (7.5 versus 14.6 percent; relative risk = 0.52; 95% confidence interval, 0.27 to 0.95). Ondansetron was well tolerated, except for increased episodes of diarrhea for up to 48 hours after use. Another meta-analysis showed that ondansetron decreased persistent vomiting, need for intravenous fluids, and hospital admissions in children with gastroenteritis. Other antiemetic should not be used because of potential adverse effects.

Administration of intravenous fluids requires at least four to six hours in the emergency department or an overnight stay in the hospital. Rehydration with intravenous fluids replaces the sodium and water deficit, as well as the ongoing fluid deficit. Depending on the severity of dehydration, a child might need two intravenous lines or an intraosseous line. A rapid fluid bolus is given at a rate of 20 mL per kg of body weight. A bolus of 10 mL per kg should be used for a frail child. The intravenous fluid of choice is normal saline 0.9%, although a lactated Ringer solution also may be used. The choice of intravenous fluid depends on the level of serum sodium. Urinary output and serum electrolyte, blood urea nitrogen, creatinine, and serum glucose levels should be checked often. Maintenance fluids should be given at a daily rate of 100 mL per kg for the first 10 kg, 50 mL per kg for the next 10 kg, and 20 mL per kg for the next 10 kg. As soon as adequate rehydration has been achieved, oral rehydration therapy can begin along with a regular diet, and the patient should be weaned from intravenous fluids. Patients at high risk of aspiration due to obtundation from electrolyte imbalances can be given an ORS via nasogastric tube. Complications of rehydration with intravenous fluids include hyponatremia, hypernatremia, and hypoglycemia; serum electrolyte levels should be monitored closely.

Probiotics

Probiotics are beneficial in modulating the immune response against foreign antigens in children with gastroenteritis. Probiotics do not colonize the gastrointestinal tract and are eliminated within one to two hours after ingestion. Probiotics degrade and modify dietary antigens and balance the anti-inflammatory response of cytokines. There is no known interaction between probiotics and medications. Probiotics are widely used in countries outside the United States because they are available over the counter, can be given orally at home, and are commonly recommended by physicians to limit the duration of diarrhea when it occurs. Their use is much less common in the United States.

Table 1. Principles of Treating Children with Gastroenteritis and Dehydration

Rehydration should be administered orally with an over-the-counter oral rehydration solution
Children should receive rapid oral rehydration (within three to four hours of symptom onset)
In infants who are breastfed, breastfeeding should continue
In infants who are formula-fed, diluting the formula is not recommended, and special formulas usually are not needed
As soon as the dehydration is corrected, a regular diet should resume
Ongoing diarrhea losses should be replaced with additional doses of an oral rehydration solution
Medications and unnecessary laboratory tests should be avoided

Fluid Replacement in Children with Gastroenteritis

Level of dehydration (percent body-weight loss)	*ORT*	*Intravenous fluids*
Mild (3 to 5)	50 mL per kg over three to four hours	Not recommended*
Moderate (6 to 9)	100 mL per kg over three to four hours	Not recommended*
Severe (10 or higher)	100 to 150 mL per kg over three to four hours†	20 mL per kg bolus over one hour‡
Ongoing body-weight loss	10 mL per kg for each stool or emesis	10 mL per kg for each stool or emesis

ORT = oral rehydration therapy.

**—If able to take ORT.*

† —*If clinically stable, alert, and taking ORT well.*

‡ —*Normal saline or lactated Ringer's solution.*

Antibiotic therapy in Acute Gastritis in children

Acute gastroenteritis (AGE) is one of the most common problems in infants and young children, especially in poor countries. It is caused by viral, bacterial, and parasitic agents, with an age-, host-, and location-based pattern. Etiology usually is not looked for, and oral rehydration therapy is the universal therapy. Active treatment with probiotics and antidiarrheal agents is suggested in adjunct to rehydration, as it reduces the duration and intensity of symptoms independently from etiology. There are no clear indications for antimicrobial therapy; however, antibiotics are frequently prescribed.

Indication for antibiotic therapy

Clinical conditions and circumstances that may indicate antibiotic therapy.

Condition	Putative bacterial agent	Suggested antibiotic
Dysenteric diarrhea	*Shigella, Yersinia, Campylobacter*	Azithromycin, ciprofloxacin
Fever, increased inflammation markers	*Shigella*	Azithromycin, ceftriaxone
Prolonged diarrhea	Gram-negative enterobacteria, *Clostridium difficile*	Metronidazole, co-trimoxazole
SIBO	Gram-negative enterobacteria	Metronidazole, rifaximin, co-trimoxazole
Antibiotic-associated diarrhea	*Clostridium difficile*, others	Metronidazole, vancomycin (only if *Clostridium difficile* is detected)
Traveler's diarrhea	ETEC, EPEC	Azithromycin, ciprofloxacin
Toxic state	Gram-negative enterobacteria, *Clostridium difficile*	Ceftriaxone

Risk factors indicating antibiotic therapy in children with acute diarrhea.

Risk factors	Evidence
Host-related risk factors	
Age <3 (or 6) months	Poor evidence but strong indication in neonates
Severity of clinical presentation	Poor evidence but strong indications
Malnutrition	Strong evidence
Chronic underlying disease Immune deficiency	Strong evidence for children with IBD or HIV Oncologic patients in immunosuppression therapy
Setting-related risk factors	
Day-care centers, hospitals, Iand close institutions	Strong evidence, if spreading of bacterial infection is an issue
Traveler's diarrhea	Strong evidence in adults, poor evidence in children

Antibiotic choice based on etiology.

Organism	Preferred therapy	Alternative agents	Efficacy
Campylobacter jejuni	Azithromycin	Ciprofloxacin, vancomycin	Proven if started within 3 days of symptom onset
Clostridium difficile	Metronidazole	Vancomycin	Proven in severe cases
Non-typhoidal Salmonella	Amoxicillin or ceftriaxone	Trimethoprim-sulfamethoxazole	Proven in children with toxic status, in children under 3 months of age, in at-risk children, and if systemic or focal infections
Salmonella typhi	Third-generation cephalosporins	Chloramphenicol	Proven
Shigella	Azithromycin, ceftriaxone	Cefixime, ciprofloxacin	Proven
Yersinia	Trimethoprim-sulfamethoxazole	Ceftriaxone	Proven in severe disease or bacteremia
Vibrio cholerae	Azithromycin	Doxycycline (>8 years), ciprofloxacin	Reduces duration by 50% and shedding
ETEC	Azithromycin (only for traveler's diarrhea)	Trimethoprim-sulfamethoxazole	To be considered in selected cases

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Chapter 6: Complications

Saad Javed, Eesha Yaqoob

Diarrheal diseases represent a leading cause of morbidity and mortality in children less than 5 years of age (1). More than 20 different microorganisms have recently been identified as the etiological agents of acute gastroenteritis (AGE), a significant increase over the previous four decades (2). Numerous risk factors have been discussed; the most important ones are age (5 years or younger), malnutrition, and other illnesses and comorbidities, which also represent potential causes of disease progression (2). The most frequent causes of AGE are viral pathogens, particularly rotavirus and norovirus (2). Bacterial pathogens like Escherichia coli, Campylobacter jejuni, Salmonella spp., and Shigella spp. are some of those in question.

Acute gastroenteritis, though frequently regarded as a benign condition, continues to be a major contributor to pediatric morbidity and mortality worldwide, killing 533,800 children under the age of 5 every year (more than other well-known illnesses like malaria, HIV, and TB for the same age group). (3)

Although several bacterial species also play a significant role in acute gastroenteritis, especially in low-resource settings, viruses continue to be by far the most frequent cause of acute gastroenteritis in children in both high- and low-resource settings. The following are the two main mechanisms that cause acute gastroenteritis:

- Osmotic diarrhea results from damage to the villous brush border of the intestine, which causes malabsorption of intestinal contents.
- Toxins that attach to enterocyte receptors to release chloride ions into the intestinal lumen, resulting in secretory diarrhea

Box 1 | Causes of acute gastroenteritis in children

Viruses (about 70%)
- Rotaviruses
- Noroviruses (Norwalk-like viruses)
- Enteric adenoviruses
- Caliciviruses
- Astroviruses
- Enteroviruses

Protozoa (<10%)
- Cryptosporidium
- *Giardia lamblia*
- *Entamoeba histolytica*

Bacteria (10-20%)
- *Campylobacter jejuni*
- Non-typhoid *Salmonella* spp
- Enteropathogenic *Escherichia coli*
- *Shigella* spp
- *Yersinia enterocolitica*
- Shiga toxin producing *E coli*
- *Salmonella typhi* and *S paratyphi*
- *Vibrio cholerae*

Helminths
- *Strongyloides stercoralis*

Signs and symptoms

These include the following:

- Diarrhea

- Vomiting
- Increase or decrease in urinary frequency
- Abdominal pain
- Signs and symptoms of infection - Presence of fever, chills, myalgias, rash, rhinorrhea, sore throat, cough; these may be evidence of systemic infection or sepsis
- Weight loss, an increase in malaise, lethargy, or irritability, changes in the quantity and frequency of feedings, and alterations in the child's level of thirst are all examples of changes in the child's appearance and behavior.
- History of recent antibiotic use - Increases the likelihood of *Clostridium difficile*
- History of travel to endemic areas

Evaluation of dehydration:

The World Health Organization (WHO) states that a patient can be deemed to have some degree of dehydration if they display two of the following symptoms:

- agitated, restless
- Sunken eyes
- thirsty, eager to drink
- Skin pressure slowly dissipates.

The WHO defines severe dehydration as the presence of two of the following symptoms in a patient:

- sluggish or unresponsive
- Sunken eyes
- Having trouble drinking or drinking poorly
- Taking a skin pinch back very slowly

To distinguish gastroenteritis from other causes of vomiting and diarrhea in children and to gauge the level of dehydration, the history and physical examination serve two crucial purposes. Although this will rarely have an impact on management, the history and physical examination can sometimes help in identifying the type of pathogen that is causing the gastroenteritis.

Diarrhea

The length of the diarrhea, the frequency and quantity of stools, the interval since the last episode, and the consistency of the stools should all be recorded. While stools with blood or mucus are a sign of a bacterial pathogen, frequent, watery stools are more consistent with viral gastroenteritis. A parasitic or noninfectious cause of diarrhea is more likely to be the cause of prolonged diarrhea (>14 days).

Vomiting

Find out how long the vomiting lasted, how much and what kind of vomitus was produced (food particles, blood, bile, etc.), and how long it had been since the last episode. Consider other illnesses like gastroesophageal reflux disease (GERD), diabetic ketoacidosis, pyloric stenosis, acute abdomen, or urinary tract infection when vomiting symptoms predominate.

Box 3 | Complications of acute gastroenteritis

- Dehydration
- Metabolic acidosis
- Electrolyte disturbance (hypernatraemia, hyponatraemia, hypokalaemia)
- Carbohydrate (lactose, glucose) intolerance
- Susceptibility to reinfection
- Development of food (cow's milk, soy protein) intolerance
- Haemolytic uraemic syndrome
- Iatrogenic complications (due to inappropriate composition or amount of intravenous fluids)
- Death

Urination

Analyze the number of wet diapers, the interval since the last urination, the color and concentration of the urine, and the presence of dysuria to determine whether the frequency of urination has increased or decreased. With frequent watery stools, it may be difficult to determine urine output.

Abdominal pain

Based on a report from the parents and/or child, determine the location, quality, radiation, severity, and timing of pain. In general, abdominal pathology other than gastroenteritis is more likely to be to blame for pain that comes before vomiting and diarrhea.

Signs of infection

Examine the patient for any symptoms of immunocompromised status, such as fever, chills, myalgias, rash, rhinorrhea, sore throat, or cough. These could be symptoms of sepsis or a systemic infection.

Appearance and behavior

Weight loss, feeding quality, quantity and frequency, thirst level, alertness level, increased malaise, lethargy, or irritability, crying quality, and presence or absence of tears with crying are among the factors.

Antibiotics

The risk of contracting Clostridium difficile infection rises with recent antibiotic use in the past.

Travel

Consideration of organisms that are relatively uncommon in the United States, such as parasitic diseases or cholera, may be prompted by a history of travel to endemic areas.

Dehydration is measured in what ways?

In cases of gastroenteritis, it's critical to evaluate hydration levels because they affect how this condition should be treated right away. The infant or child who experiences frequent, watery vomiting in addition to severe diarrhea. Clinicians frequently exaggerate how dehydrated a patient. Typically, clinical symptoms do not appear until a child has lost at least 5% of body weight. if the person's weight. Recent weight loss that has been documented is a good gauge of how much dehydration, but it's rarely possible to find this information. The best clinical indicators of more than 5% dehydration are abnormal skin turgor, prolonged capillary refill, and lack of tears. (4)

The classification used by the World Health Organization served as the basis for the assessment and management of dehydration recommendations, which have been supported by research. (4,5,6) Despite not being frequently needed, serum electrolytes should be checked before and after starting intravenous fluids.

Table 1: Dehydration assessment and treatment

Dehydration (% weight loss)	**Clinical signs**	**Pinch test***	**Management**
No dehydration	None	Typical (skin fold retracts right away)	Most conditions can be treated at home; promote a regular diet and fluid intake (keep up breastfeeding); consider admission if there is a high risk of dehydration (very young, uncertain diagnosis, significant losses).
Mild (5%) and moderate (6–9) dehydration, which are previous categories of some dehydration, are included.	Sunken eyes, two or more signs of restlessness or irritability, and thirst (a desire to drink)	Slow (skin fold visible <2 sec)	Some can be treated at home with oral rehydration therapy; others need to be watched and may require nasogastric or intravenous fluids over a 4-6 hour period if therapy is not tolerated or significant ongoing losses occur; normal diet when tolerated

Severe dehydration (≥10%) with or without shock	Two or more who appear unusually drowsy or lethargic, have sunken eyes, and either drink poorly or not at all	Very slow (skin fold visible >2 sec)	Check the patient's electrolytes, urea, and acid-base status before starting intravenous fluids; if shock is present, start with an intravenous bolus and then rehydrate intravenously (enteral fluids have already been used) over the course of 4-6 hours with routine clinical and biochemical monitoring.

Eosinophilic Gastroenteritis:

Depending on the area of the gastrointestinal tract and the depth of the bowel wall involvement, patients with eosinophilic gastroenteritis may present in a variety of clinical ways. The and the small bowel are typically affected by the disease. Many of the cases involve atopy and allergies in the past. (7, 8) Rarely, autoimmune connective tissue disease may be linked to eosinophilic gastrointestinal disease. (9)

Keep this in mind:

Vomiting, dyspepsia, abdominal pain, diarrhea, blood in the stools, iron deficiency anemia, malabsorption, protein-losing enteropathy, and failure to thrive are symptoms of the mucosal form of eosinophilic gastroenteritis.

The muscularis form, which is characterized by the presence of eosinophils primarily in the muscularis layer, can cause symptoms that resemble pyloric stenosis or gastric outlet syndrome and cause gastrointestinal obstruction.

Significant bloating, exudative ascites, and higher peripheral eosinophil counts are symptoms of the less frequent serosal form.

Pediatric Salmonella Infection:

In many nations, infections caused by Salmonella species are a serious public health issue. Nontyphoidal Salmonella (NTS) is the most frequent pathogen linked to food-borne gastroenteritis in the United States. (10) NTS typically results in mild gastroenteritis and is self-limiting; however, it can also cause a wide range of complications, such as bacteremia, enterocolitis, and extremely serious local infections like meningitis and osteomyelitis. (11,12,13) Enteric fever, also known as typhoid fever, is a serious and persistent bacteremic illness caused by Salmonella serotype typhi. (14)

Colitis and Crohn’s

Some people with gastroenteritis may develop an inflammatory bowel disease such as ulcerative colitis or Crohn’s disease — conditions that cause inflammation of your digestive tract. (15,16)

Researchers believe an abnormal immune system reaction may be the trigger. When your immune system tries to fight off a virus or bacteria, it might also attack the cells in your digestive tract. (15)

Another type of colitis, called hemorrhagic colitis, can happen when you have gastroenteritis caused by *Escherichia coli* (*E. coli*) bacteria. With this condition, *E. coli* infects the large intestine and produces a toxin that causes bloody diarrhea and other problems. (17)

Gastroenteritis and Pregnancy Complications:

As many as one-third of pregnant women will have gastroenteritis during their pregnancy. (18)

While most pregnant women will recover from the sickness without any problems, it can lead to complications.

Severe dehydration from the illness may prompt preterm labor. (18)

In a 2017 study, gastroenteritis during pregnancy was also linked to miscarriages, low birth weight, and stillbirth. (19)

It's a good idea to see your doctor if you're pregnant and have symptoms of gastroenteritis. If you do develop the stomach flu, be sure to drink plenty of liquids and get adequate rest.

Gastroenteritis and Aneurysms:

Having gastroenteritis may up your risk of developing an aortic aneurysm — a bulge in the wall of the major blood vessel that carries blood from your heart to the rest of your body. (20)

In a 2008 Swedish study, researchers found a person's risk of an aortic aneurysm was higher within three months after having a salmonella infection. (21)

Aortic aneurysms may not cause any symptoms at first, but if they burst, they can be deadly. (22)

Gastroenteritis and Reactive Arthritis:

A bout of gastroenteritis can lead to reactive arthritis — a painful form of inflammatory arthritis. It used to be called Reiter's syndrome. (23)

Reactive arthritis can occur "in reaction" to an infection caused by salmonella, campylobacter, yersinia, shigella, *E. coli*, vibrio, or other bacteria.

In a 2001 study, about 29 percent of people who had a salmonella infection developed symptoms of reactive arthritis. (24)

Reactive arthritis may cause painful, red, and swollen joints, especially in the knees, ankles, and feet. Additionally, some people experience swelling of the membrane lining the eyes (conjunctivitis) or inflammation of the urinary tract. (25)

Recovery for this type of arthritis varies from person to person. Some people get better after their first flare of symptoms. Symptoms usually last from 3 to 12 months. For about 30 to 50 percent of people, symptoms return or become chronic. (25)

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Chapter 7: Prevention

Wajiha Arshad, Nida Nisar.

Acute gastroenteritis is a common disease in paediatric age groups. It causes significant morbidity and mortality in developing countries and significant economic burden to developed countries. [1] In terms of prevention, multiple options like hygiene measures such as frequent handwashing, use of clean water and immunization particularly against rotavirus (RV) strongly reduce morbidity and mortality. These measures can reduce the feco-oral contamination which helps in decreasing the incidence of acute gastroenteritis in developing countries. For that, the effective education of mothers is extremely important, particularly in developing countries, in terms of hygiene measures, early recognition of acute diarrhoea as a potentially dangerous condition, and what actions to take if any symptoms are observed. [2]

Below are some measures which helps in prevention of acute gastroenteritis:

Handwashing

Hygiene-promotion is one of several strategies identified by the World Health Organization (WHO) for control of acute diarrhoea. [3] The habit of washing hands properly after the use of toilet, and again before eating can reduce the risk of fecal contamination. A meta-analysis of 30 studies showed that improved hand hygiene reduced the incidence of gastrointestinal illness by 31 percent (95% confidence interval, 19 to 42). The use of regular soap was seen to be most beneficial, and antibacterial soap provided little additional benefit. [4]

Clean drinking water

Use of clean drinking water also comes under the umbrella of improved hygiene measurements and help in reducing the chances of contamination. There are many ways to make the water safe for drinking such as boiling and use of filters etc. A Cochrane review found that point-of-use water purification methods reduces the incidence of diarrhoea by one-half, specifically the use of ceramic and biosand filters (i.e, column devices with a biofilm top and layers of sand and gravel). [5]

Vaccination

Nearly all children in developing world are affected by rotavirus by the age of 5 years, good sanitation and hygiene alone are proving to be inadequate for prevention of diarrhoea. [6] Multiple enteric vaccines have been developed to attempt to decrease the incidence of acute diarrhoea including cholera, typhoid, and rotavirus (RV) vaccines. [2]

Rotavirus vaccination was licensed in 2006 and in next 10 years after vaccine licensure, Burnett et al conducted a systematic review of 57 articles from 27 countries showed that emergency department visits and hospitalizations due to rotavirus gastroenteritis were reduced by a median of

67% overall and 60%, 59% and 71% in countries with high, medium and low child mortality, respectively. [7]

There is another study which collected data from eight high-income and middle-income countries which showed a 49–89% decline in rotavirus-associated hospital admissions and a 17–55% decline in all cause gastroenteritis related hospital admissions in children younger than 5 years of age, within 2 years of vaccine introduction. [8]

Breastfeeding

Breastfeeding is recommended for the first year of life with exclusive breastfeeding for the first 6 months. Human milk contains various bioactive components which confer protection against viral infections in early life. Intestinal epithelial cells (IEC) have key roles in preventing enteric viral infections. [9] The World Health Organization (WHO) and The United Nations Children's Emergency Fund (UNICEF) recommend exclusive breastfeeding (EBF) for 6 months and continued breastfeeding up to 2 years of age along with improvement of case management in health facilities for protection, prevention and treatment of diarrhoea. [10]

Breastfeeding reduces the incidence of gastroenteritis and shortens the duration of diarrhoea. Population-attributable fractions suggest that about 53% of diarrhoea related hospitalizations could have been prevented on monthly basis by exclusive breastfeeding and 31% by partial breastfeeding. [11]

Probiotics

European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Working Group (ESPGHAN WG) states that recommendations for probiotic use should always be strain specific and the goal is to recommend only the strains which have proven efficacy by well-designed randomized controlled trials (RCTs). [12]

Based on currently available evidence, certain probiotic strains (*Lactobacillus rhamnosus* GG [LGG] and *Saccharomyces boulardii*) have proven highly effective in the treatment of acute gastroenteritis and prevention of antibiotic associated diarrhoea. LGG was proven to be effective in prevention of nosocomial diarrhoea also. [13] Guarino et al also shows that there is strong evidence that probiotics have some efficacy in prevention of Antibiotic Associated Diarrhoea. (ADA) [14]

VACCINATION:

Vaccines are considered an effective and practical preventative approach against the predominantly feco-oral transmitted gastroenteritis particularly in developing countries or regions

where implementation of sanitation systems and supply of safe drinking water are not currently achievable.

The efficacy rates of the currently available oral killed whole-cell oral cholera vaccine are between 50% and 60%, so its inclusion in national immunization programs of endemic countries will depend on the prevalence of cholera, the frequency of outbreaks, and accessibility of healthcare services. A similar approach may be applied to typhoid vaccination. Therefore, until further developments, wide-scale implementation of typhoid vaccinations has be evaluated in the light of efficacy rates and the burden of the disease in a particular region or setting. [2]

Orally administered live attenuated vaccines do offer effective protection against rotavirus; as of December 2013, national immunization programs of 51 countries include rotavirus vaccine. These programs have reduced morbidity and mortality from gastroenteritis to a great extent. [6]

American Academy of Paediatrics gives these Guidelines for Use of Rotavirus Vaccine [15]

1. A second rotavirus vaccine, live, oral human attenuated rotavirus vaccine (RV1) (Rotarix [GlaxoSmithKline, Rixensart, Belgium]), administered in a 2-dose series at 2 and 4 months of age.
2. Maximum ages for doses:

   Maximum age for dose 1 of rotavirus vaccine is 14 weeks, 6 days of age.

   Maximum age for the last dose of rotavirus vaccine is now 8 months, 0 days of age.

3. The minimum interval between doses of rotavirus vaccine is 4 weeks.
4. Rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product, including antibody-containing blood products. The previous recommendation was to defer immunization for 42 days after receipt of an antibody-containing product, if possible.

Licensed vaccines currently available for enteric pathogens.[16]

	Vaccine (Manufacturer)	Type	Components	Availability	Indication
Viral disease					
Rotavirus	Rotarix (GSK Biologicals)	Live oral	Attenuated human rotavirus strain (G1P[8])	Global	Infants >6 weeks age, two doses
Rotavirus	RotaTeq (Merck)	Live oral	5 human-bovine reassortant rotaviruses (G1, G2, G3 G4, P[8])	Global	Infants >6 weeks age, three doses
Rotavirus	Rotavac (Bharat Biotech)	Live oral	Attenuated human rotavirus strain (G9P[11])	India, Palestine	Infants >6 weeks age, three doses
Rotavirus	RotaSiil (Serum Institute of India)	Live oral	5 human-bovine (UK) reassortant rotaviruses (G1, G2, G3, G4, G9)	India	Infants >6 weeks age, three doses
Bacterial disease					
Cholera	Dukoral (SBL)	Inactivated	Mix of inactivated *V. cholerae* O1 of Inaba classical, El Tor biotypes and Ogawa serotypes with rCTB subunit	Over 60 countries including Europe, Canada, Australia, and New Zealand, (not in USA)	Adults and children age ≥6 yrs: oral, two doses; Child 2–6 yrs: oral, three doses
Cholera	Shanchol (Shantha Biotechnics)	Inactivated	Mix of inactivated *V. cholerae* O1 Inaba E1 Tor strain Phil 6973, O1 Ogawa classical strain Cairo 50, O1 Inaba classical strain Cairo 48, O139 strain 4260B	Global Oral Cholera Vaccine stockpile	Adults and children age ≥1 yr: oral, two doses
Cholera	Euvichol (EuBiologics)	Inactivated	Mix of inactivated *V. cholerae* O1 Inaba Cairo 48 (H), O1 Inaba Phil 6973 El Tor, O1 Ogawa Cairo 50, and O139 4260B	Global Oral Cholera Vaccine stockpile	Adults and children >1 yr, 2 doses
Cholera	mORC-Vax (Vabiotech)	Inactivated	Mix of inactivated *V. cholerae* serogroups O1 classical and El Tor and O139	Vietnam	Adults and children age ≥1 yr: oral, two doses
Cholera	Vaxchora (PaxVax)	Live oral	*V. cholerae* strain CVD 103-HgR	USA	A single dose

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Chapter 8: Recent Advances

Hasnain Aslam , *Hafsa Arshad Azam Raja*

INTRODUCTION

Gastroenteritis is the inflammatory condition associated with diarrhea with or without vomiting, abdominal pain, fever, and anorexia. (1) One of the leading causes of death in children is acute gastroenteritis due to fluid loss, necessitating advances in treatment, diagnosis, and effective control measures. There are conventional methods still in use and new methods are being executed only for sake of the betterment of patients. We will discuss recent advances in diagnosing first followed by recent advances in treatment

Conventional methods are stool culturing and microscopic examination. Culture-independent proteomic and genomic tests are making their way. Antigen testing for stool pathogen are applied on routine examination However, molecular test are now in the market as well in different forms from multiplex to simple waived point-of-care tests. Furthermore, meta-genomic next-generation sequencing is also in use. Biomarkers of hosts can also be used as detectors of gastrointestinal infections. (2)

Gastroenteritis is treated based on the etiology. For bacterial causes, antibacterial agents are given but the affected patients have developed resistance against that specific pathogen. The same goes for viral and parasitic causes.

ANTIDIARRHOEAL DRUGS:

Enkephalins:

Enkephalins, since their discovery in 1975 have proven their anti-secretory role in GIT. Racecadotril, an enkephalinase inhibitor, preserves the antisecretory activity of enkephalins and does not slow intestinal transit or promote bacterial overgrowth. It has no neurotoxic effects or physical dependence. (3) Before racecadotril may be consistently advised for the treatment of acute gastroenteritis, more studies are required.

Smectite/Diosmectite:

The adsorbent smectite/diosmectite has been used to alleviate diarrhea in European countries. The results of a 2018 Cochrane systematic review of 18 randomized and quasi-randomized trials (n=2616 children) demonstrated that smectite increased clinical resolution at day 3 (RR 2.01; 95% CI 1.30-3.39; 312 children, 5 trials; low-certainty evidence), lowered the output of stools (mean difference 11.37; 95% CI 30.91 to 17.85), and lessened the duration of diarrhea to around 24 hours. (4) Smectite would effectively cure diarrhea in children with acute viral infections based on the above low-certainty data.

Ondansetron, Dimenhydrinate, Domperidone, Granisetron, Metoclopramide, And Dexamethasone:

Ondansetron, when used constructively, can maximize ORT's success rate and lessen the need for IV therapy and hospitalization. Ondansetron was the only intervention that showed an effect on the cessation of vomiting in a meta-analysis of 24 randomized clinical trials assessing the antiemetic effects of ondansetron, dimenhydrinate, domperidone, granisetron, metoclopramide, and dexamethasone. (5)

Antimicrobials:

Antimicrobial drugs are traditionally not recommended for the treatment of viral gastroenteritis. (6) Several studies have demonstrated that nitazoxanide, a broad-spectrum antiparasitic, and antiviral drug, shorten the duration of diarrhea in kids with viral gastroenteritis. To formally suggest the use of nitazoxanide in the treatment of viral gastroenteritis in children, the effectiveness of this drug must first be established through well-designed, large-scale, randomized, double-blind, and placebo-controlled studies.(7)

Probiotics:

With varying degrees of efficacy, probiotics such as Lactobacillus reuteri, Lactobacillus rhamnosus GG, Saccharomyces boulardii, Bifidobacterium bifidum, and Streptococcus thermophilus have been used to treat viral gastroenteritis. (8) Probiotics presumably function by enhancing the intestine's barrier function, competing for nutrients essential for pathogen survival, competitively blocking receptor sites, boosting immune response, and producing chemicals that render virus particles inactive. Probiotics can reduce the length of diarrhoea in individuals suffering from acute viral gastroenteritis, according to a systematic review and meta-analysis published in 2020. (9)

Zinc Doses:

When given zinc supplements, diarrheal ailment in children in impoverished countries is less severe and lasts a shorter period. (10) Mixing zinc and ORS is one method of giving it to someone who is experiencing acute diarrhea. For children with acute diarrhea, the recommended daily allowance of zinc supplements is 20 mg per day for 10–14 days (or 10 mg per day for infants under the age of 6 months).

Human Immunoglobulins: According to a pilot trial, giving hospitalized immunocompromised children with acute diarrhea human serum immunoglobulin by mouth resulted in a 50% reduction in stool production. In hospitalized immunocompromised children with acute diarrhea, the routine administration of oral human serum immunoglobulin requires well-designed, large-scale, randomized controlled studies. (22)

Improvements In The Gastroenteritis Diagnosis Using Biosensors:

The viral etiology of gastroenteritis has called for novel breakthroughs. It accounts for the maximum number of deaths, especially in infants. According to the Centers for Disease Control, 20, 000 children die of viral gastroenteritis. (13) Previously, electron microscopic examination, cell cultures, and immunoassay techniques were used. Nowadays, molecular techniques like PCR

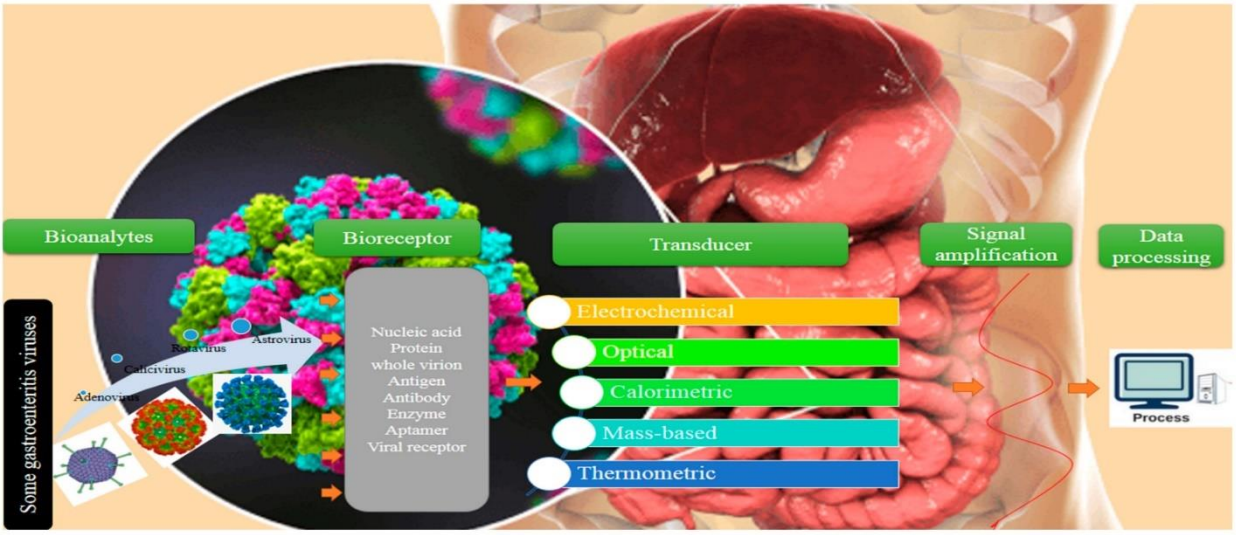
and biosensors are used. The biosensor technique is easy to use, economical, highly sensitive, and most importantly accurate. This technique works by recognizing directly or indirectly biological markers which can be viral proteins, enzymes, whole cells, nucleic acid, or a receptor. The first bio detector was of blood glucose used successfully in1962. Currently, microbial detection via biosensors is captivating for bio-scientists in combination with traditional techniques. There are various types of bio-sensing techniques based on the type of transducer

1. Electrochemical
2. Optical
3. Calorimetrical
4. Mass based
5. Thermometric type.

Most frequently used are electrochemical, optical, and piezoelectric biosensor techniques.

Electrochemical Biosensors:

It works by analyzing data in the form of chemical events like hybridization, antigen-antibody complex and converting them and into an analytical signal. (14)



Figure#1 A schematic presentation of biosensor components applied for diagnosis of viruses associated with gastroenteritis.

OPTICAL BIOSENSORS:

It measures the signals formed between the analyte and the recognition element either in label-free mode or label-based mode. It is preferred over all sensor techniques because of real-time

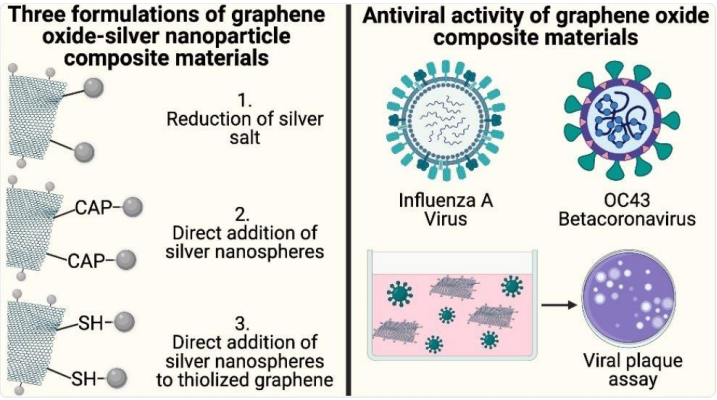
detection and sensitivity, and specificity. (15) One of the optical biosensors is SRP, Surface Plasmon Resonance is the widely used version of the optical biosensor. (16)

Pizoelectric Sensors:

These bioanalytical systems incorporate biorecognition elements into the optical transducer system to measure the signal when a complex forms between the recognition element and a type of mass-based biosensing technique that relies on the alteration of oscillations brought on by a mass tied to the sensing surface. The most often created and tested piezoelectric biosensing platform is the quartz crystal microbalance (QCM) platform, which consists of a thin layer of quartz crystal wafer sandwiched between two layers of metallic electrodes. The crystal deforms elastically as a result of the altered electric field, which then induces an acoustic wave. Building piezoelectric biosensors is quicker and less expensive than creating them using the other biosensing techniques listed since they are constructed using straightforward, affordable, and widely accessible components. Meanwhile, QCM is a well-liked label-free method for diagnosing viral infections as well as viruses linked to gastroenteritis due to its benefits, which include adequate sensitivity, cheap, small size, and few reagents. (2)

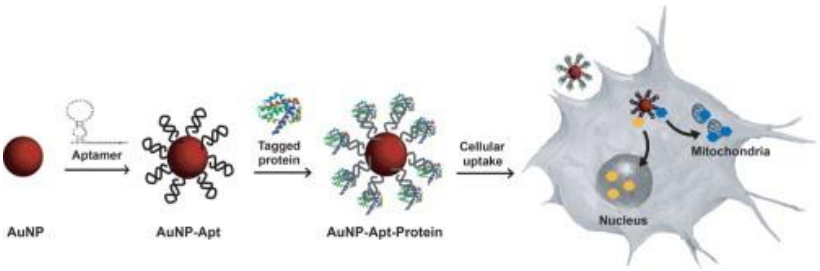
Detection Of Rotavirus and Enterovirus:

ELISA and other techniques due to their limitations require the use of biosensors. More than 500,000 children under the age of five have succumbed globally from severe acute gastroenteritis caused by the double-stranded RNA human rotavirus. Rotavirus has been spotted employing graphene oxide (GO)-based biosensors with a variety of sensing modalities, including luminescent and electrochemical biosensors. (17)



Detection Of Enterovirus:

Enterovirus, which cause most gastric infection is detected by gold-aptamer nanoparticles which can detect a nucleic acid. The 3D structure of aptamers, which are short single-stranded synthetic DNA or RNA oligonucleotides, allows them to attach to their complementary nucleic acids in a precise way. (18)



Detection Of Norovirus:

Norovirus (NoVs), belonging to the Caciviridae family cause gastroenteritis in all age groups. (19).They are not cultivable. Reverse transcription PCR (RT-PCR) is the only suggested and accepted standard norovirus test in clinical laboratories, despite the existence of genetic, immunological, and electronic microscopy Biosensors approaches. Even with its constraints, RNA detection from stool and blood samples of gastroenteritis patients. Electrochemical biosensor techniques have been employed for this. The most widespread type of optical sensor for norovirus detection is SPR biosensing.

Detection Of Enteric Adenovirus 40 And 41:

The viral family adenoviridae, which has more than 60 different known serotypes, includes adenoviruses, which are small, quasi, linear double-stranded DNA viruses (20). Serotypes 40 and 41 cause gastric infections and are responsible for 5 to 10% of hospitalizations for diarrhea in affluent nations. (21) While there is just one published study for enteric adenovirus 40 and 41, other types of biosensing techniques, particularly electrochemical versions, have recently been explored for diagnosing various viral serotypes in clinical samples. (22)

CONCLUSION:

In industrialized nations, acute viral gastroenteritis is linked with severe morbidity, but in developing nations, it is associated with substantial death. In areas where standard children immunization programs include the rotavirus vaccine, norovirus has surpassed rotavirus as the most prevalent aetiologic agent. As more developed countries are adopting recent better diagnostic measures and revolutionizing the treatment, many of developing nations are still following the old methods. With better diagnostic tools and innovative medications, we are aiming for decreased morbidity and mortality in this regard.

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