

Gastrointestinal Infections

Zafer Kurugöl¹, İlker Devrim²

¹Department of Pediatrics, Ege University Faculty of Medicine, *İzmir, Turkey*

²Pediatric Infection Unit, Dr. Behçet Uz Pediatrics Surgery Training and Research Hospital, *İzmir, Turkey*

Abstract

Gastroenteritis is one of the most common reasons for physician visits worldwide. Annually, 2 or 3 billion people are estimated to suffer from gastroenteritis. Children under 5 years old are reported to experience gastroenteritis 3.2 times a year. Gastrointestinal infections are more prominent in geographic regions with poor sanitation and health systems. Acute gastroenteritis is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24 h). Diarrhea typically lasts less than 7 days and not longer than 14 days. Viruses, bacteria, protozoa, helminths, and fungus cause gastrointestinal system infections. Antibiotic treatment is indicated only for bacterial enteric infections and indications. The most important step for treatment of gastroenteritis is rehydration and replacement therapy for restoring fluid and electrolyte balance. In most of the cases, oral rehydration therapy is adequate for the treatment.

(*J Pediatr Inf 2014; 8: 71-81*)

Keywords: Acute gastroenteritis, rotavirus, dehydration

Introduction

The gastroenteritis are one of the most frequent reasons for visits to physicians all over the world. Annually two or three billions of people are estimated to suffer from gastroenteritis worldwide. The children under 5 years old have been reported to experience gastroenteritis 3.2 times a year. Gastrointestinal infections are more prominent in the geographic regions with poor sanitation and health system, and in developing countries with insufficient infrastructure and food sanitation. While diarrhea incidence in children under 3 years old in Europe is 0.5-1.9 per child, it may be one of the reasons of mortality in childhood period in the developing countries. Gastroenteritis continues to be one of the most reasons of mortality and morbidity (1-6). According to the 2008 data of the World health Organization, diarrhea is the most frequent disease in the 1-59 month group with 1.25 billion cases. 68% (5,970) of under 5-year-old mortality estimated to be around 8,795 million is caused by infectious diseases, and pneumonia (18%, 1,575 million) and diarrhea (15%, 1,336) among the infectious diseases occupy

the top two places in the list (4). Most of this mortality is prevalent in the developing countries.

Due to the fighting against the diseases program and prevalence of oral fluid treatment underway in Turkey for the last 15 year, diarrhea-related mortality has significantly dropped. However, infant mortality occurs even today due to diarrhea-related or complications caused by diarrhea. According to the National Diseases Load-Cost Effectivity Study carried out by the participation of the Ministry of Health, gastroenteritis diseases are responsible for the 8.4% of pediatric mortality in the 0-14 age group children (7). Majority of this mortality occurs in the East and Southeast regions of Turkey. Despite a drop in diarrhea-related diseases, when compared with previous years, it is clearly seen that there has been no decline in the prevalence of diarrhea in Turkey. The prevalence of gastroenteritis diseases has been similar to that of previous years. According to the Turkish Population and Health Research (TPHR), the 25% prevalence of diarrhea in children under 5 year olds in 1993 had been continuing with a similar frequency of 23% in 2008 despite intervening 15 years (8).

Received: 11.05.2013
Accepted: 24.01.2014
Available Online Date:
08.05.2014

Correspondence

Address:
İlker Devrim,
Dr.Behçet Uz Çocuk
Hastalıkları ve Cerrahisi
Eğitim ve Araştırma
Hastanesi, Çocuk
Enfeksiyon Ünitesi,
İzmir, Türkiye
Phone: +90 506 309 07 07
E-mail:
ilkerdevrim2003@yahoo.
com

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Pediatric Infectious Diseases
Society - Available online at
<http://www.jpediatrinf.org>
DOI:10.5152/ced.2013.1509



Table 1. Clinical characteristics of acute diarrhea (39)

Clinic Observation	Anatomic Issues	Potential Patojens
Little, large stool	Small bowel related diarrhea	<i>Vibrio cholerae</i> , Enterotoxigenic <i>E. coli</i> , Shigella (early infection), <i>Giardia lamblia</i> , <i>Vibrio parahaemolyticus</i>
Very small stool passage	Large bowel related diarrhea	Shigella, Salmonella, Campylobacter, diarrhoeagenic <i>E. coli</i> , <i>Yersinia enterocolitica</i> , <i>Entamoeba histolytica</i>
Tenesmus, fecal pressure, dysentery	Colitis	Shigella, Salmonella, enteroinvasive <i>E. coli</i> , enterohaemorrhagic <i>E. coli</i> , Campylobacter, <i>E. histolytica</i> , <i>V. parahaemolyticus</i> (rare)
Main symptom is vomiting	Gastroenteritis	Viral agents (rotavirus, calicivirus) or food intoxication (<i>Bacillus cereus</i> , <i>S. aureus</i>)
Main symptom is fever	Mucosal invasion	Shigella, Salmonella, Campylobacter, enteroinvasive <i>E. coli</i> , viral agents

Table 2. Diarrhea caused by viral infections (39)

Acute sporadic/endemic diarrheas in adults and children	Epidemic diarrhea	Diarrhea in a host with immune deficiency
Rotavirus (in children)	Calicivirus (in 90% of the cases)	Cytomegalovirus
Calicivirus	Astrovirus	Epstein-Barr virus
Astrovirus	Rotavirus	Adenovirus
Adenovirus	Adenovirus	Astrovirus
Torovirus		Picornavirus

1. Acute gastroenteritis

Acute gastroenteritis is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of stool (typically ≥ 3 in 24 h).

Fever and vomiting may accompany it. Diarrhea typically lasts less than 7 days and not longer than 14 days. All the diarrhea and vomiting attacks lasting less than two weeks are defined as acute gastroenteritis (4). Especially in healthy individuals who receive sufficient rehydration treatment, the disease limits itself and heals spontaneously. However, it may cause morbidity and mortality in children and infants.

Viruses, bacterias, protozoans, helminths and fungus cause gastrointestinal system infections. Infected agent-related acute gastroenteritis and clinical features are summarized in Table =1 (9). Acute gastroenteritis will be analyzed etiologically in the following sections.

1. a. Viral gastroenteritis

Viral gastroenteritis comprises majority of the infections in this group and is one of the main reasons of mortality especially in children under 5 year old. It is commonly known that enteric viruses cause systemic diseases and fecal-oral way of infection is the common feature of these viruses.

The most prevalent viral agent is rotavirus (Table 2). Rotaviruses are the leading causes of diarrheas in infants and children all over the world, the serious gastroenteritis especially causing hospitalizations and infant mortality (10). While rotaviruses cause morbidity in the developed countries, they cause both morbidity and mortality in the

developing countries. Rotaviruses are responsible for the daily deaths of 1600 children a day and for 500 thousand children annually the world over (11). Before routine vaccination, rotaviruses in the United States of America caused 60.00 hospitalizations and 37 deaths annually (12). The studies carried out in Turkey revealed that rotaviruses were responsible for the 30-50% of the diarrheas in children under 5 years old (13). In 53 % of hospitalizations due to diarrhea indications, rotavirus was found (14-15). In a recent study in Turkey, it was found that G1P [8] (76%) was the most prevalent serotype, followed by the types of G2, G4 and G9 (15). Similarly, in a study done in 2000-2001, G1 (75.1%) was reported to be the most prevalent one (15). In a compiled study in 2001, it was reported that G1P [8], G4P [8] and G2P [4] were the most prevalent serotypes in Central and Eastern Europe (16).

Rotavirus diarrhea is primarily an acute infection for children under 2 and is characterized by liquid stool and vomiting. While rotavirus infections may progress asymptotically, it may also cause severe diarrheas. It was higher mortality and morbidity in comparison to other enteric viruses. Especially first rotavirus infection has a severe course causing dehydration, acidosis and electrolyte imbalance. The following infections are usually milder and progress asymptotically in adolescents and adults. While the first rotavirus infection is prevalent in 6-9 months in developing countries, it is prevalent in later months (9-15 months) in the developed countries. The incubation period varies between 1 and 5 days; however, the onset of liquid stool and vomiting is shorter than 48 hours. Vomiting usually occurs in the first two days and

low-grade fever is seen (17). Rotavirus diarrhea differs from acute bacterial gastroenteritis with regards to early occurrence of fever and vomiting, impacting of children under 2 years old and its prevalence in cold weather (17).

Norovirus-group viruses (previously defined as Norwalk-like agents) and other human caliciviruses cause sudden-onset, and transient vomiting and diarrhea (18). Diarrhea without vomiting or vomiting without diarrhea is possible. In studies done in developing countries revealed that the fact that specific antibodies were prevalent against these viruses leads one to think that these infections are prevalent in children under 1 year old. The incubation period for Norwalk disease on average is 24-48 hours. The diseases progresses slowly and lasts 1-3 days (19). Myalgia, headache, lack of appetite, fever and abdominal cramps may accompany (20). It is impossible to differentiate it from other viral acute gastroenteritis with clinical picture. It is reported that noroviruses are responsible 2/3 of food-related gastroenteritis epidemics and 23 million cases are prevalent in the United States of America (21, 22). Risk-groups are children, the elderly, immune-system suppressed patients, those travelling frequently, cruise passengers, military personnel, nursing homes and hospitalized patients (23). When compared with rotavirus infections, the impacted population is older. Norovirus-related gastroenteritis epidemics have been reported in Turkey as well (24). In a pediatric study done in 2006-2007 in central Anatolia, norovirus infections were found 17% (25). The most frequent GIIb/Hilversum strain was established via sequence analysis (25).

Astrovirus infections usually impact infants; however, patients with immune deficiency and hospitalized patients are under risk. Especially in AIDS patients, they are among the significant reasons of diarrhea (26). They cause infections in children under one year old in developing countries (20). In a Turkish study, it was found that astrovirus frequency in pediatric diarrheas was 3.7% (27). They usually cause minor diarrheas in individuals with a normal immune system. The disease lasts 2-5 days. When compared with calicivirus infections, vomiting is less prevalent. Fever, anorexia, vomiting and abdominal pains may occur. In comparison to rotavirus infections, dehydration in infants is less severe; however, the symptoms in patients with immune deficiency may last longer (28).

Enteric adenoviruses are the second group of viruses requiring hospitalization after rotaviruses. There are six groups of adenoviruses existing and enteric adenoviruses belong to F group. Two serotypes (40 and 41) stand out in diarrhea cases (29). The diseases occur at the end of 8-10-day incubation period and is characterized liquid diarrhea lasting 10 days. It impacts children under 2 years old especially in developing countries. In adenoviruses gastroenteritis, seasonal distribution is prevalent.

Vomiting and fever may occur; however, they progress mildly. Secondary lactose malabsorption may develop. In a Turkish study, it was reported that adenovirus was positive in 10.5% of children with diarrhea; in other words, adenoviruses follow rotavirus infections with regards to prevalence (27).

1. b. Diagnosis of treatment of viral gastroenteritis

The viral gastroenteritis is diagnosed by showing the virus in the stool via electron microscopy or molecular tests or by ELISA (especially for rotavirus) and other immunological tests.

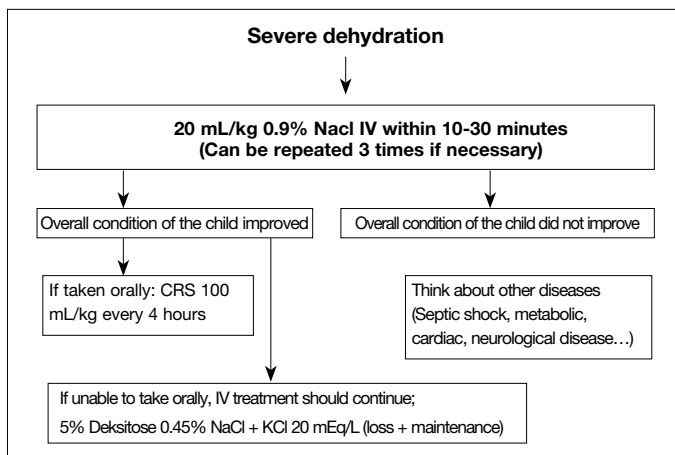
Adequate rehydration constitutes the main treatment of viral gastroenteritis (29). Oral rehydration is sufficient in mild and medium-severity cases; however, the treatment should be comprised of liquids able to supply for the patients' loss of liquid and electrolyte (30). Early application of oral rehydration therapy (ORT) enables less hospitalization and mortality (31). According to Cochrane 2010, it was found that in the comparison made by assessments such as rehydration failure, death, gaining weight, hospitalization period, hypernatremia, hyponatremia, diarrhea duration, total liquid intake, Na intake and its level and complication, it was found that there was no significant clinical difference between the ORT treatment and parenteral treatment. Due to slow and balanced electrolyte absorption, lack of complication such as vascular access and phlebitis in IV treatment, the lack of risks such as fluid load and electrolytic irregularity, need for fewer personnel and its affordability, ORT should be preferred in mild-medium, even in severe oral dehydrated cases. When they are used in cases where electrolytes cannot be measured, it is the other superiority of ORT to self-determine the level of thirst based on the children's level of thirst. ORT should start with 50 mL/kg/3-4 hour in mild dehydration; 100 mL/kg/3-4 hour in medium level dehydration; and 100-150 mL/kg/3-4 hour in severe dehydration. The child should be assessed after 4 hours; if the child is calm, there is urine discharge and turgor is back to normal, feeding should be started. In maintenance treatment, 100 mL/kg/24 hour ORT is recommended until the diarrhea stops in children with medium level dehydration. Practically, regarding the giving ORT equal stool, if it cannot be calculated, adding 10-15 mL/kg ORT/hour for every stool is recommended.

In the case of severe dehydration, fluid may be given intravenously; however, giving fluid is not an obstacle for the start of OFT (30). Intravenous rehydration may be used in children with persisting vomiting. Parenteral fluid treatment indications are summarized in Table 3.

The aim of the parenteral fluid treatment is stop hypovolemia, repair electrolyte irregularity or maintain it in balance, meet the normal daily fluid requirement, meet the

Table 3. Parenteral fluid treatment indications

Those with a loss of the consciousness
With severe dehydration
• In shock
• Aged <6 month and premature
• Under 3 months and fever>38C, 3-36 months and fever >39C
• Bloody stool
• With no good urination,
With no sufficient oral fluid intake
• Stool volume 10 mL/kg/hour, persistent vomiting
• Suspicion of ileus
Despite fluid intake; 25/1
• cannot put on weight
• lose weight
With monosaccharide intolerance

**Figure 1.** Management of severe diarrhea cases

previous or current losses of fluid and provide the required calories. In severe dehydrated cases, 20 mL/kg %0.9 NaCl should be given within 10-30 minutes. If necessary, the procedure can be repeated three times. The management of severe dehydrated cases is summarized in Figure 1.

There are some common beliefs especially in developing countries regarding the neglect of other nutrients such as breast milk for children with diarrhea; this is in fact a factor that increases malnutrition and eventually mortality and morbidity (31). Only in children with heavy lactose intolerance, oral intake may be reduced one level until the intestinal mucosa improves itself (31). Especially the antimotility drugs, antidiuretic agents, antisecretory agents and adsorbents should be used. There are many studies in the relevant literature regarding vitamin A and recently the use of probiotics in the treatment of diarrhea. Despite the fact that vitamin A support was reported to have decreased diarrhea-related mortality in 6-59 months 32%, it was revealed that it did not have any impact on

diarrhea morbidity (32). Routine vitamin A is not recommended for the treatment of acute diarrhea. WHO and UNICEF, for the treatment of acute diarrhea in low social-economic regions, recommend 10 mg/day zinc given orally to children under 6 months, and 20 mg/day to children older than 6 months for 10-14 days (33). However, in studies done in European countries, since it was proved that zinc did not have any impact in previously healthy children without malnutrition over duration and severity of diarrhea, zinc therapy can be recommended for children with malnutrition (34).

Studies proved that probiotics, the fashionable drug of recent years, were effective and reliable agents in reducing the duration of infectious diarrhea and stool frequency. Probiotics (*Lactobacillus GG* and *Saccharomyces boulardii*) were proved to be effective in antibiotic-related diarrhea. Major institutions such as ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) and ESPID (European Society for Pediatric Infectious Diseases) recommend the use of *Lactobacillus GG* and *S. boulardii* together with OFT for the treatment of acute diarrhea in children (35). However, it should be remembered that their beneficial effects are strain-specific and dose-dependent. It is not yet known which type/types are effective and most beneficial dose is. It was proved that their effectivity was related to the start of the diseases at an early stage. A probiotic strain effective on its own may lose its effectivity within a combination. Likewise, the practical significance of few hours or few days shortening accomplished by the probiotics in the duration of diarrhea is not clear. Cost efficiency should be debated. Because of all these reasons, apart from the antibiotic diarrheas, it will be more reasonable to use probiotics not routinely, but based on individual assessment of patients.

Sanitation, improving the hygiene conditions, preventing the human wastes from mixing into the domestic or drinking water and habituation of hand washing are the AGE- preventive factors. Two new rotavirus vaccines (monovalent human rotavirus vaccine [Rotarix, GlaxoSmithKline] and pentavalent human-bovine reassortant rotavirus vaccine [RotaTeq, Merck]) obtained license as of 2006 and went into use in many countries (13). The WHO recommended the addition of rotavirus vaccines into the routine vaccination schemas of all countries.

2. Enteric Bacterial Infections

Shigella is one of the most important frequent reasons of bacterial dysentery. *Shigella* is divided into 4 main serogroups: *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii* and *Shigella sonnei*. There are annually 164 million shigellosis and shigellosis-related 1.1 million deaths (36) all over the world. In some developing coun-

tries, in 60% of children applied with the diagnosis of bloody diarrhea, *S. flexneri* was isolated (37). Ratio of case fatality may rise as high as 20% (38). Shigella types belong to enterobacteriaceae family and are closely related with *Escherichia coli*. They are immotile gram negative bacillary and have specific biochemical features. Humans are natural hosts and infected dose may be in amounts as low as 10 to 100. The disease is prevalent especially in crowded households, bad sanitation and insufficient water sources. Following 1 to 5-day incubation in shigellosis patients, diarrhea may occur (39). This period may be as long as 6-8 day with *S. dysenteriae* type 1. *S. flexneri* ve *S. dysenteriae* may cause more severe diseases in comparison to *S. sonnei* and *S. boydii* (the most prevalent type in developed countries). Two enterotoxins were proved to be small bowel secretion and watery diarrhea (40). An important feature of dysentery is to invade large bowel walls and grow, thus causing cell death in mucosal epithelial cells. Toxemia, exhaustion, abdominal cramps, tenesmus and bloody diarrhea are followed by the first diarrhea attack. Vomiting and attacks are prevalent in children. *S. dysenteriae* type 1 causes epidemics especially via shiga toxin and complications of the diseases. Shiga toxin is related with A:B5 subunit exotoxin hemorrhagic enterocolitis and hemolytic uremic syndrome (HUS) (41, 42). In a Turkish study in which 198 shigella gastroenteritis children were examined, *S. sonnei* (83.3%) was isolated most frequently; other serotypes were reported as *S. flexneri* (10.1%), *S. dysenteriae* (5.1%), *S. boydii* (1.5%) (43).

Escherichia coli (*E. coli*) is a member of enterobacteriaceae family; although they are in the normal intestinal flora, they have some diarrhea-causing strains. Hemorrhagic colitis may be common in relation to watery diarrhea, dysentery and HUS. These syndromes are frequently related with some strains and the differences between them may vary on molecular level and expressed virulence genes (39).

Eteropathogenic *E. coli* (EPEC) is the reason for primer acute diarrhea affecting children under 6. Infection is fecal-oral (38). It is usually characterized acute diarrhea and extended diarrhea is rare. Vomiting and low level fever is frequent. Diarrhea is watery and mucus. Sudden dehydration is prevalent. It usually improves on its own (39).

Eteropathogenic *E. coli* (ETEC) usually causes travel diarrhea and diarrhea in infants who are no longer breast-fed and fed on supplementary nutrients (42). The disease begins in a short period and diarrhea usually has watery diarrhea consistency without blood, mucus and leukocyte. Fever and vomiting is prevalent in only few patients. Diarrhea can be mild and self-limiting but excess stool may also be seen typical of cholera. It is the most frequently isolated bacterial enteropathogen in children

under 5 years old in developing countries and it is estimated that it causes nearly two hundred million diarrhea cases and nearly 380.000 fatalities (43-45).

Enteroinvasive *E. coli* (EIEC) invades the colon mucosa and is characterized by abdominal cramps, fever, exhaustion, watery diarrhea and toxemia. Dysentery is prevalent in 10% of the patients and little blood and mucus is present. Epidemics are usually food and water-originated (45). Incubation period is between 3 and 4 days. Mild cases are difficult to differentiate from other etiologic agent-related diarrhea cases; however, EHEC shiga toxin and abdominal cramp cause bloody diarrhea accompanied by severe hemorrhagic colitis. Hemolytic uremic syndrome is more prevalent in children and presents itself with disseminate intravascular coagulation, hemolytic anemia, thrombocytopenia and renal failure (46, 47). In developing countries, it cannot be clinically separated from *S. dysenteriae* type 1-related HUS. The most widespread strain is O157:H7 and used its bacterial fimbriae for attachment (48); when infection is detected with especially O157: H7, there is no preventative measure to stop HUS development (49).

Enterogressive *E. coli* (EAggEC) is a frequent factor in developing countries as well as developed countries. Diarrhea usually presents itself in the form of watery mucoid secretory diarrhea; vomiting and fever are also prevalent. Bloody diarrhea was reported in 33% of the cases (39).

Salmonella typhi and non-typhoidal salmonellas (NTS) belong to the same type and include different serotypes of *Salmonella enterica*. Typhoid (enteric fever) is composed of *S. typhi*, gram negative bacilli. It is a worldwide social public health problem and may have a high incidence rate of 1000 per 100,000 people especially in developing countries (50). Extended fever may initially improve on its own, but in time may be permanent. Besides, headache, exhaustion, lack of appetite and coughing may be prevalent in acute and non-complicated cases (50). While constipation is prevalent in adults, diarrhea is more common in children. "Spot rose" is seen in 25% of the patients and is in the form of localized lesions especially on the body. The disease progresses severely through complications in 10% of the patients with acute diseases. While massif melena is prevalent in 3% of the patients, occult blood is present in 10-20% of the patients. Intestinal perforation may occur together with peritonitis. Impaired mental state is related with high fatality speed. Hepatitis, myocardia, pneumonia, disseminated intravascular coagulation and hemolytic uremic syndrome may be common together with typhoid fever. In an article published in 2009, it was reported that when children with bloody diarrhea and anemic watery diarrhea are assessed, salmonella species were the most frequently isolated (51). In another study done in Turkey,

clinical samples taken from different regions were examined, *S. enteritidis* (47.7%) was the most frequently isolated strain out of 620 *S. enterica* isolates (52). The other strains were reported to be *S. typhimurium* (34.7%), *S. paratyphi* B (6%), *S. typhi* (2.9%), *S. paratyphi* A (0.2%), serogroup C1 (6.1%) and serogroup C2 (2.4%) (52).

In gastroenteritis generated by non-typhoidal salmonellas, congestive agent is present in animals and especially in domesticated animals such as chickens, turkeys, pigs, cattle and horses and eggs. These animals may be infected through the immediate environment or contaminated food. Infection developed especially with the intake of contaminated food and water (53). These organisms generate nosocomial infections and epidemics (54). Gastroenteritis occurs 6-82 hours after the intake of contaminated food and water, and is characterized by sudden stomach ache, mucus and watery diarrhea involving blood. Vomiting and nausea are very frequent, but rarely severe. Fever is around 38-39 degrees. In non-complicated cases, acute period starts within 48 hours. However, fever may rarely continue at a low degree for 10-14 days. Symptoms progress severely in infants, the elderly and people with an underlying disease. Therefore, these groups with a high risk of being able to invade and produce bacteria have a higher level of mortality compared to other groups (55). Moreover, NTS may spread to the whole body and cause localized abscesses. Especially, those with HIV infection have as high as 23-47% of mortality (56, 57).

Campylobacter jejuni is one of the most frequent factors of contaminated water and food-related diarrheas in infants in developing countries. Incidence rate in children under 5 years old was reported to be between 40,000 and 60,000 in 100,000. This rate is as low as 300 in 100,000 in developed countries (58). Especially domestic animals, chicken coops and other animal barn-related infections are prevalent and uncooked food and non-pasteurized milk consumption are ways of infection. Human strains in developing countries have 71% similarity with the strains of domestic animals living nearby (59). The inoculum amount needed to generate enteritis is low (between 50 and 100) and this amount drops even more in the presence of food increasing the stomach pH. The average incubation period is three days and at the end of three days, the main symptoms of stomachache and diarrhea are prevalent. It has a wide spectrum such as watery, anemic, non-inflammatory diarrhea as well as severe inflammatory diarrhea. Fever, shivering, headache and exhaustion are common. It is more prevalent especially in weak and malnourished children (60). 25% of *Campylobacter jejuni* infections progress asymptotically (60). Together with this, post-infectious complications such as Guillain-Barre syndrome and Reiter syndrome have been defined (39).

In a Turkish study, 400 children with enteritis were examined in terms of *C. jejuni* and after shigella, it was in the second place in etiology with 8.3% rate (61). It was reported that the most prevalent symptoms were stomachache (51.5%), vomiting (36.4%) and fever (30.3%) (61).

Cholera is among the important epidemic diseases in tropical climates (62). It is estimated that as of 2010, cholera has affected 3-5 million people worldwide and caused between 100,000 and 130,000 deaths (63). It is among the diseases with international obligation to report together with yellow fever and plague. Cholera agent is *Vibrio cholera* bacillus that is gram negative, active and does not produce spore. Especially two serogroups *V. cholerae* O1 and *V. cholerae* O139 are related with epidemic diseases. *V. cholerae* O1 has an identified serotype (Ogawa, Inaba and Hikojima). Hikojima is divided into biotypes as biochemical and epidemiologic, and as classic and El Tor (63). It was revealed that majority of the patients were infected with classic *V. cholerae* O1 and *V. cholerae* O1 El Tor. Especially *V. cholerae* O1 El Tor is responsible for the last pandemic and has replaced the classic *V. cholerae* O1 in many geographic regions (64).

Transmission usually occurs with the intake of water and food contaminated *V. cholerae* O1 and *V. cholerae* O139 (62). In a study done with the inclusion of volunteers, it was revealed that the number of particles infected with cholera was between 106 and 1011 (65). Especially in regions where cholera is endemic, it reaches its seasonal peak point warm summer months and drops in winter months. The disease occurs via A:B5 subunit-toxin and causes gastrointestinal lumen active secretion of electrolyte and water. Eventually, intensive, watery anemic diarrhea occurs. While subunit B is attached to subunit small bowel epithelial cells, subunit A is an active one and increases the cyclic adenosine monophosphate by activating the intracellular adenylate cyclase (cAMP). As a result, an intensive electrolyte release and later osmotic loss of water occur (66-68). Incubation period of cholera varies between hours and 5 days depending on inoculum number. While a short prodromal period is characterized by appetite, stomachache and basic diarrhea in patients, a great deal of watery stool may be common. Vomiting occurs just few hours after the onset of diarrhea. In cholera gravis cases, the patient may lose one liter water every hour and eventually tachycardia, hypertension and death are common. The stool in the typical form of "rice-water" is associated with severe diarrhea and common only in a very small group of patients (62). Non-cholera strains may cause gastroenteritis. These are *V. cholerae* non-O1, non-O139, *V. mimicus*, *V. parahaemolyticus*, *V. fluvialis* and *V. Furnisii*. *V. parahaemolyticus* may cause epidemics via the contaminated sea food (64).

Bacterial gastroenteritis diagnosis

Cholera diagnosis is made via the isolation of *V. cholerae* from patient's stool. Especially fresh sample should be added to the appropriate selective and non-selective culture average and the sample should be carried in the place of Cary-Blair food carriage. *V. cholerae* may be carried for weeks in this way. It is not necessary to take the culture of every patient, but culture may be taken to analyze the intermittent continuation of *V. cholerae*'s presence, the presence of other agent and antimicrobial resistance. Quick tests (dipstick) may be used especially in clinics, but confirmation via culture may be required (39). Furthermore, in addition to triplex PCR method that is able to differentiate toxigenic and non-toxigenic *V. cholerae* (69); the quick immunochromatographic dipstick kit to be used in epidemics has been developed (70).

In shigellosis, polymorphonuclear cells and red blood cells may be common in the stool microscopy. Specific diagnosis may be made via the culture. Fresh sample is the most appropriate, but if this is not possible, Cary-Blair or buffered glycerol saline carriage medium should be used. Culture should be added to the appropriate selective medium such as xylene lysine deoxycholate (XLD) and Hektoen enteric (HE) agar. Salmonella-shigella (SS) agar is not appropriate for the isolation of *S. dysenteriae* type 1. Serotyping is done via specific antiserum and a different serogroup and type is defined (39).

Diagnosis of *E. coli* diarrhea is made through stool culture and phenotypic and genotypic characterization. Especially for characterization of *E. coli* causing diarrhea, specific tests such as immunoassay, molecular diagnosis methods and HEp-2 cell adherence (71). For *E. coli* O157 causing the EHEC disease, MacConkey Agar should be used and sorbitol-negative colonies should be preserved for serotyping (39).

Diagnosis of typhoid fever is made through the isolation of *S. typhi* (from the blood, bone marrow or a specific anatomic region). Blood cultures especially should be added to the appropriate medium and should be transferred on time. Its biochemical features are quite beneficial in the differentiation of *S. typhi*, but definite diagnosis should be made through the analysis of suspicious isolates O:9 (somatic), H:d (flagellas) and Vi (capsule) antibodies. Moreover, as multiple drug-resistant *S. typhi* has increased in recent years, an antibiotic sensitivity test should definitely be made. Widal test is a common diagnosis method, especially in developing countries and measures the antibodies agglutinant against *S. typhi* O and H antigen. However, the fact that it is 30% negative in culture-positive cases generates the disadvantage of low level of sensitivity and specificity (72). It causes cross-reactivity especially in such diseases as malaria, cirrhosis and typhus. Therefore, the cut-off values in the society

should be known and the test should be assessed two times, on in the acute and convalescence periods. In addition to culture, the most promising diagnosis technique is to perform PCR-based DNA amplification from the blood of enteric fever patients, but this technique is not available in every hospital (73). It was revealed in a study that culture positivity in enteric fever cases with especially the history of antibiotic use was lower and Widal tests were not sufficient in diagnosing these patients (74). However, there is a need for more studies for the effectivity of PCR-dependent tests. Non-typhoidal salmonellas may be isolated from infected food and stool.

Campylobacter types can be visible directly from the fresh stool through dark microscopy or phase-contrast microscopy. Stool culture requires an enriched environment eliminating the flora and isolation conditions. The organisms grew within 72 hours (39).

Bacterial gastroenteritis treatment

Antimicrobial treatment in bacterial gastroenteritis is summarized in Table 4. In non-complicated bacterial gastroenteritis, antibiotics are rarely indicated.

Shigellosis treatment depends on the condition of the patient, clinical picture and symptoms. In non-complicated diarrheas, only rehydration will be sufficient. Specific antimicrobial treatment is especially recommended in case of bloody diarrhea (39). It was reported that in a meta analyses antibiotics such as ciprofloxacin (for the appropriate age group) and ceftriaxone reduced the dysentery symptoms and clinical and bacteriologic findings (75). However, the resistance that has recently been increased starts to pose a significant problem (76). It was reported that resistance developed against former frequently used antibiotics such as ampicillin, cotrimoxazole, tetracycline and nalidixic acid (77-79). In recent years, fluoroquinolones in appropriate age children have become important. In a study done in Turkey, shigellas isolated between 1987-1994 and 1995-2002 were compared in terms of resistance; and it was concluded that the resistance of trimethoprim/ sulfamethoxazole rose from 39% to 70%; and the resistance of ampicillin dropped from 41% to 23% (79). However, it was found that especially the resistance of *S. flexneri* against ampicillin was high (72.9%). In this study, ciprofloxacin resistance was not found and the ratio of multiple drug resistance was 24% (79). In another Turkish study, it was reported that in many of the shigella types, there was trimethoprim/ sulfamethoxazole resistance (90.4%); however, ampicillin sensitivity ratio was high (86.4%) (80). In another study done in 2008, while ampicillin resistance was 20%, all were reported to be sensitive towards gentamycin, ceftriaxone, imipenem, nalidixic acid and sparfloxacin (81).

Table 4. Antimicrobial treatment in bacterial gastroenteritis (39)

Infection, Antimicrobial Treatment ¹	Pediatric Dose	Adult Dose
Ampicillin	From 50 mg/kg/dose to 4 doses, 3 days	
Trimethoprim-sulfamethoxazole (Cotrimoxazole)	From 8 mg TMP, 40 mg SMX/kg/dose to 2 doses, 3 days	160 mg TMP, 800 mg SMX 2 doses, 3 days
Furazolidone	From 5 mg/kg/dose to 4 doses, 3 days	100 mg, 4 doses, 3 days
Doxycycline	7 mg/kg (max 300 g)	300 mg
Erythromycin	From 50 mg/kg/dose to 3 doses, 3 days	250 mg, 4 doses, 3 days
Ciprofloxacin*	30 mg/kg (max 1 g)	1 g
Non-complicated bacterial gastroenteritis	Antibiotic rarely indicated	Antibiotic rarely indicated
Bacterial dysentery		
Ampicillin	100 mg/kg/dose, 4 doses, 5 days	1 g, 4 doses, 5 days
Trimethoprim-sulfamethoxazole (Cotrimoxazole)	10 mg TMP, 50 mg SMX/kg/dose, 2 doses, 5 days	160 mg TMP, 800 mg SMX 4 doses, 5 days
Nalidixic acid	60 mg/kg/dose, 4 doses, 5 days	1 g, 4 doses, 5 days
Ciprofloxacin	10 mg/kg/dose, 5 days	500 mg, 2 doses, 5 days
Ceftriaxone	50 mg/kg/dose, 5 days	1 g, 2 doses, 5 days
Typhoid		
Ampicillin	100 mg/kg/dose 4 doses, 14 days	1 g, 4 doses, 14 days
Chloramphenicol	75 mg/kg/dose, 4 doses, 14 days	500 mg, 4 doses, 14 days
Trimethoprim-sulfamethoxazole (Cotrimoxazole)	8 mg TMP, 40 mg SMX/kg/dose, 2 doses, 14 days	160 mg TMP, 800 mg SMX 2 doses, 14 days
Ciprofloxacin*	10 mg/kg/dose, 5-7 days	500 mg 2 doses 5 days
Ceftriaxone	50-70 mg/kg/dose, 5 days	1-2 g 2 doses 5 days
Azithromycin	10 mg/kg/dose, 7 days	500 mg 7 days
Campylobacter		
Erythromycin	30-50 mg/kg/dose, 4 doses, 7 days	250 mg, 2 doses, 7 days
Ciprofloxacin	-	500 mg, 2 doses, 7 days
Azithromycin	-	250 mg, 2 doses, 7 days

Campylobacter jejune infections limit themselves and recovery lasts 2 to 6 days. Dispersion in untreated patients may last for week and months, but long-term carriage is especially limited to immune system. Antibiotic treatment is not indicated, but erythromycin is still effective against resistance development (39). Ciprofloxacin is indicated at appropriate ages, but resistance was common.

The main therapy in cholera is rehydration treatment. Given the fact that diarrhea heals itself, the failure to ensure sufficient rehydration in the world is still a significant cause of mortality. Therefore, rehydration therapy should start at an early period. Mortality rate with early therapy has a course of less than 1% (39). Despite the fact that antibiotics were not used in a previous cholera epidemic in Africa, mortality rate with appropriate rehydration was as low as 0.2%. It was found that antibiotic use diminished the period and volume of *V. cholerae*-related diarrhea, but failed to show that it decreased the

mortality rate (39). *V. cholerae* did not show any reaction to antibiotics for a long time, but this has changed in recent years (82). Especially broad spectrum beta lactamase production in isolated strains in the world, ability to have multiple drug efflux pump activity, plasmid-mediated quinolone and fluoroquinolone resistance, and chromosomal mutations constitute the resistance mechanisms (82). There was resistance to the drug such as ampicillin, cotrimoxazole, tetracycline (doxycycline) and erythromycin that were previously first step treatment drugs. Fluoroquinolones are also effective, but the fact that resistance developed against nalidixic acid in some parts of the world generated concern that resistance could be developed against this antibiotic as well (76-78). Therefore, antibiotic should be chosen according to the result of culture test.

Antimicrobial treatment in non-complicated children who suffered *E. coli*-related diarrhea is not necessary.

Table 5. Conditions increasing bacteremia risk in salmonella gastroenteritis cases

Neonatal and under 3-month infants
AIDS, chronic granulomatous disease or immune deficiencies
Cancer (especially leukemia and lymphoma)
Immunosuppressive and corticosteroid treatment intake
Hemolytic anemia and crescent-cell anemia
Malaria and schistosomiasis
Collagen vascular diseases
Inflammatory bowel disease
Gastrectomy or gastroenterostomy
Achlorhydria or antacid drug use
Reduced bowel movement
Malnutrition

However, resistance development in *E. coli* strains ETEC's leading the way, has become all the more important. Antibiotics should be used especially in dysentery. In many diarrhea cases, appropriate rehydration treatment together with prognosis is acceptable and diarrhea limits itself (39). In a study in Peru involving 1000 neonatal cases, it was reported that *E.coli* that had diarrhea agent resistance against ampicillin (85%), cotrimoxazole (79%) and tetracycline (65%) (83).

There is mostly no need for microbial treatment in salmonella enteritis. It was reported that antimicrobial treatment was not affective, removal of salmonella via stool could be extended (84) and the risk of chronic carriage increased. Even though antibiotic treatment in Salmonella gastroenteritis is not recommended in healthy individuals, as was summarized in Table 5, it should only be used in cases where there is the risk of complication development. If it is not treated, antibiotic treatment should definitely be implemented for the enteric fever picture that has complication risk and high mortality rate. However, antibiotic resistance has been gradually increasing both in Turkey and in the world. In the case of resistant microorganisms existence in children, ampicillin treatment with ceftriaxone or cefotaxime is appropriate until antibiogram results are obtained. It was reported that as an addition to the antibiotic treatment, dexamethasone treatment (initially 3 mg/kg and in the follow-up 1 mg/kg in 6 hours for 2 days) helped to increase the rate of survival in the presence of shock, stupor and coma. Fluid and electrolyte balance of the patient should be maintained and supplement treatment, if necessary, should be provided through vasopressor agents.

While typhoid fever-related mortality rates were around 40% before antibiotic use, this rate dropped after antibiotic use. Therefore, antibiotic use is a must, but antibiotic choice should be made with regards to regional resistance

patterns. Multiple-drug resistant strains have been reported in the World. Resistance was reported to be against especially first step drugs such as ampicillin, cotrimoxazole and chloramphenicol. Fluoroquinolones, third generation cephalosporins or azithromycin can be used in alternative treatment. In case of non-complicated diarrheas not related to non-toroidal salmonellas, there is no need for the use of antibiotics; only rehydration will be sufficient (54). Therapy should especially be given only to children with dysentery and underlying disease like HIV that disorders the immune system. Since plural resistance may be common in NTSs with especially *S. enterica* serotype typhimurium leading the way, the resistance status of the salmonella infections in that region should be assessed. The resistance mechanism usually occurs through broad spectrum beta lactamase. Especially for the abscesses sites, surgical drainage, in addition to antibiotic use, may be necessary (39).

The most important step in the treatment of gastroenteritis is the rehydration and replacement therapy in order to maintain the fluid and electrolyte balance of the child. Oral rehydration is sufficient in most of the patients. Since the drugs minimizing intestine motility may inhibit pathogenic bacteria and toxic cleansing, they are never recommended for pediatric use.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.K.; Design - Z.K., İ.D.; Supervision - Z.K.; Funding - Z.K., İ.D.; Materials - Z.K., İ.D.; Collection and/or Processing - Z.K., İ.D.; Analysis and/or Interpretation - Z.K., İ.D.; Literature Review - Z.K., İ.D.; Writing - Z.K., İ.D.; Critical Review - Z.K., İ.D.; Other - Z.K., İ.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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