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Epidemiological evaluation of acute gastroenteritis and therapeutic approaches in Middle East Countries

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Abstract. – OBJECTIVE: Gastroenteritis represents with respiratory tract infection the most common infectious disease syndrome of humans in developing countries. Gut microbiota regional variation and dysbiosis play a crucial role in triggering and worsening this devastating GI disease.

MATERIALS AND METHODS: With this manuscript, we want to explore and emphasize the critical aspect of acute gastroenteritis in Middle-East Countries and its correlation with the clinical aspect of gut microbiota modification and intestinal homeostasis.

RESULTS: Approximately 1 of 50 children born each year in developed nations is hospitalized for acute gastroenteritis sometime during childhood. The highest rate of illness occurs in children between 3 and 24 months of age. The common causes of diarrhea are infections with viruses and bacteria, diarrhea due to a systemic infection other than gastrointestinal, diarrhea associated with antibiotic administration, and feeding related diarrhea. The single most common diarrheal disorder observed in the Emergency Department and general practice is viral gastroenteritis. In particular, Rotavirus is the cause of more than 2 million hospitalizations and over half a million deaths from acute GE in infants and young children. This burden produces also direct and indirect economic costs. The use of probiotics to counterbalance commensal dysbiosis is emerging as a standard medical practice in these countries.

CONCLUSIONS: In this scenario, one of the most interesting aspects is that probiotics and gut microbiota modulation could deeply improve the prevention and treatment of this devastating GI pathology. At the same time, vaccination might represent a cost-effective strategy to reduce the health and economic burden of some pathogens, such as rotavirus.

Key Words:
Microbiota, Probiotics, Gastroenteritis, Middle east, Acute diarrhea.

Introduction

The gastrointestinal (GI) tract is man's most widely exposed organ system to the external environment. It is characterized by an interplay between different cells and their defense systems, food particles, molecules derived from digestion and the vast array of residing microbial species with their secretory products. This ecosystem acts as a functional unit. It is organized as a semipermeable system, which allows the absorption of nutrients and macromolecules, required for metabolic processes and, at the same time, protects the body from invasive microorganisms. These functions are carried out in a dynamic environment inhabited by about 1 kg of commensal microbial species, which contain more than 3 million of genes. It encloses the three domains of life: *Bacteria, Archaea and Eukarya*, but also

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viruses. Our knowledge about the presence and the role of fungi and viruses is poor. On the other side, increasing evidences are emerging on the analysis of bacterial species that make up the gastrointestinal microbiota[1]. Gut microbiota can be considered a real organ in our organisms. Because of its continuous and constant crosstalk with intestinal mucosa, it is supporting several physiological processes including intestinal barrier effect, immune system modulation (inducing tolerance and/or activation), metabolic and trophic functions by the production of butyric acid or other products, drug and toxin metabolism, or behavior conditioning[2-4].

Age, diet and origin are the main regional factors that can shape gut microbiota. Indeed, human beings are genetically adapted to the environment in which their ancestors survived and which conditioned their genetic makeup. Important changes in diet and lifestyle conditions began with Neolithic revolution with the introduction of agriculture and animal husbandry[5]. After that time, food resources became more abundant and constant, the concentration of large populations in limited areas created selective pressure that favored pathogens specialized in colonizing human hosts and probably produced the first wave of emerging human diseases[6]. Furthermore, it is well known that changes in food production agricultural and preparation have profoundly influenced the intestinal microflora[7]. These changes led to the actual regional differences in gut microbiota, which have produced a different world map of disease incidence. The western developed countries successfully controlled infectious diseases during the second half of the last century, by improving sanitation and using antibiotics and vaccines. At the same time, a rise in new diseases such as allergic, autoimmune disorders, and inflammatory bowel disease (IBD) both in adults and in children has been observed[6]. It is hypothesized that improvements in hygiene together with decreased microbial exposure in childhood are considered responsible for this increase[8].

On the other side, large cohorts of metagenomes from completely different countries identified three robust clusters (enterotypes) that are not nation- or continent-specific[9]. The enterotypes are generally stratified, not continuous. This further indicates the existence of a limited number of well-balanced host-microbial symbiotic states that might respond differently to diet and drug intake. The enterotypes are identifiable by the variation in the levels of one of 3 genera: *Bacteroides, Prevotella, Ruminococcus*. Moreover, abundant molecular functions are not necessarily provided by abundant species, and this highlights the importance of a functional analysis for each enterotype[9]. However, further studies have proposed that the number of unique configurations that form functional, stable communities may be large and may not be easy to classify into a manageable number of distinct enterotypes[10]. Considering this concept, further evaluations should consider that each individual, even in the same population, has many unique phylotypes not found in the other. This individual enterotype is produced by different ages, cultural traditions, geographic locations, and also physiological or disease states[10]. This understanding is crucial to aid in the design of therapies that target gut microbiota all over the world. The gut microbiota is immensely diverse, varies between individuals and can fluctuate over time, especially during disease and early development. Viewing the microbiota from an ecological perspective could provide insight into how to promote health by targeting this microbial community in clinical treatments[10].

An intricate and mutualistic symbiosis modulates the relationship between the host and the gut microbiota[1,11-13]. This relationship is constantly challenged by several factors such as rapid turnover of the intestinal epithelium and overlaying mucus, exposure to peristaltic activity, food molecules, gastric, pancreatic and biliary secretions, defense molecules, drugs, pH and redox potential variations, and exposure to transient bacteria from the oral cavity and esophagus, and can lead to the collapse of the microbial community structure[14]. Unfavorable alteration of microbiota composition, known as dysbiosis, has been implicated in acute and chronic gut, and perhaps also systemic, immune disorders, such as in the pathogenesis of IBD, and other gastrointestinal disorders, including gastritis, peptic ulcer, liver diseases and their complications, irritable bowel syndrome (IBS) and even gastric and colon cancer. Even diabetes, metabolic syndrome, multiple sclerosis and mood disorders have been correlated to dysbiosis[2,15-18]. One of the most common symptoms related to dysbiosis is acute and chronic diarrhea. In developing countries, diarrhea is frequently caused by bacterial, mycobacterial, and parasitic infections, although functional disorders and malabsorption, are also common. In developed countries, common causes of diarrhea are irritable bowel syndrome (IBS), in-

flammatory bowel disease, celiac disease, malabsorption syndromes, including lactose intolerance and small intestinal bacterial overgrowth (SIBO), or chronic infections, particularly in immune-compromised patients[19]. In some of these conditions, such as IBS and SIBO, diarrhea can be associated to bloating and abdominal pain. On the other side, especially in developing countries, diarrhea can be linked to severe malnutrition, including Kwashiorkor, and dehydration, which together could lead to septicemia and death.

Dysbiosis resolution and gut microbiota modulation can be obtained through different medical interventions: diet and nutritional support, treatment of predisposing conditions (*i.e.,* diabetes mellitus, motility disorders), antibiotics and biotherapy. Biotherapy includes the use of prebiotics, probiotics and symbiotics, and also of fecal microbiota transplantation. Probiotics are single or multiple specific bacterial or yeast species, which reach the intestine and interact with gut mucosa and microbiota, thereby resulting in transient gut flora alteration and clinical benefit to the host[20,21]. The number of probiotics is increasing and includes Lactobacillus spp., cocci Gram-positive, bacillus Gram-positive and negative, *bifidobacterium spp*., and yeast.

They can provide a beneficial effect on intestinal epithelial cells in several ways. For example, some strains can block pathogen entry into the epithelial cell by providing a functional and physical barrier. In fact, probiotics are able to reinforce mucus barrier by inducing the mucin granules release from goblet cells, and maintain intestinal permeability by increasing the intercellular integrity of apical tight junctions. Indeed, they can up-regulate the expression of zonula-occludens 1 (a tight junction protein) or prevent tight junction protein redistribution, thereby, stopping the passage of molecules into the lamina propria[22-24]. Probiotic can antagonize pathogenic bacteria by reducing luminal pH[25], inhibiting bacterial adherence and translocation, or producing antibacterial substances like defensins and bacteriocins. Some bacteriocins inhibit lactobacilli or related Gram-positive bacteria, others are active against a wider range of Gram-positive and Gram-negative bacteria and yeasts[26]. Probiotics are also involved in the modulation of immune response and inflammation. They can shape the mucosal immune system toward a non-inflammatory, tolerogenic pattern through the induction of T cells with regulatory properties. Probiotics can down-regulate the Th1 response and inhibit the production of pro-inflammatory cytokines, such as IL-12, TNF-alpha, and IFN-alpha or increase the production of antiL-10 and TGF-β[23].

Various probiotics can be useful in treating acute and chronic diarrhea. The strongest data are for traveler's diarrhea[26] and *Clastridium (C) difficile* infection[12]. Probiotics are moderately efficacious also in IBS-D and partially in IBD[27-33], while their use in infectious diarrhea is controversial[34-38]. Although emerging data are suggesting a crucial role for probiotics as a microbial therapy for the prevention and treatment of many digestive and extra-digestive diseases correlated to dysbiosis and gut barrier impairment, many issues still have to be resolved. New studies are needed to deeply evaluate the mechanisms of action of each strain, the optimal dose and the duration of treatment, and the best selection of strains between bacteria and yeast. Few data also exists on their safety and stability. The purpose of this manuscript is to explore and emphasize the critical aspect of acute gastroenteritis in Middle-East Countries. Based on this, detailed studies could improve the development of microbial therapies that may modulate the composition of the gut microflora with the end goal of promoting gut health.

Epidemiology, Pathogenesis and Clinical Consequences of Acute Gastroenteritis in Children

Gastroenteritis (GE) ranks with respiratory tract infection as the most common infectious disease syndrome of humans. Approximately five billion episodes of diarrhea occur worldwide annually, accounting for 15 to 30 percent of all deaths in some countries[39]. Diarrhea is defined by a passage of liquid or watery stools (taking the shape of the container), with a frequency of more than three times/day, and by a recent change in the character of the stool. In children less than two years, diarrhea is also defined as a daily stool with a mass more than 10 ml/kg.

Epidemiology

Approximately 1 of 50 children born each year in developed nations is hospitalized for acute gastroenteritis sometime during childhood (< 18 years of age). Viral gastroenteritis accounts for approximately 3 to 5 percent of all hospital days and 7 to 10 percent of hospitalizations each year for children younger than 18 years[39,40]. More than 95 percent of viral gastroenteritis hospitalizations

occur in children younger than 5 years. The highest rate of illness occurs in children between 3 and 24 months of age. Among children younger than 5 years, the average rate of illness ranges from one to five episodes per child-year, resulting in a total of 15 to 25 million episodes of acute gastroenteritis per year in the USA[40-42]. Approximately 3 to 5 million of these episodes result in clinician visits, and 200,000 in hospitalization.

Etiologic Agents

Many microbial pathogens cause acute gastroenteritis. The common causes of diarrhea are infections with viruses and bacteria, diarrhea due to a systemic infection other than gastrointestinal, diarrhea associated with antibiotic administration, and feeding related diarrhea[43]. The single most common diarrheal disorder observed in the Emergency Department and general practice is viral gastroenteritis. In one series of children two months to two years of age, a viral etiology was identified in 60% of all cases of diarrhea and in 85% of moderately severe and severe episodes[44]. Viral gastroenteritis occurs in both developed and developing countries. Bacterial and parasitic gastrointestinal infections have decreased in frequency as a result of improvements in public health infrastructure from the treatment, piping, and proper delivery of drinking water and disposal of sewage. However, viral gastroenteritis has not declined in a comparable fashion from these interventions[45].

Microbes generally are called "enteritis pathogens" when their infection results in intestinal symptoms. Enteritis pathogens newly recognized since 1970 include viruses, parasitic agents (e.g., *Isospora belli*, *Cryptosporidium*, *Giardia*), and bacterial agents (e.g., *Campylobacter jejuni*, *Campylobacter upsaliensis*, *Clostridium difficile*, some *Escherichia coli*, *Salmonella* strains, Mycobacteria such as *Mycobacterium avium* complex). The proven pathogens of viral gastroenteritis are: *Rotaviruses*, *Caliciviruses*, *Astroviruses*, *Enteric* adenovirus serotypes 40 and 41 (group F), Some picornaviruses (e.g., *Aichi virus*), *Rotavirus* accounts for the majority of cases of severe viral gastroenteritis in developing countries[46-48].

Rotavirus is the cause of more than 2 million hospitalizations and over half a million deaths from acute GE in infants and young children worldwide, especially in developing parts of the world such as Africa and Asia, where 85% of Rotavirus deaths occur[49]. In a study by Afifi and Nabih[50] in Jeddah, Saudi Arabia, all GE cases constituted 8.8% of the total pediatric hospital admissions in the year 2010. Rota positive cases accounted for 3.8% of the total pediatric hospital admissions and 42.9% of all pediatric cases admitted for GE. Different studies were conducted to estimate the prevalence of GE among Saudi children, and these studies showed similar results. In a review of 22 published studies of Rotavirus and the etiology of diarrhea carried out from 1982 to 2003, the prevalence of Rotavirus infection ranged from 10% to 46% with a median of 30%[51]. Another study[52] showed that Rotavirus was the pathogen most frequently detected among children with GE in Saudi Arabia, either alone (44.3%)or in combination with other enteropathogens (7%). Rotavirus was detected in 10% of GE cases in a study done in Makkah. This could be due to the geographical location of Makkah with very hot and dry summer, and mild winter and almost no rain throughout the year[53]. Similarly, different results were shown in other regions of Saudi Arabia, 11.5% in the Eastern Province, 23.7% in Dammam and 12% in Gizan (54-56).

In the Middle East and North Africa region, the annual proportion of RPG among reported episodes of pediatric GE was 42%[57]. However, when Middle Eastern and North African countries were compared with each other, large variations in the proportion of RPG estimates were observed, with a low of 16%-23% reported in Saudi Arabia, Tunisia, and Egypt, and a high of 44%-61% in Syria, Oman, and Kuwait.

Epidemiological surveys worldwide showed variable results. The occurrence of Rotavirus causing acute diarrhea ranged between 12 and 71%, with an average of 34% in children under 3 years of age[58]. The incidence was found to be between 5 and 71% in India, 12% to 42% in Brazil, 23.4% in Turkey, 24% in Zambia, 40% in Israel and 45.4% in Uganda in two studies done in 1987 and 2010[58-61]. These results show that the burden of this disease has not changed over the years. It also shows that the incidence of RPG is similar in both developed and developing countries worldwide.

In a recent study by Kotloff et al[62] on the burden and etiology of diarrheal disease in infants and young children (0-59 months) in developing countries found that most cases of moderate to severe diarrhea where due to four pathogens: rotavirus, *Cryptosporidium*, *E. coli* and *Shigella*. The causative agents were different in each age groups and in different countries.

Pathogenesis of Infectious Diarrhea

Pathogenesis and severity of bacterial disease depend on whether organisms have preformed toxins (*Staphylococcus aureus, Bacillus cereus*), produce toxins, or are invasive and on whether they replicate in food. Enteropathogens can lead to either an inflammatory or non-inflammatory response in the intestinal mucosa. Enteropathogens elicit non-inflammatory diarrhea through enterotoxin production by some bacteria[63], destruction of villus (surface) cells by viruses[64], adherence by parasites, and adherence and/or translocation by bacteria. Inflammatory diarrhea is usually caused by bacteria that directly invade the intestine or produce cytotoxins with consequent fluid, protein, and cells (erythrocytes, leukocytes) that enter the intestinal lumen. Some enteropathogens possess more than one virulence property. Some viruses, such as rotavirus, target the microvillous tips of the enterocytes and can enter the cells by either direct invasion or calcium-dependent endocytosis[64]. This can result in villus shortening and loss of enterocyte absorptive surface through cell shortening and loss of microvilli.

Most bacterial pathogens elaborate enterotoxins; the rotavirus protein NSP4 acts as a viral enterotoxin. Bacterial enterotoxins can selectively activate enterocyte intracellular signal transduction, and can also affect cytoskeletal rearrangements with subsequent alterations in the water and electrolyte fluxes across enterocytes[63]. Upregulation of these pathways results in inhibition of NaCl-coupled transport and increased efflux of chloride, resulting, in turn, in net secretion and loss of water into the intestinal lumen[63]. Coupled transport of sodium to glucose and amino acids is largely unaffected. The nitric oxide pathway can also be involved, as endogenous nitric oxide production is significantly higher in infectious compared with noninfectious diarrhea.

Enterotoxigenic E. coli (ETEC) colonizes and adheres to enterocytes of the small bowel via its surface fimbriae (pili) and induces hyper secretion of fluids and electrolytes into the small intestine through one of two toxins: the heat-labile enterotoxin (LT) or the heat-stable enterotoxin. LT is structurally similar to the Vibrio cholera toxin, and activates adenylate cyclase, resulting in an increase in intracellular cyclic guanosine monophosphate (cGMP). In contrast, *Shigella* spp. cause gastroenteritis via a superficial invasion of colonic mucosa, which they invade through M cells located over Peyer patches. After phagocytosis, a series of events occurs, including apoptosis of macrophages, multiplication and spread of bacteria into adjacent cells, release of inflammatory mediators (interleukin (IL)-1 and IL-8), transmigration of neutrophils into the lumen of the colon, neutrophil necrosis and degranulation, further breach of the epithelial barrier, and mucosal destruction.

Risk Factors of Acute Gastroenteritis

Major risks include environmental contamination and increased exposure to enteropathogens. Additional risks include young age, immune deficiency, measles, malnutrition, and lack of exclusive or predominant breast-feeding. Malnutrition increases several fold the risk of diarrhea and associated mortality. The fraction of such infectious diarrhea deaths that are attributable to nutritional deficiencies varies with the prevalence of deficiencies; the highest attributable fractions are in sub-Saharan Africa, South Asia, and Andean Latin America. The risks are particularly higher with micronutrient malnutrition; in children with vitamin A deficiency, the risk of dying from diarrhea, measles, and malaria is increased by 20-24%. Zinc deficiency increases the risk of mortality from diarrhea, pneumonia, and malaria by 13-21%.

The majority of cases of diarrhea resolve within the 1st wk of the illness. A smaller proportion of diarrheal illnesses fails to resolve and persist for > 2 wk. Many children (especially infants and toddlers) in developing countries have frequent episodes of acute diarrhea. Although few individual episodes persist beyond 14 days, frequent episodes of acute diarrhea can result in nutritional compromise and may predispose these children to develop persistent diarrhea, protein-calorie malnutrition, and secondary infections.

Age Distribution.

A review of 22 published studies of Rotavirus in Saudi Arabia in 21 years showed that most cases were among children less than 2 years of age, and particularly in the first year of life[55]. Other studies[61,65,66] performed worldwide confirmed the higher incidence of Rotavirus in younger ages, with the age group most affected between 0 and 1-year old.

Season

Hospitalizations for viral gastroenteritis peak in the winter; 70% to 90% of viral gastroenteritis-related hospitalizations occur during the

winter. During the peak month, which varies from region to region, viral gastroenteritis may account for 20% to 25% of pediatric hospitalizations. In Jeddah area, RPG was present all through the year with the highest peak in November, a lower peak in April, and the lowest peak in August, denoting an increased incidence in autumn and spring months. Some countries in the Middle East reported seasonality data including Egypt, Iran, Libya, Morocco, Oman, Saudi Arabia, Tunisia, and Turkey. For most of these countries, as in different European countries, the peak season for RPG is in winter from November to April. Earlier studies performed in Jeddah showed an increase in the frequency of infection in the cooler months[58]. A pattern of higher RPG cases was seen in warmer months in Al-Taif[67]. No significantly different seasonal variation in the prevalence of Rotavirus was shown in another study in Dammam[55]. These differences could be owed to the vast geographic distribution of Saudi Arabia with different types of weather in different regions. Moreover, many people, from all over the world, come to Saudi Arabia for pilgrimage and employment all through the year. They travel to and fro countries with different weather circumstances and Rotavirus prevalence.

National Distribution

Saudi Arabia: one study[69] from Saudi Arabia published in 2013 concluded that most of the causative agents of diarrhoea in young children in Saudi Arabia are of viral origin (33%), where Rotavirus ranks first (22%) followed by Adenovirus (7%) and Astrovirus (4%). *Salmonella* (3%) and *Shigella* 2%) represented the bacterial etiology of pediatric acute diarrhoea (1%) and *Giardia lamblia* (1%) was the parasitic cause (68). Another study from Saudi Arabia (2010) showed that 22% of acute diarrhea was caused by a viral agent 17.2%, 3.7% and 1.2% for rotavirus, adenovirus and astrovirus, respectively. Bacterial pathogens accounted for 10.7% of the cases, including 8.6% and 2.1% of the samples for *Salmonella* and *Shigella* spp. isolates, respectively. Pathogenic parasites were detected in only 1.2% of the samples, including 0.9% *Giardia lamblia* and 0.3% *Entamoeba histolytica* of the isolates.

Qatar: different distribution of the pathogens was found in a study published in 2013 in Qatar[69] were viral and bacterial pathogens were detected in 45.5% and 12.2% respectively of the 288 patients recruited. The most commonly detected pathogens were norovirus (28.5%), rotavirus (10.4%), followed by adenovirus (6.25%) and astrovirus (0.30%). Norovirus was the most commonly detected viral pathogen amongst all the age groups with an almost even distribution in all age groups. Rotavirus and adenovirus were more common in children under 5 yr of age. Astrovirus was found in only one person.

Jordan: in an article assessing the pathogens causing acute diarrhea in Jordan[70], Enteropathogens were identified in 66.4% of patients. A single enteric pathogen was detected in 50.9% of the children, and multiple pathogens were detected in 15.5%. The prevalence of enteropathogens identified was as follows: rotavirus (32.5%), *enteropathogenic Escherichia coli* (12.8%), *enteroaggregative E. coli* (10.2%), *enterotoxigenic E. coli* (5.7%), *Shigella spp.* (4.9%), *Entamoeba histolytica* (4.9%), *Salmonella spp.* (4.5%), *Campylobacter jejuni/coli* (1.5%), *Cryptosporidium spp.* (1.5%), *enteroinvasive E. coli* (1.5%), *eae-, Ehly-positive E. coli* (0.8%), Giardia lamblia (0.8%) and *Yersinia enterocolitica* (0.4%). No *Vibrio cholerae*, *Shiga toxin-producing E. coli*, microsporidia, adenovirus or small round virus were detected.

Pakistan: Alam et al[71] investigated 1306 stool samples from hospitalized children under 5 years of age for the presence of rotavirus strains and its genotypic diversity in Lahore. The prevalence rate during 2008 and 2009 was found to be 34% (n = 447 out of 1306).

Eastern Mediterranean countries: a systematic review conducted by Malek et al[72] analyzing rotavirus-induced diarrhea in countries of the Eastern Mediterranean region found that amoung patients with diarrhea, rotavirus was detected in 40% of inpatients and 23% of outpatients. Circulation of rotavirus occurred year-round, and no clear relationship between the timing of the rotavirus peak with either season or latitude was observed. Comparison of country-specific rotavirus detection rates indicated that the proportion of hospitalizations for rotavirus infection increased with income.

Lebanon: Dbaibo et al[74] showed that gastroenteritis attributable to rotavirus was 27.7% and nearly 75% of the rotavirus gastroenteritis cases occurred in children under 2 years of age. Rotavirus is a leading global cause of severe

gastroenteritis and dehydration in young children below the age of 5 years. Naous et al while studying intestinal amebiasis among hospitalized lebanese children found that the bacterial gastroenteritis were due to the following bacteria: *Salmonella* species (65.5%), *enteropathogenic E. coli* (30.8%) and *Shigella* (3.7%).

The most prevalent identified enteropathogen was Rotavirus (30.6%), followed by *Entamoeba histolytica* (22.3%) and then enteric bacteria (7.7%), the rest of the enteropathogens were unidentified (39.4%)[73,74].

India: in a study looking to assess the epidemiology of rotavirus in India, Kahn et al ([75]) found that Rotavirus accounts for close to 40% of hospitalizations for diarrhea in India, with more recent studies showing an increased proportion compared with older studies. Diarrheal disease in children constitutes a considerable economic burden in India. An appropriately priced and effective rotavirus vaccine may provide significant economic savings for the Indian household and healthcare system[76].

Social Cost in Developing Countries

Rheingans et al[77] evaluated the economic burden of rotavirus and the cost-effectiveness of vaccination from the health care perspective in developing countries. His estimates were based on existing epidemiological data, cost estimates, vaccine coverage, and efficacy data, as well as hypothetical vaccine prices. Outcome measures included health care and societal costs of rotavirus and benefits and incremental cost-effectiveness ratio of vaccination. He showed that treatment costs increased with income level, and health burden decreased; however, burden varied across regions. On the basis of current vaccination coverage and timing, rotavirus vaccination would annually prevent 228,000 deaths, 13.7 million hospital visits, and 8.7 million disability-adjusted life-years, saving $188 million in treatment costs and $243 million in societal costs. At $5 per dose, the incremental cost-effectiveness ratio in low-, lower-middle-, and upper-middle-income countries was $88, $291, and $329 per disability-adjusted life-year averted, respectively, and $3,015, $9,951 and $11,296 per life saved, respectively. Vaccination would prevent around 45% of deaths and 58% of associated medical visits and costs. Thus, he showed that vaccination is a cost-effective strategy to reduce the health and economic burden of rotavirus. The cost-effectiveness of vaccination depends mostly on vaccine price and reaching children at highest risk of mortality.

Thus, in addition to being a major cause of mortality in South Asia, childhood diarrhea creates an economic burden for affected households. Rheingans et al[78] used survey data from sites in Bangladesh, India, and Pakistan to estimate also the costs borne by households due to childhood diarrhea, including direct medical costs, direct nonmedical costs, and productivity losses. Mean cost per episode was $1.82 in Bangladesh, $3.33 in India, and $6.47 in Pakistan. The majority of costs for households were associated with direct medical costs of treatment. Mean costs understate the distribution of costs, with 10% of cases exceeding $6.61, $8.07, and $10.11 in Bangladesh, India, and Pakistan, respectively. In all countries, there was a trend toward lower costs among poorer house-holds and, in India and Pakistan, there were lower costs for episodes among girls. For both poor children and girls, this may reflect rationing of care, which may result in increased risks of mortality.

The use of Probiotics in Middle East Countries

500 clinicians participated to our survey on the use of probiotics in Middle East-South East Asia. 227 were from KSA, 51 from India, 50 from Pakistan, 100 from UAE, and 38 from Lebanon. The majority of these clinicians are pediatricians (84%). They are working in a hospital (51%), a medical center (31%) and a lone clinic (20%).

27% of the participants declared to always use probiotics in the management of acute diarrhea in children, 40% occasionally, 19% rarely, while 13% never. In the 42% of cases, probiotics were used independently of the age, in the 21% only between 2 and 5 years old, in the 16% only under 1-year-old, and in the 5% over 5 years old. The 30% of clinicians used probiotics as a second choice, the 24% only as an adjuvant, and the 18% as a first choice. This decision was taken for the 40% on the base of the medical experience, for the 24% on the base of literature review, for the 14% following guidelines or professional briefing.

The 57% thinks that a probiotic should be prescribed as a medicinal format, while the 22% as a food supplement. Interestingly, the 44% preferred a multiple strains format, with the 19% using lactic acid producing bacteria, the 20% bifido bacteria, the 27% spore from bacteria (*Bacillus*

Clausii), the 3% Yeast, the 21% a combination of some of these. The 39% thinks that a symbiotic format may provide better results. 64% of the participants consider safe the use of probiotics and is more likely to prescribe probiotics if the child is not breast fed. Finally, the 35% uses them only for 1 week, while the 9% also for 1 week after the disease is healed.

In conclusion, this survey underlined that probiotics are more used in pediatric acute diarrhea in south Asian/Gulf countries than in other ME countries. In term of age, most of the probiotics use is in over the age of 1 (except in KSA). About 50% of responders believe in the use of probiotics as a first/second line of therapy in acute diarrhea. In those using probiotics, the treatment is mainly driven by personal practice and literature review and mostly as a medicinal agent rather than a food supplement. Spore form, Bifidobacteria and lactic producing are the three most commonly used strains. Almost 65% of the responders believe in the general safety of probiotics with almost 40% of responders that care in the value of synbiotics. Finally, most of the responders indicated a 1-week treatment as the best therapy with probiotics.

Conclusions

Gastroenteritis ranks with respiratory tract infection as the most common infectious disease syndrome of humans in developing countries. Approximately five billion episodes of diarrhea occur worldwide annually, accounting for 15 to 30 percent of all deaths in some countries. Rotavirus is the cause of more than 2 million hospitalizations and over half a million deaths from acute GE in infants and young children worldwide, especially in developing parts of the world such as Africa and Asia, where 85% of Rotavirus deaths occur. Several studies showed that vaccination might represent a cost-effective strategy to reduce the health and economic burden of rotavirus. At the same time, detailed studies could improve the use of microbial therapies, such as probiotics, that may modulate the composition of the gut microflora with the end goal of promoting gut health.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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