ACUTE GASTROENTERITIS IN CHILDREN. CURRENT EPIDEMIOLOGICAL AND ETIOLOGICAL CONSIDERATIONS

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ACUTE GASTROENTERITIS IN CHILDREN. CURRENT EPIDEMIOLOGICAL AND ETIOLOGICAL CONSIDERATIONS (Abstract): Acute diarrheal disease ranks second among the causes of specific morbidity (after respiratory infections) with higher incidence values in economically undeveloped or developing countries (3 to 7 episodes of diarrhea / year / child compared to only 1-2 episodes / year / child in highly industrialized countries). Infection with Campylobacter globally was the most frequently reported zoonanthroponosis, with 214,268 confirmed human cases in 2012. Almost any pathogen involved in the etiology of acute diarrheal disease may be involved in the occurrence of healthcare-associated infections; among these, the rotavirus and Clostridium difficile are most prevalent. General hygiene measures change the epidemiological aspect of acute diarrheal disease by modifying the factors which favor the transmission of pathogens. Keywords: ACUTE DIARRHEAL DISEASE, EPIDEMIOLOGY, HEALTHCARE-ASSOCIATED INFECTION.

Acute gastroenteritis (including acute diarrhea, acute diarrheal disease) is commonly the second cause of death worldwide (after cardiovascular diseases) and the second cause of specific morbidity (after respiratory infections) (1, 2, 3). The social and economic impact is difficult to estimate, considered to be very high: only in the United States and only for rotavirus infections the medical and social costs are over a thousand billion dollars yearly (4, 5, 6).

There are major differences between the manifestation forms of the epidemiological process in developed countries as compared to developing countries. There are also differences in terms of etiology, type of clinical forms and evolution of the disease, prognosis, therapeutics and age groups: child versus adult. Despite the progress made in understanding the pathogenic mechanisms and the management therapy, the acute gastroenteritis / acute diarrheal disease (AGE / ADD) remains one of the most important causes of infant morbidity and mortality.

In the early 1980s, it was estimated that the world’s “biggest child killer” was diarrheal diseases, which were responsible for 4-6 million deaths every year. The latest studies show that, currently, diarrheal diseases are responsible for the death of 2 to 5 million children, mostly in poorly industrialized countries or developing countries. The annual number of diarrheal episodes...
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occurring in children under the age of 5 is approximated to 1 billion. It is worrying (but not unexpected) that morbidity is still in excess in developing or underdeveloped countries, with 3 to 7 episodes of diarrhea / year / child as compared to only 1-2 episodes / year / child in highly developed countries (7).

In the USA, the studies with wide coverage of the general population showed the presence of 1.05 episodes of acute diarrhea / person / year; considering that gastrointestinal signs are due to respiratory diseases for one in four people, the final figure was lower: 0.79 episodes / person / year. For the United States, the estimates indicated approximately 211 million cases of AGE / ADD for the entire population and 210,000 / year for the hospitalized pediatric population, resulting in approximately 10,000 deaths (3). From a financial point of view, these hospitalizations represent 4% of the total cost of all admissions of any cause. Acute gastroenteritis of viral etiology has a large clinical impact on children younger than 5 years old. In the United States, more than 500,000 consultations / year are reported, with about 55,000 hospitalizations and over 500 deaths / year for AGE / ADD of viral etiology.

In Australia, 15,000-20,000 children under the age of 5 years are hospitalized annually for severe acute gastroenteritis (8).

A case-control study carried out in the Netherlands, based on a “sentinel”-type surveillance system, estimated the impact of this disease on the general / family medicine network: 128,000 people call for annual family doctor consultations for acute gastroenteritis; basically 79.9 in 100,000 people have an episode of AGE / ADD / year; Campylobacter is by far the most frequently involved etiological agent (10%), followed by Giardia lamblia (5%), Rotavirus (5%), Norwalk-like virus (5%), and Salmonella (4%). The data varies widely depending on the territory under analysis (AGE / ADD has a lower incidence in the North) and on the degree of urbanization (a greater incidence in rural areas) (9, 10, 11).

Questions arise regarding the true extent of the spread of infections with Campylobacter spp. other than C. jejuni / C. coli, requiring more efficient diagnostic methods.

In the Czech Republic, Salmonella and Campylobacter infections are reported as early as 1951 and 1984, respectively. In 2003, they represented 92% of the etiologic spectrum of acute gastroenteritis (52% - infection with Salmonella, most often Salmonella Enteritidis and nearly 40% infections with Campylobacter); the most affected age group was 0-4 years. The incidence of infections with Salmonella in the Czech Republic recorded a steady rise until 1995, followed by a sharp decline since 1998; infections with Campylobacter showed an upward trend starting with 1984, with a peak in 2002 and a current slow decline (12).

A communication signed by some authors in Poland (13) states that, among the cases hospitalized in Warsaw, without generalizing to the whole territory, nontyphoid infections with Salmonella are common among children aged 0-5 years: 90% of the samples were positive for Salmonella Enteritidis. The same authors remarked the emergence of antibiotic-resistant Salmonella. The incidence of the antibiotic resistance of these pathogens ranged from 60% in Taiwan to 4% in Greece and 2% in Italy (14, 15).

In Norway, the incidence of AGE / ADD had a value that is like those found by FoodNet in the United States: 1.2 episodes of acute diarrhea / person / year. The risk factor often met among children less than 15 years old was water consumption from private sources; in contrast, chlorinat-
ed water consumption was not associated with AGE / ADD (16).

Ireland (Food Safety Authority of Ireland, Dublin) (17) reports 0.6 episodes of acute diarrhea / person / year; however, only 29.2% cases of the total number of reported cases presented themselves to the family physician / general practitioner and fecal samples were collected for investigation in only 2%. The authors considered that new ways of promoting prevention measures need to be found given the increased spread of AGE / ADD in the population.

A case-control study conducted in Denmark over a period of two years, with 0-5 years old children as the target population, presents in detail data regarding the etiology of AGE / ADD. In 26% of cases, the viral etiology was determined; in 17%, the etiology was bacterial; in 4%, the etiology was parasitic. The most frequent pathogen was rotavirus, followed by Salmonella, Norovirus, Campylobacter, and Adenovirus. Rarely, Giardia lamblia, Blastocystis hominis, Cryptosporidium, Ascaris spp. were found. Agents such as Yersinia enterocolitica (3% of samples), Shigella, E. coli are highly prevalent in Denmark (18).

Salmonellosis. In 2003, Germany reports an epidemic outbreak of Salmonella enterica serotype Agona infection among children with the average age of 13 months. 42 cases were diagnosed; after an epidemiological investigation, the route of transmission was identified: contaminated anise tea imported from Turkey. Rarely isolated, Salmonella Agona is involved in human pathology especially in relation to the consumption of powdered milk, snacks and industrially processed cereals. In similar situations, other serotypes were also involved in various food categories (in 2001-2002 there was an outbreak of epidemic scale, impacting several European countries; Salmonella Oranienburg was involved, which was isolated from samples of chocolate produced in Germany) (19, 20).

A study conducted in France in 2003 focused on estimating the number of cases hospitalized for AGE / ADD in children less than 5 years old and the costs associated with their hospitalization. The results showed that 51,125 children were hospitalized with this diagnosis; 56% of cases were “probably infectious”, 36% had viral etiology (of these, 43% were coded as “rotavirus”) and 8% had bacterial etiology (60% of which were coded as “Salmonella”). Complications (particularly acute dehydration) followed “viral” gastroenteritis in 21% of cases and “bacterial” gastroenteritis in 17% of cases, followed by 14 deaths. The mean length of stay was 3.2 days and the costs were estimated to reach 62 million EUR (21).

The report of the European Food Safety Authority (EFSA, Parma, Italy) and of the European Centre for Prevention and Control (ECDC, Stockholm, Sweden) published on July 17th, 2014 based on the information presented by 27 EU member states shows that the number of diseases caused by Salmonella continued to decrease in 2012. Thus, a total of 92,916 cases diagnosed with salmonellosis were reported by the 27 EU member states, with 91,034 confirmed cases, representing a 4.7% decrease in the confirmed cases compared to 2011. In 2012, the Czech Republic and Slovakia reported the highest number of cases of contracted diseases caused by Salmonella (≥85 cases per 100,000), while Portugal, Greece and Romania reported the lowest figures (≤4 in 100,000 cases). The proportion of endemic cases versus imported cases (favored by population movement) varies significantly from one country to another: most cases associated with travels (>70%) were reported by the Nordic countries, Finland, Sweden, and Norway. The
seasonal trend of salmonellosis is confirmed by the 2008-2012 Reports, with most cases reported during the summer months. The downward trend in the number of salmonellosis cases in the EU is significant; this has been noted for several years and continued in 2012 as well (p < 0.001 with linear regression), particularly in the 15 member states and in two non-EU countries: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Lithuania, Norway, Portugal, Slovakia, Slovenia, Sweden, and the United Kingdom (14, 22).

Ten EU Member States have reported data according to which 45% of the hospitalized cases were admitted for *Salmonella* infection: 45.1% of the confirmed cases of salmonellosis were hospitalized; the highest rates of hospitalization have been reported in Greece, Romania, Cyprus, and Portugal (73-91% of cases). It was revealed that three of these countries also reported the lowest rates of notification for infections with *Salmonella*, which indicates that the surveillance systems in these countries capture the most severe cases first. A total of 61 fatal cases have been reported by eight EU member states (23).

Contaminated food that was most often involved in causing *Salmonella* infections are: meat and meat products (intended to be eaten as such or heat-treated), mechanically separated meat, gelatin, collagen, cheese, butter, cream, powdered milk, whey powder, ice cream, eggs and products containing raw eggs, crustaceans, shellfish, sprouted grains, fruit and pre-cut fruit, vegetables, unpasteurized juices, dehydrated diet foods (24).

Among infectious diseases, including those of the gastrointestinal tract, such as some types of food poisoning, they are currently considered as “emerging” diseases either because they are too frequently encountered or because they are caused by recently discovered pathogens, or because the role of contaminated food or water has recently been determined for the transmission of etiologic agents. For example, there have always been outbreaks of salmonellosis; however, in the last 25-30 years, their incidence has greatly increased in almost all regions of the globe. In Western Europe, *Salmonella* Enteritidis has become the dominant strain (23, 25).

Salmonellosis has stood out over the last decades; it is the first among the pathogens which can contaminate food and the external environment, and which have also been involved in the occurrence of sporadic cases of AGE / ADD as well as in the appearance of foodborne outbreaks. Morbidity and mortality data are inaccurate: there is no system for reporting isolated cases of salmonellosis in humans, animals or foods of animal origin. In addition, regarding the cause of death, the etiology of salmonellosis is not always detected. Only the investigation of foodborne salmonellosis outbreak can provide a clearer picture of this public health issue. Given the wide spread and the possibility of outbreaks, several types of surveillance and control programs for *Salmonella* infections have been proposed, such as those in Denmark, the USA, Australia, etc. Since 2003, a Control Program for these diseases has been implemented for the EU states, with the focus on food quality (especially for poultry and pork) (13, 19, 20).

*Campylobacteriosis* today tends to rank on the same position as the infections caused by non-typhoid *Salmonella*. The incidence is higher in summer in temperate zones; there are no differences related to seasons in the tropics. The morbidity assessment is made based on bacteriologically-confirmed cases.

The reported data generally come from...
laboratories and hospitals but also from epidemiological surveys carried out in foodborne outbreaks; some countries have “sentinel”-type systems of supervision and reporting. CDC reports show values of incidence of 5-6% for these infections in the USA. *Campylobacter* infections can be hyperendemic, endemic or epidemic outbreaks (almost characteristic of economically developed countries with high sanitary standards). In Thailand, *Campylobacter* infections seem to dominate bacterial etiology, *Campylobacter jejuni* serotypes 36, 4, and 11 are found quite frequently, rather than *Salmonella* and *Shigella* infections (26).

In 2012, at a worldwide level, campylobacteriosis was the most frequently reported zoonanthroponosis, with 214,268 confirmed human cases. In developed countries, *Campylobacter spp* was the most important cause of AGE / ADD; thus, in 2009, in England and Scotland, there were over 64,000 cases but due to the phenomenon of underreporting, the actual number of cases is estimated at 450,000; about 10% of all reported cases are hospitalized; variable percentage of patients experience complications – severe abdominal pain and impaired musculoskeletal, neurological or articular functions, Guillain-Barré syndrome (15% of all cases are due to infection with *Campylobacter spp*) and others (25). Epidemiological studies have shown that 50-80% of diseases in humans are caused by the consumption of contaminated poultry (21, 22, 27, 28).

Young children in rural areas are the category at the highest risk of catching the disease due to their lifestyle that is why prevention should be promoted everywhere the world. In 2006-2007, New Zealand recorded the highest incidence ever reported in the world (12,778 cases); however, after the implementation of the new regulations concerning the marketing and consumption of fresh poultry, the figures fell dramatically in 2008 (6,693 cases) (23).

Among the measures limiting the occurrence AGE / ADD, the following are included: the proper handling and operation of water supply stations and the reduction of bacterial load in the poultry destined for consumption (*E. coli* O 157, *Cryptosporidium*, *Campylobacter spp* and *Salmonella*).

In Iceland, before 1996, the consumption and marketing of refrigerated poultry was banned, and only frozen meat was allowed; the measure was established to control *Salmonella* infections (23), but it also led to fewer cases of *Campylobacter* infection; after 1996, the ban was withdrawn, and refrigerated meat products were allowed for consumption once again. The reports have shown a significant increase in the number of people who caught the diseases caused by both *Salmonella* and *Campylobacter* (29, 30).

The highest rates of hospitalization for infections with *Campylobacter* (74-78%) were reported by Cyprus, Latvia, Lithuania, Romania and the UK. At the same time, Cyprus, Latvia and Romania have the lowest number of reported cases, revealing that the surveillance in these areas includes only the severe cases. In 2012, the UK reported 20 of the 31 deaths reported by the EU member states (23, 31).

In the United States, the incidence of campylobacteriosis decreased in the late ‘90s and still remains at low levels due to the establishment and revision of hygiene measures on decontamination of drinking water and on the chlorination of the water used for washing chicken carcasses – the latter is still highly controversial in the European Union (32).

**Listeriosis.** In the European Union countries, *Listeria monocytogenes* has seldom been detected above the legal safety
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limit when the food distributed for consumption was analyzed. However, the number of confirmed cases of human listeriosis increased in 2012 to 1,642 (compared to 1,583 cases in 2006, considered the largest number of cases in the EU up to that moment) (22, 23). Relatively rarely reported, listeriosis is a zoonanthroponosis which causes high morbidity, hospitalization and mortality especially for the population at risk; the most vulnerable are fetuses, newborns, immunosuppressed patients of any age, seniors (especially men) over 74 years old. Symptoms range from mild, flu-like, with associated diarrhea, life threatening such as septicemia and meningoencephalitis; in pregnant women, Listeria can affect the conception product, usually causing severe diseases of the fetus, premature birth or miscarriage. The incriminated foods were not only milk products (soft varieties of cheese were often involved) but also fish and derivatives (4 samples reported in 2012 by Slovenia, but also by Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Germany, Hungary, the Netherlands, Latvia, Poland, Romania, Estonia, Spain) (38). Mollusks and crustaceans have been identified as contaminated in Bulgaria, Hungary, Poland, Portugal and Spain (23). There were additional red flags concerning the foods for consumption (pre-cut vegetables and fruit, sandwiches, pasta, salads, dishes based on eggs); however, in the last EFSA / ECDC Report, there are relatively few laboratory investigations in this regard and the results are virtually insignificant (23).

Colibacillosis. Many Escherichia coli serotypes are said to produce verotoxin (VTEC), yet those with the ability to cause severe diseases in humans are found in a limited number of serotypes; of these, E. coli O157 is the most frequently reported (synonymous terms: VTEC - verotoxin-producing E. coli and STEC - Shiga toxin-producing E. coli). It is normal to see occasional manifestations; in humans, the evolution of the infection includes bloody diarrhea and abdominal pain, usually without being accompanied by fever; the appearance of the hemolytic-uremic syndrome (HUS) aggravates the clinical picture (renal failure, hemolytic anemia and thrombocytopenia); about 10% of cases of infection with E. coli-VTEC will develop into SHU. In 2012, a total number of 5,671 confirmed cases of infection with E. coli VTEC were reported in the EU (23).

Since 1982 (when it was first described) until today, the infection with Escherichia coli serotype O157: H7 is considered a major cause of acute bloody diarrhea and acute renal failure, sometimes progressing to death, especially in children.

In Japan, in 1996, the largest outbreaks of infection with Escherichia coli serotype O157: H7 was reported and it involved almost 10,000 people, mostly school children (14 outbreaks). The largest outbreak included 6,300 children. There were 2 deaths (30).

Spain was faced with several outbreaks of infection with VT2 verotoxin-producing Escherichia coli O157: H7, first reported in 1986, 1994, 1997, which involved only foreign tourists. In 2000, the infection with E. coli O157: H7 affected 158 people (children from 6 schools), and 6 of them had the hemolytic uremic syndrome (23).

Cyclosporidiasis. An emerging pathogen in the United States is Cyclospora cayetanensis. Recently, it has been categorized as an enteropathogenic in humans. It causes outbreaks, some of which can be quite extensive. In 1997, in the USA and in 1998, in Canada, Cyclospora cayetanensis caused many diseases (over 1,500 cases in the USA); all the cases were related to the consumption of raspberries imported from Guatemala. There were no fatalities; the
infection was self-limiting in immunocompetent patients. In patients with HIV / AIDS, there is the risk of massive dehydration and unfavorable evolution or chronicization of diarrhea. Again, the most vulnerable age group is represented by children aged 0-2 years (33).

In the USA, the prevalence of the infection with *Cyclospora cayetanensis* in the community outside outbreaks is below 1%. In Peru, among the children from disadvantaged environments, the prevalence is estimated to be between 6% and 18%, where most cases are symptomatic (27). Two outbreaks reported in two successive voyages of an Australian cruise ship, affecting 73 passengers (confirmed with the laboratory) of the total number of 241 suspects required investigation using a case-control study, which failed to incriminate a certain food product or a food product available aboard that ship (41). In some areas (Egypt), 10-17% of the immunocompetent child population, with or without clinical signs of AGE / ADD, had fecal samples positive for *Cyclospora cayetanensis* (28, 34, 35).

**Cholera**, endemic in Asia and Africa and in some South American countries, was no longer an issue for the USA in the twentieth century. *Vibrio cholerae* got into the South Coast waters of the United States in 1991, when a cargo unshipped contaminated ballast; basically, the first case of cholera reported in South America after 1900 was recorded in 1991 in Peru; an extensive epidemic broke out and lasted for almost five years; it extended to other countries in South America, Mexico and Central American countries and it resulted in 1,099,882 cases and 10,453 deaths. In 1993, a new serotype was identified, O139 (Bengal), which was involved in outbreaks of cholera in India and Bangladesh. A history of infection with *V. cholerae* O1 does not confer immunity, which explains the endemic manifestation of serotype O139 cholera (36, 37).

**Shigellosis** manifests endemically worldwide and it is extremely prevalent in undeveloped countries. Shigellosis is a highly contagious disease, especially for children younger than 5 years old, who are very receptive to it and who can die because of it. Even today, the United States still must deal with a prevalence of 6-10‰ of the population. The most affected age group is 0-4 years (where there were 10 times more isolations compared to people over the age of 20). In Romania, the incidence of infections with *Shigella* has a downward trend, from 130.6‰ in 1975 to 31.8‰ in 1990 and 6.7‰ in 2004. The most frequent in Romania are *S. flexneri* followed by *S. sonnei* (especially in Banat and Transylvania). It can be noted that, at a worldwide level, the circulation of *S. sonnei* is more intense in the areas that are better developed economically. In Romania, the disease remains endemically manifested; there is a certain summer-autumn seasonality. In the territories where the epidemiological process manifests epidemically, the most affected is the age of childhood. Infants who are exclusively breastfed are rarely affected. Receptivity decreases with age, in parallel with the increase in the number of anti-LPS antibodies and a higher concentration of these antibodies. Epidemiological observations suggest the installation of a serotype-specific immunity (24, 38).

**Yersiniosis.** *Yersinia enterocolitica* causes gastroenteritis or enterocolitis with self-limiting evolution; it is a frequent cause of acute infectious diarrhea and abdominal pain syndrome, especially in children, who are most receptive to it between 5 and 15 years old; the ratio boys: girls is 1: 3. The emergence of outbreaks in schools or other centers for children is possible. *Yersinia enterocolitica* is univer-
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Sally widespread (cases have been reported in tropical areas, as well); the prevalence of these infections is higher in Northern European countries, where the climate is cooler, and in North America, in winter. The Report for 2003 on the evolution of zoonanthroponosis in the EU includes 9,399 reported cases of AGE / ADD with *Yersinia enterocolitica*. A study on the prevalence of acute gastroenteritis in children, conducted in Iran, places the infections with *Yersinia spp.* right after the infections with the enteropathogenic *E. coli* and *Shigella spp.* There was no reported antibiotic resistance (24).

**Enteroviruses.** In economically developed countries like the United States, Japan, Great Britain, countries in Northern Europe, the pathogens causing AGE / ADD with sporadic manifestation are caliciviruses (Norwalk, Sapporo) in patients of all ages, except for infants and toddlers in who rotaviruses are the most common. Adenovirus serotypes 40, 41 and astroviruses are also found quite frequently. Coronaviruses, picornaviruses and picotriviruses, pestiviruses, and toroviruses are considered pathogens that cause acute gastroenteritis, being associated with AGE / ADD in animals; however, they have not yet been isolated from the fecal samples collected from the people who had specific symptoms. Caliciviruses are considered responsible for 50% of the foodborne outbreaks (39) and 90% of the outbreaks in the United States, with approximately 23 million cases of AGE / ADD each year; the estimates also based on questionnaires applied to the general population show much higher numbers, nearly 74 million cases / year in the USA. The small inoculum (less than 100 viral particles), the very short incubation period (12-48 hours), the resistance to the environment and to usual decontaminants correlate with the high incidence attack rates (estimated value in practice: 41%; experimentally obtained value: 50-80%). The transmission can take place indirectly through food and contaminated water or directly through the phenomenon of aerosolization during emesis (40, 41).

In the Iasi County, acute gastroenteritis recorded averages values, comparable to other counties from Romania (2.3 - 3% of all cases reported nationwide). The etiological diagnosis was not possible for most laboratory tests, but the 0-1 age group positivity rate is higher (42).

**CONCLUSIONS**

Acute diarrheal disease ranks second among the causes of specific morbidity (after respiratory infections). Morbidity has higher values in economically undeveloped or developing countries, with 3 to 7 episodes of diarrhea / year / child compared to only 1-2 episodes / year / child in highly industrialized countries.

There are numerous etiological bacterial agents which cause acute diarrheal disease globally, but the infection with *Campylobacter* was the most frequently reported zoonanthroponosis, with 214,268 confirmed human cases in 2012.

Almost any pathogen involved in the etiology of ADD may be involved in the occurrence of healthcare-associated infections; among these, the rotavirus and *Clostridium difficile* are most prevalent.

In our opinion, general hygiene measures could change the epidemiological aspect of ADD by modifying the factors which favor the transmission of pathogens: crowds (number of children in care), the occurrence of a case of disease (or more), the presence of sick children in the community (without isolation), two or more children sharing the same bed, common areas for changing diapers, lack of personnel’s compliance.
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