Acute Infectious Diarrhea Lessons Learned From the Past?

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The *Journal of Pediatric Gastroenterology and Nutrition* (*JPGN*) has been at the forefront of many of the seminal advances into research on infectious diarrhea. In 1982, the first article of the *JPGN* was entitled "Oral Therapy for Dehydration in Diarrheal Diseases as a Global Problem" and has set the scene for several thousand subsequent articles. In his initial editorial, Finberg (1) posed several questions, which still have relevance 30 years later:

1. When is oral rehydration not appropriate, if ever?
2. What should be the composition of the oral solution and should there be more than one?
3. Should recommended practice be different in lesser-developed countries from those in developed countries?
4. Should the salts and glucose be prepackaged or should home supplies be used by instructed mothers?
5. When should standard feedings be resumed?

Although there has been considerable improvement during the last 30 years, infectious diarrhea and pneumonia remain the common most causes of childhood (<5 years) morbidity and mortality globally. According to a 2009 UNICEF/WHO report (2), >2 billion cases of diarrhea occur in children around the world and nearly 79% of childhood deaths attributed to diarrhea occur in Africa and south Asia, with 75% being confined to just 15 countries.

Significant reductions in diarrheal disease fatality rates were made following oral rehydration solution (ORS) becoming the mainstay of therapy, but unfortunately momentum has slowed and today only about 40% of children with acute diarrhea in the developing world receive ORS and continued feeding, a figure that has changed little since 2000. At present, there is little debate about the merits of early feeding, which may decrease the intestinal permeability changes induced by infection, reduce illness duration, and improve nutritional recovery.

The development and availability of targeted vaccines have also seen an early reduction in the global burden of disease in particular with rotavirus-associated gastroenteritis but more needs to be done to ensure that the potential efficacy and availability of each vaccine is maximized.

GLOBAL PATTERNS OF CHILDHOOD INFECTIOUS DIARRHEA

Asia

Globally, 56% of the annual childhood deaths caused by diarrhea occur in just 5 Asian countries with India contributing 386,600 deaths in 2007 alone (1).

An increasing variety of viruses associated with gastroenteritis are constantly being reported across Asia. A Thai study found that in 160 fecal specimens collected from children admitted to hospital with acute gastroenteritis, diarrhea viruses were detected in 53.1% (3). Group A rotavirus was the most common with a prevalence of 27.5%, followed by norovirus GII, sapovirus, enterovirus, human parechovirus, and norovirus GI, astrovirus, and adenovirus (3).

Kawai et al (4) looking at the burden of rotavirus gastroenteritis in Asia between 2000 and 2011 found that approximately 145,000 deaths every year in Asia are related to rotavirus, with India, Pakistan, and Indonesia being most affected. The incidence rates of hospitalizations in children younger than 5 years attributable to rotavirus ranged from 2.1 to 20.0 cases per 1000 children per year (4). The highest rates were found in Bangladesh, South Korea, Taiwan, Thailand, and Vietnam. Rotavirus was responsible for 37.5% of hospitalized gastroenteritis cases throughout the year, especially in Southeast Asia (4).

Although rotavirus remains the leading cause of severe diarrhea in children in Asia (4), numerous studies also highlight the importance of norovirus as a causative agent of pediatric diarrhea in this region (3). In Singapore, a recent outbreak of norovirus occurred during which a total of 305 cases were reported with clinical symptoms of diarrhea, abdominal cramps, vomiting, and fever (5).

Throughout Asia, the increasing occurrence of multidrug resistance (MDR) in enteropathogens is being reported. Twenty years ago, a study of nontyphoid *Salmonella* gastroenteritis in Malaysia found that >94% of *Salmonella* isolates were susceptible to commonly prescribed antibiotics (6); however, in a 2011 report from Cambodia involving children ages 3 months to 5 years with acute diarrhea, >33% of *Salmonella* isolates were reported to be resistant to ampicillin and tetracycline (7). A major factor associated with this increase in MDR among some *Salmonella* species is the national and international spread of certain clonal genotypes, the most recent being the global epidemic spread of multidrug-resistant *Salmonella typhimurium* DT104, since the early 1990s (8).

MDR in *Shigella* species is also becoming more common. In a population-based study in Bangladesh, China, Pakistan, Indonesia, Vietnam, and Thailand, the majority of *Shigella flexneri* isolates in each site were resistant to amoxicillin and cotrimoxazole.

Ciprofloxacin-resistant *S flexneri* isolates were identified in China (6%), Pakistan (3%), and Vietnam (2%) (9).

It is felt that the indiscriminate use of antibiotics in developing countries, as well as the widespread use of antibiotics in animal husbandry in developed countries, has contributed to the increasing problem of antibiotic resistance worldwide, particularly in the developing countries of Asia

Africa

The World Health Organization (WHO) estimates that in 2010, nearly 386,000 diarrhea deaths in children younger than 5 years, or approximately half of all of the diarrhea-related deaths worldwide, occurred in Africa (10).

Social and Environmental Determinants of Diarrhea Incidence

Poverty and underdevelopment together with an attendant lack of sufficient safe water and persisting high levels of under nutrition play the major role. In South Africa, the burden of disease caused by unsafe water, sanitation, and hygiene in children younger than 5 years was estimated to be 9.3%. Ethiopian children with diarrhea had significantly less access to protected water sources than those without diarrhea. Even in urban areas, contamination of stored drinking water with *Escherichia coli* meant it was not safe for infant formula without additional household-based water treatment (11).

The recent large cholera epidemic in Zimbabwe was attributed to a breakdown of potable water supplies and sanitation systems, but lack of access to treatment facilities, inappropriate case management, and shortage of experienced health care personnel contributed to the high case fatality rate (12).

Societal instability and refugee populations result in collapse of public health systems with numerous outbreaks reported. In the biggest refugee crisis, simultaneous epidemics of cholera and dysentery caused by *Shigella dysenteriae* type 1 resulted in the death of many thousands within a month in Goma in 1994.

HIV-associated Diarrhea

Africa is home to >90% of all of the children infected with HIV. They experience more episodes of diarrhea than uninfected children, as the multifactorial gut dysfunction mediated by HIV occurs against a background of environmental contamination, high incidence of infective diarrhea, and malnutrition in Africa. Consequently, children with severe diarrhea and HIV infection have more comorbidity and worse indicators of mucosal damage than those without, and a disproportionately high number of diarrhea deaths are associated with HIV infection (13).

The hope for increase in postnatal HIV-free survival by breast milk replacement feeding or early weaning has, in many areas, been offset by serious increases in gastroenteritis and malnutrition-associated mortality (14). Renewed emphasis on safe breast-feeding and effective prevention of mother-to-child transmission will hopefully reduce the effect of the public health dilemma of feeding choice for HIV-positive mothers.

Developed World

In industrialized countries, viruses remain the most clinically significant agents in infant acute diarrhea with rotavirus group A, recognized as the single most common cause of severe acute gastroenteritis in infants and young children. Other viruses involved are human calicivirus, norovirus, and sapovirus, formerly known as Norwalk and Sapporo virus, astrovirus, and enteric adenovirus (15).

The sporadic form of viral gastroenteritis affects all of the children in the first 5 years of life and rotavirus is the main agent. In the epidemic form, human calicivirus is considered the most common cause of nonbacterial gastroenteritis outbreaks in adults and children. There is seasonality in infection and in temperate climates rotavirus infections peak during the winter months; in tropical areas seasonal variations are less pronounced (15). The most common bacteria causing gastroenteritis are *Campylobacter* sp and *Salmonella* sp, followed by *Shigella*, *Yersinia*, and *E coli*.

ADVANCES IN MANAGEMENT OF ACUTE INFECTIOUS DIARRHEA

ORS

Arguably the most significant progress in the management of childhood acute diarrhea during the last 4 decades has been the control of the predominant common final pathway of mortality namely dehydration. ORS has prevented the deaths of millions of children since its widespread introduction more than 30 years ago and at the time was acclaimed by *The Lancet* as the most important medical advance in the 20th century (16). During the ensuing years, *JPGN* has made key contributions to the development and programmatic application of ORS through dissemination of research results as well as dialogue and exchange of ideas, some of which have contributed to an improved understanding of basic physiology and pathophysiology, others that had meaningful effect on diarrheal disease case management, and still others with programmatic and policy implications.

Cotransportation of Na^+ with a specific carrier (sodium glucose transport protein [SGLT-1]) at the apical surface of the villus in the small intestine is responsible for most Na^+ and water absorption following ingestion of ORS (17). SGLT-1 binds 2 Na^+ molecules to 1 glucose molecule, transporting them into the cell. Active exchange of intracellular Na^+ for extracellular K^+ follows along the basolateral membrane into the bloodstream by the energy-expending Na^+-K^+-ATPase. Glucose concomitantly accumulates within the enterocyte in higher concentration than adjacent intercellular compartments and ultimately diffuses across the basolateral membrane mediated by a glucose transporter. The net result is a hypertonic environment in the extracellular space, and water movement from the lumen through the paracellular tight junction to maintain osmotic balance. In most diarrheal disease states, the SGLT-1 and glucose transporter 2 are preserved and is the basis for oral rehydration therapy (ORT). More than 90% of dehydration can be safely and effectively managed with ORT using a prescribed fluid and electrolyte oral rehydration. Since its introduction by the WHO in 1979, ORS is mainly responsible for the reduction in childhood diarrheal disease mortality from an estimated 4.6 million in 1980 to 1.3 million in 2008. This original WHO solution that achieved this remarkable result was an ORS with 90 mmol of sodium, 20 mmol potassium, 80 mmol chloride, 30 mmol base, and 111 mmol of glucose per liter of water.

Since the introduction of ORT, there have been numerous attempts to improve the original ORS formulation primarily through the addition of components that increase intestinal fluid absorption. The primary driver of this research has been that, although ORS effectively treats dehydration, it does little to visibly decrease diarrheal volume or duration. This limitation is cited, as the principal reason rates of ORS use by caregivers remain incorrigibly low, <35% for children with diarrhea younger than 5 years.

Several modifications of ORS have been explored, most of which have been aimed to further enhance intestinal fluid absorption. These include nonglucose substrates (alanine, glycine, glutamine) using nonglucose sodium cotransport mechanisms in addition to or in place of glucose as well as glucose polymer–based ORS (eg, wheat, sorghum, maize) that increase the amount of glucose substrate without increasing osmolality. Others such as resistant starches fermented by colonic bacteria into short-chain fatty acid (SCFA) precursors employ nonglucose, SCFA-dependent Na^+ cotransporters in the colon, providing a site in addition to the small bowel for fluid absorption. Potential ORS additives mediated by mechanisms other than Na^+-coupled fluid absorption include glutamine and SCFAs as fuel for intestinal epithelium, zinc, recombinant human milk proteins, probiotics and prebiotics, and various food additives such as tea extract, carob pod, among others. Of all of the potential modifications of ORS that have been explored, the reduction of osmolality from the original WHO ORS to one with less sodium and glucose has had the greatest effect on diarrheal disease case management when it became the new standard ORS in 2002 and since globally applied.

What can be expected during the next 30 years? Certain interventions that have been subject of recent investigations such as resistant starch continue to hold significant promise. With this, as well as other ORS additives or modifications shown to be efficacious, feasibility from a cost and production standpoint will surely need to be defined. Whether or not zinc added to ORS can achieve the efficacy of the presently recommended zinc as an adjunct supplement alone will need to be clarified. We can expect to see reports of studies of ORS containing individual prebiotics and probiotics as well as certain of their innumerable potential content and dose combinations and ORS as a vehicle for pharmaceuticals or to manipulate the gut microbiome to promote recovery.

Micronutrients

Zinc has been the main micronutrient implicated in the diarrheal process. Studies undertaken in developing countries have shown the effectiveness of zinc supplementation in the treatment of acute and persistent diarrhea in children younger than 5 years; however, it is unclear which is the specific mechanism (18). The effectiveness of its administration has led the WHO and UNICEF to recommend treatment with zinc in all of the children with diarrhea in developing countries (19).

Probiotics

The agents commonly employed as probiotics have been *Lactobacillus*, mainly *casei* subsp *rhamnosus* (*Lactobacillus* GG), *reuteri,* and *boulardii* (20). A recent revision of 4 meta-analyses of randomized controlled trials has shown a statistically significant benefit and a moderate clinical benefit of these probiotics in the treatment of acute watery diarrhea, mainly in rotavirus infections and in infants and young children (20).

Drugs

Most antidiarrheal drugs such as inhibitors of intestinal motility, modifiers of the intestinal secretion, or adsorbent substances are not recommended in childhood because they have not demonstrated either effectiveness and/or the existence of important adverse effects (21).

Effectiveness and good oral tolerance of a specific inhibitor of enkephalinase, racecadotril, has recently been described in children (22). Racecadotril is an antidiarrheal drug with intestinal antisecretory mechanism of action and has been suggested to have a clinically relevant effect in reducing diarrhea (22).

Vaccines

In the last 30 years, we have seen a substantial expansion in our knowledge of the etiology and human and financial burden of enteric infections. This has led to the so-called ''Decade of Vaccines,'' which has seen unprecedented support from philanthropic bodies including the Bill and Melinda Gates Foundation, increasing availability of rotavirus vaccine, and concerted efforts to improve the coverage and timeliness of the WHO Expanded Programme on Immunization.

The advent of molecular diagnostics has revolutionized the ascertainment of causative organisms in infectious diarrhea. Traditional microscopy and culture, augmented with electron microscopy and antigen detection techniques, served the diagnosis of *Salmonella*, *Campylobacter*, enterohemorrhagic *E coli*, *Shigella*, *Vibrio cholera*, and the larger viruses of rotavirus and adenovirus quite well. Recently, the ''no organism detected'' gap has been reduced to <25% in some studies of acute gastroenteritis by improved detection of other pathogenic forms of *E coli* (especially enteroaggregative), smaller viruses (noroviruses, sapoviruses, astroviruses), and protozoa (*Giardia*, cryptosporidia); however, increased sensitivity may carry risk of detecting carriage, rather than the diarrheal pathogen (23,24).

Rotavirus serotypes G1-4 have caused >95% of global disease. Its segmented dsRNA genome enables easy swapping of segments with coinfecting rotaviruses, creating new reassortant viruses (ref). This has been used to create reassortant vaccines by inserting human G1-G4 and P8 genetic segments into an animal rotavirus ''backbone.'' The rhesus-human reassortant vaccine (RRV-TV, Rotashield, Wyeth Laboratories, Marietta, PA) was introduced into the US infant immunization schedule in 1998; however, following strong temporal association with intussusception in the 21 days following the first dose, it was withdrawn voluntarily in 1999. The next rotavirus vaccines, a pentavalent bovine-human reassortant (RV5, Rotateq, Merck, Whitehouse Station, NJ) and an attenuated human monovalent (RV1, Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium), were introduced in 2006. Efficacy and safety trials, involving >60,000 infants each, did not show the same association with intussusception with these newer rotavirus vaccines. Following their implementation, these vaccines have had immediate reductions in morbidity and mortality from rotavirus and ''all-cause gastroenteritis.'' All of the rotavirus vaccines have shown higher efficacy in developed countries, but have the greatest effect on mortality in developing settings. They may still be associated with a slight elevation of intussusception risk after dose 1 and/or dose 2 in some populations, but in all settings the health benefits vastly outweigh the potential risk (25–27). There are now numerous candidate vaccines in clinical development many of which are in association with developing world manufacturers aiming to introduce vaccines at an affordable price for Expanded Programme on Immunization schedules.

Norovirus is the most common cause of sporadic infectious diarrhea in adults and is responsible for most food-borne outbreaks. It is also increasingly recognized as the second most important cause in children. In the United States, norovirus disease is estimated to cost >$2 billion annually. Vaccine development has previously been hampered by the extreme difficulty in culturing the virus, and the relatively brief duration of naturally acquired immunity, usually <1 year. Recent work has identified the role of all 3 major histo-blood groups (ABO, Lewis and secretor families)

in binding norovirus, with many ''non-secretors'' non-susceptible to disease from common norovirus genotypes (G1.1, G2). Candidate vaccines using virus-like particles, some in conjunction with newer adjuvants designed to recruit T-helper 1 help, are presently in clinical development (28).

Cholera is caused by infection with *Vibrio cholera* 01 and 0139 and results in an estimated 100,000 deaths per year with the greatest burden being in Africa. Infection in developing countries follows 2 epidemiological patterns of epidemic and endemic with children younger than 5 years being at the highest risk in the endemic form (29,30). Once infected, severe secretory diarrhea is caused by the A subunit of the toxin that induces active chloride secretion. Almost all of the deaths are attributable to dehydration and hence the cornerstone of treatment is the correct use of rehydration, which will reduce mortality to <1%. Other treatment modalities such as antibiotics have also been used, but there are substantial concerns about effectiveness and the development of drug resistance. These simple measures can limit mortality but during the last decade it has become apparent that the severity of infection is worsening. Hence, there is a move by the WHO to assess the options of pre-emptive vaccination in areas at risk for epidemics and widespread vaccination in endemic areas (26). Presently, only killed oral vaccines are commercially available and include WC (Shanchol, ShantaBiotechnic, India, and mORC-VAX, VaBiotech, Vietnam) and WC-rBS (Dukoral, Crucell). Both require to be administered 10 to 14 days apart and can induce herd immunity with a protective efficacy of these vaccines ranging from 67% to 85%, respectively (23). The concern with using these vaccines in epidemics is with respect to logistics and feasibility. The other issue is limited global supply, which is limited to about 2 million doses. Developed countries need to consider the option of contributing to a global cholera vaccine stockpile that will allow rapid mobilization during epidemics. In addition to this, fieldwork is required to assess the effectiveness of immunization strategies further (31).

Typhoid fever is caused by *Salmonella enterica* servar *typhi* or *paratyphi* A with most cases caused by the former. It is estimated that there are 2 million cases per year with the majority of infections affecting children and there is an associated mortality rate of 10%. Antibiotic treatment will reduce severity and mortality but vaccination as a preventative option may well be more appropriate in the future (32). Presently, WHO recommends vaccination only to travelers and people who reside in an endemic region. There are 2 vaccines that are commercially available, Ty 21a (oral) and Vi polysaccharide (parenteral). They are safe and efficacious with a protection rate of 50% to 70% at 3 years but the main limitation in both cases being an inability to protect children younger than 2 years and *S paratyphi*. There is further development of the Vi polysaccharide vaccine with binding to recombinant *Pseudomonas aeruginosa* exoprotein A (VirEPA) that increases the immunogenicity and efficacy of the vaccine to 89%. This remains at a development stage (33). Mention should also be made of non-typhoid *Salmonella* that is endemic in sub-Saharan Africa with a high-risk population being children younger than 6 months. Although antibiotics may be the cornerstone of treatment, there are vaccination options particularly of livestock, which may reduce transmission to this at-risk group (32).

In terms of childhood acute infectious diarrhea, what can be expected for the next 30 years? Because improvement in the chronically low rates of ORS use by caregivers is an area for potential major gain, identification of effective behavior change interventions and modifications or additives that consistently and visibly decrease diarrheal stool output and duration remains the ''Holy Grail.''

Improvements in vaccine development are imperative such that at-risk populations have easy access to highly efficacious and safe vaccines. The transfer of vaccine production to developing countries will reduce the cost, increase supply, and provide a sense of achievement to developing nations. This step has already been taken and ought to be encouraged so long because there are strict manufacturing and safety guidelines. Global warming and its effect on disease burden are unpredictable but will need to be considered with respect to changing patterns of infections.

CONCLUSIONS

In 2007, it was estimated that the introduction and use of ORS has led to 50 million children saved around the world, which is clearly a positive outcome and testament to the UN Millennium Development Goals and numerous other government and nongovernment organization's strategies (34). Should these advances and strategies come to fruition, we should see further reductions in the morbidity and mortality directly attributable to infectious diarrhea in the next 30 years. This concomitant increase in the global population will undoubtedly have some possible negative implications with respect to food availability and other public health issues in certain regions but appropriate planning and strategies should obviate these issues.

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