Original Article

An Overview of the Aetiologic Agents of Diarrhoea Diseases in Children: How far Have We Gone in Management and Control?

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ABSTRACT

Diarrhoea disease is the second leading cause of death amongst Nigerian children (after malaria) with a prevalence rate in Nigeria of 18.8% which is one of the worst in sub-Sahara Africa. A major contributor to childhood morbidity and mortality, causes 4 million deaths each year in under-fives with each child experiencing about 5 episodes of diarrhoea yearly. We review diarrhoea diseases in children with focus on infectious diarrhoea with the aim of looking at the progress made so far in its management and control. Diarrhoea can be classified into acute and chronic; secretory, osmotic, inflammatory or due to impaired motility; infectious and non-infectious. In developing countries, infections are the most common causes of acute watery diarrhoea in children, whereas chronic diarrhoea results from non-infectious causes like inherited metabolic disorders, sensitivity to gluten or neoplasm. Diagnosis includes a careful history from the patient, examination of stool sample and examination of faecal swab samples where stool is not available. Diarrhoea in this age group is mostly of infectious origin and can be viral, bacterial, parasitic or fungi. Treatment in this environment is primarily supportive with oral or intravenous fluid and preventive measures include domestic hygiene promotion, breast-feeding promotion, improved weaning practices, probiotic use, oral rehydration therapy with additional L-glutamine, zinc supplementation and vaccination against childhood infectious diseases like rotavirus, measles and cholera. An aluminmagnesium silicate, Smectite® has been found to be of potential benefit in the management of diarrhoea. Use of Rotavirus vaccines, probiotics and Smectite® is being advocated.

INTRODUCTION

Diarrhoea can be defined as passage of loose or watery stools often associated with increased frequency of bowel movement. It can also be defined as the passage within 24 hours of three or more watery or loose stools; a loose stool takes to the shape of the container.[1,2,3] In developing countries higher rates of diarrhoea disease is seen in children under the age of 2 years. Approximately 1.3 billion episodes of diarrhoea and 4 million deaths occur in under-five children each year with an annual prevalence rate of 4.9 episodes of diarrhoea per child per year.[3] In Nigeria, reports show that a child under the age of 5 years experiences an average of 3 to 4

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episodes of diarrhoea annually.[4,5] In Brazil, the incidence of acute diarrhoea among infants less than 1 year old was 26.7 cases per 1,000 children per month.[6]

Dehydration is the main cause of death in acute watery diarrhoea. Malnutrition, also an important complication of diarrhoea, results from reduced feeding and impaired ability to absorb nutrients in the face of increased nutrient requirement as a result of infection during the diarrhoeaic phase. Consequently, prolonged episodes of acute watery diarrhoea have adverse impact on growth.[3]

We hereby review this important cause of childhood morbidity and mortality, with the aim of looking at progress so far made in the management and control of the disease.

CLASSIFICATION

Diarrhoea can be classified based on duration, pathophysiological mechanisms, and aetiological factor, among others. Based on duration, diarrhoea can be acute, persistent or chronic. Acute diarrhoea is of sudden onset, usually lasting less than 14 days and may be associated with fever and vomiting. Persistent diarrhoea usually begins as acute diarrhoea and lasts for about 14 days but not more than 28 days. Chronic diarrhoea usually begins insidiously and lasts longer than 28 days; it may be recurring or continuous. Infectious agents are the most common causes of acute watery diarrhoea among children in developing countries while chronic diarrhoea results from non-infectious causes like inherited metabolic disorders, sensitivity to gluten or neoplasm. Implicated aetiologic agents include rotavirus, enterotoxigenic *Escherichia coli*, *Shigella* spp, *Campylobacter jejuni*, and *Cryptosporodium* spp.[1,3,4,7]

Based on pathophysiological mechanisms, diarrhoea can be secretory, osmotic, inflammatory or due to impaired motility. Secretory diarrhoea occurs when there is active secretion of water into the intestinal lumen. This usually results from intracellular accumulation of cyclic Adenosine monophosphate (cAMP) or cyclic Guanosine monophosphate which is stimulated by secretagogue or toxin bound to a receptor on the surface epithelium of the bowel. Secretory diarrhoea may be infectious or non-infectious in origin. Osmotic diarrhoea on the other hand follows the ingestion of poorly absorbed solutes like magnesium, phosphate, lactulose, and sorbitol, or in small bowel disorder where solutes are not well absorbed as seen in lactase deficiency syndrome where lactose is not absorbed. Osmotic diarrhoea secondary to malabsorbsion of solutes is also seen in rotavirus infection where glucose is not well absorbed. Inflammatory diarrhoea can be caused by inflammation of the intestine resulting in loss of fluid and electrolyte from exudation of mucus, protein, and blood into the intestinal lumen leading subsequently to diarrhoea. The most common cause of inflammatory diarrhoea is acute infection though chronic diseases like inflammatory bowel disease, celiac disease, tuberculosis, and cancer of the colon has also be implicated. Other pathophysiologic classification of diarrhoea is impaired gut motility which can complicate vagotomy, intestinal resection, diabetic neuropathy, menstruation, hyperthyroidism and drugs.[1,3,6]

Based on aetiologic classification, diarrhoea can be classified as infectious or non-infectious. Infectious diarrhoea is far more common and can be viral, bacterial, parasitic or fungal. Other basis of classification include association with underlying clinical conditions such as systemic diseases and congenital disorders.[6]

AETIOLOGIC AGENTS OF INFECTIOUS DIARRHOEA

Bacterial agents include diarrhoeagenic *Escherichiacoli* [which include enteropathogenic *E. coli* (EPEC), entero-invasive *E. coli* (EIEC), verocytotoxin-producing *E. coli* (VTEC), entero-aggregative *E. coli* (EAggEC), entero-toxigenic *E. coli* (ETEC), and attaching and effacing *E. coli* (A/EEC)][8-10,44-46], *Shigella* species,[7-9] *Salmonella* species,[9-13] *Vibriocholerae*, *Campylobacterjejuni*/*coli*, *Yersiniaenterocolitica*,[14]

enterotoxigenic *Bacteroidesfragilis*,[7] *Aeromonas* species, and *Plesiomonas* species.[13]

Salmonella species seen include *S. typhimurium, S enterica, S infantis, S anatum, S.Newport* and *S. ohio*.[9,12] *Shigella* species include *Shigella flexneri, Shigella sonnei, S. boydii*.[7-9] High prevalence of resistance of diarrhoeagenic *E. coli* and *Shigella* spp to ampicillin, chloramphenicol, and to trimethoprim/ sulfamethoxazolewas noted.[7]

Parasitic causes of diarrhoea include *E. histolytica* or *E. dispar, Giardia lamblia* or *G. intestinalis, Trichomonas intestinalis, Cryptosporidium* species, *Dientamoebafragilis, Trichuristrichiura, Hymenolepisnana, Strongyloidesstercoralis, Ascarislumbricoides, Necatoramericanus* and *Cyclosporacayetanensis*.[9,11,14-23] Other parasitic agents include *Blastocystishominis*, *Endoclimaxnana* and *Isosporabelli*.[24]

Viral agents of diarrhoea include rotavirus, astrovirus, enteric adenovirus (adenovirus type 40 and 41), Norovirus, Sapovirus and Coronavirus.[25-29] Other viral agents such as enterovirus and toroviruses have been found in diarrhoea stools but their significance is not well established.[26,29] Fungal agents of diarrhoea include *Candida albicans, C krusei, C albicans, C tropicalis, C pseudotropicalis, C globrata, C parapsilosis*.[25,30,31]

EPIDEMIOLOGY

Transmission of infectious agents of diarrhoea is usually faeco-oral.[32] Identified risk factors that predispose a child to diarrhoea include failure to breastfeed adequately, use of feeding bottles, water and food contamination with faecal materials, poor food storage techniques, poor hand hygiene in both child and caregiver, poor nutrition and lack of portable water supply. Presence of co-morbidities like infections such as measles and HIV has also been implicated as predisposing to diarrhoea in children. Other independent risk factors predisposing to diarrhoea were lack of available health care services and low maternal level of education. Low maternal age in relation to maternal understanding of diarrhoea prevention in children, low family income and lack of health information has been associated with morbidity in children with diarrhoea.[2,6,7]

Causative microbial agents in diarrhoea could be single or multiple.[33] Rotaviruses is commonly associated with diarrhoea in children aged 2 years or less[34] with Coronaviruses been detected at highest rates in situations of poor sanitation.[29] Diarrheogenic *E. coli*, *Shigella*, *Salmonella*, and *Campylobacter* are the most frequently isolated bacterial pathogens[7,8] while *Entamoebahistolytica*, *Giardia*spp and *Cryptosporidium* spp are the protozoans commonly associated with parasitic diarrhoea.[15,16,19] Rotavirus and diarrhoeagenic *E. coli*infection were found to be predominant causes of acute diarrhoea episodes in children below the age of two years, while older children were mostly infected with *Shigella* species, and enterotoxigenic *B. fragilis*.[34,35] *Aeromonas* species and *Plesiomonas* species were found more in poorer regions.[13] Diarrhoea due to helminths is rare and diarrhoea resulting from helminthic and protozoa infection has been associated with low socioeconomic class, malnutrition and deteriorating environmental sanitation.[13,16] Diarrhoea due to the protozoa *Cryptosporidium* and other coccidian parasites has been associated with immunosuppression.[19,20] *Strongyloides stercoralis* induces severe diarrhoea in malnourished children which must be treated as an emergency to avoid dissemination.[23] Diarrhoea due to fungal agents has doubtful significance and are at best associated with malnutrition, antibiotic usage and other forms of immunosuppression.

Worldwide, the most common cause of acute watery diarrhoea in children less than two years of age is rotavirus[34] with the highest prevalence of rotavirus infection and hospital admission following this infection occurring in age 6-18 months.[34] Although rotavirus diarrhoea occurs with high frequency in the developed countries, mortality is low.[36,37] Diarrhoea epidemics of viral aetiology are known to occur in institutions such as daycare centres and home for the elderly, their occupants being at high risk of infection as a result of regular exposure to the

pathogen[38,39] mostly from contact with stool contaminated with the virus via contaminated hands and environmental surfaces and its resistance to common disinfectants. The virus, survives well in tap water and sewage. Stool is a known source of the virus, which resist many chemical disinfectants, temperature variations, and physical forces.[40,41] 95% ethanol has been found to completely inactivate the virus hence, the use of a disinfectant spray containing 79% ethanol and 0.1% o-phenyl phenol to clean environmental surfaces can eliminate cultivable virus from these surfaces. [40,41]

IDENTIFYING CAUSE OF DIARRHOEA

Evaluation of a child with diarrhea includes obtaining a careful history, physical examination and laboratory investigations. Stool samples are the most commonly used specimen in laboratory diagnosis and the specimen is examined macroscopically and microscopically for presence of parasites and evidences of tissue response to pathogens. Culture in appropriate media helps to isolate pathogen.[19] Biochemical tests are done on isolates recovered for identification and speciation and sensitivity testing of isolated bacteria pathogens is necessary to determine its antibiotic susceptibility pattern.

Laboratory diagnosis of viral causes of diarrhoea is becoming increasingly feasible through the use of diagnostic techniques such as antigen-antibody based tests, molecular methods and electron microscopy. Demonstration of presence of viral antigen in stool, or antibodies to the virus in blood is now commercially available in the form of ELISA or latex agglutination kits. Example of this includes The Epitope Diagnostics® Fecal Rotavirus Antigen ELISA kit. This technique is gradually replacing the more expensive, more cumbersome and not too readily available electron microscopy. The technique also requires minimal training to perform when compared with electron microscopy. Detection of viral antigens by ELISA is reportedly more sensitive than detection with the Immune electron microscopy (IEM) which in turn is superior to the plain Electron microscopy (EM).[63,64] In the diagnosis of Rotavirus however, PCR of viral genome is found to be most sensitive of all these diagnostic techniques hence preferred. For the benefit of resource limited countries like ours which is still being plagued with Rotavirus diarrhoea, putting into consideration the teeming population of the at risk group, ELISA is used in laboratory diagnosis. In the evaluation of diarrhea case suspected to be of non-infectious aetiology, presenting essentially as chronic diarrhea, other testss such as serology, histologic assessment, assay of peptide hormones, assessment of carbohydrate malabsorption, small bowel bacterial overgrowth and intestinal transit using breath tests, tests of bile acid malabsorption and imaging techniques may be used. Generally, diagnosing the cause of chronic diarrhea is being attempted through endomicroscopy and molecular pathology methods but individual differential diagnosis influences the choice of tests done. For instance, in the evaluation of a case of suspected celiac disease, serological tests are very useful but not in autoimmune enteropathies and inflammatory bowel disease. Histological assessment could be done through endoscopic examinations and biopsy of the small intestine and colon. In the diagnosis of diarrhea resulting from endocrine tumors, measurement of peptide hormones is of value. The assessment of carbohydrate malabsorption, small bowel bacterial overgrowth and intestinal transit using breath tests has many technical limitations that reduce its sensitivity and specificity. Similarly, there is limited utilization of tests of bile acid malabsorption beyond empirical trials of bile acid sequestrants.[1,4,7,42]

TREATMENT

Treatment is majorly and primarily supportive. This is because the commonest aetiologic agent of diarrhoea is rotavirus, and there is no known effective antiviral agent. [36,43-45] Oral or intravenous rehydration to prevent or correct fluid and electrolyte depletion is the mainstay of treatment to prevent dehydration, electrolyte imbalance, acidosis and death which may complicate poorly managed diarrhoea. Other treatment options include the use of

probiotics, antibiotics and anti-diarrhoeal agents. Use of antibiotics is implicated when a bacterial cause of diarrhoea can be proven, use of probiotics and anti-diarrhoeal agents however are not a function of the aetiologic cause.

Probiotics, which are live microorganisms which when administered in adequate amounts confer a health benefit on the host are not commonly used in our locality.[46] Various randomised clinical trials done in various part of the world have revealed that some probiotics reduces the frequency and duration of diarrhoea in infants and children.[47-49] *Lactobacillus* GG, *Lactobacillusacidophilus, Lactobacilluscasei, Bifidobacterium* ssp, *Streptococcus* ssp, and the yeast *Saccharomycesboulardii* were the probiotics found to be effective in controlling diarrhoea, especially the *Lactobacillus* GG and *S. boulardii*. In Benin City, Nigeria, a study carried out by Anukam et al,on the knowledge of probiotics by Nigerian physicians revealed a deficient knowledge as only 4.8% of the sampled clinicians in the study had prior knowledge of the existence of probiotics in the country and its therapeutic use especially in cases of diarrhoea.[49] In that study, only 3 out of the 62 clinicians sampled had the knowledge about the existence of probiotics and these 3 had been practicing medicine for 31 years and above. None of these 3 however is aware of the existence of any probiotic in the country.[50]

Likewise, Chukwu while assessing the awareness and knowledge on the use of probiotics by healthcare professionals in Nigeria, concluded that there is limited knowledge and awareness of probiotic products by the healthcare professionals in the country, especially amongst clinicians. Only 25.8% of the respondent in that study has ever prescribed or recommended the use of any probiotic product compared to 63.8% of the respondents that prescribed or recommended the use of antibiotics regularly. Only 33% of the respondents in that study are aware of any probiotic products in the Nigerian pharmaceutical market.[51]

Anti-diarrhoeal agents commonly used include loperamide, diphenoxylate, and recently, a new anti-diarrhoeal agent, Smectite® has been introduced. Smectite is an aluminmagnesium silicate, it is an absorbent natural clay. This agent, whose proposed mechanism of action is via an anti-inflammatory action, alteration of gut mucus barrier to reduce the rate and likelihood of penetration of microbial toxins, coupled with an adsorbtive property, is not yet introduced in our environment. In a nationwide clinical survey carried out in Italy by paediatricians, administration of Smectite® was associated with significant reduction of the duration of diarrhoea, as judged by stool frequency and consistency. Smectite® reduces the duration of diarrhoea and prevents a prolonged course.[52] Addition of L-glutamine to an oral rehydrating solution (ORS) may significantly improve fluid absorption in damaged intestinal villi. Zinc sulphate has been found to reduce both severity and duration of illness.[53,54] Vitamin A replacement therapy has been advocated but not of proven benefit[55] and breastfeeding should be continued throughout the rehydration process. Antiviral and antibiotics usage are not known to have clinical advantage.

Indications for the use of antibiotic in diarrheal disease include but not limited to the following: persistent diarrhoea, associated co-morbidities such as heart failure, lung disease, and HIV/AIDS, demonstrable presence of bacterial isolates like *shigella* or *C. difficile* on stool examination and testing, and traveller's diarrhoea.[56] Metronidazole is commonly used in the treatment of amoebiasis, giardiasis and C. difficile infections; fluoroquinolone in cholera and shigellosis. Ceftriaxone have recently been used in the treatment of shigellosis, salmonellosis and campylobacter infections. However, Erythromycin is still useful in the treatment of campylobacter infection while vancomycin is useful in management of diseases associated with *C. difficile*.[57]

There has been documented growing antimicrobial resistance to Shigella[7,58] which was initially sensitive to many antibiotics like trimethoprim-sulfamethoxazole, tetracycline, and ampicillin.[58,59]

There is therefore need for continual surveillance for antibiotics resistance of diarrhoea causing agents in order to update antibiotics recommendation for each organism. Use of starchy food low in fat and protein is without any known benefit. Opiates and loperamide may reduce visible stool output but carry the risk of ileus and vomiting. Glycoproteins such as mucins which, probably function as pseudo receptors if given orally, have been suggested but yet to be available commercially. Smectite®, an absorbent natural clay that binds digestive mucous has also been suggested to be of potential benefit in the management of diarrhoea.[60]

For children presenting with non-dehydrating chronic diarrhoea, differential diagnosis will include non-infectious causes such as surgical conditions like intussusception and malrotation, infection outside the gastrointestinal tract like urinary tract infection and meningitis, immunodeficiency states such as HIV, side effect of oral medication, spurious diarrhoea (faecal impaction with overflow), toddlers diarrhoea, primary GIT pathology (cystic fibrosis, inflammatory bowel disease, coeliac disease),etc.[61]

PREVENTION AND CONTROL

Diarrhoea disease is quite contagious, spreading easily and rapidly among groups of individuals. Route of transmission is usually faeco-oral hence the effect of improved sanitation and water treatments in its prevention and control. Good hand washing techniques, disinfection of surfaces, toilets, and toys, adequate chlorination of water and effective vaccination against rotavirus would greatly prevent severe gastroenteritis caused by rotavirus in children under the age two years of age. Measles vaccination has been effectively utilized in the prevention of morbidity and mortality associated with diarrhoea associated with measles. Despite the fact that reinfections with rotaviruses are common, homotypic immunity seems to be effective against diarrhoeal illness.

Two licensed live oral rotavirus vaccines with good efficacy against severe rotavirus disease are RotaTeq® (RV 5; Merck) and Rotarix® (RV 1; GlaxoSmithKline). These rotavirus vaccines were found in many studies to prevent 85 to 98% of severe rotavirus illness in the first year of life and 74 to 87% of all rotavirus illness episodes. Performance of these vaccines (RV1 and RV5) was found to be generally better in developed than developing countries. The World Health Organisation recommends global integration of these vaccines in national immunization programs, and following the introduction of these rotavirus vaccines there has been marked reduction in mortality in developing countries and cost saving effect on treatment of diarrhoea in industrialized countries.[54,55]

RotaTeq® is administered in a 3-dose series, at ages 2, 4, and 6 months while Rotarix® is administered in a 2-dose series, at ages 2 and 4 months. Children to receive dose 1 of rotavirus vaccine must not be younger than 6 weeks and not older than 14 weeks and 6 days. There is insufficient data on safety of dose 1 of rotavirus vaccine in older infants. The interval between doses of rotavirus vaccine must not be shorter than 4 weeks though can be longer, but all doses of rotavirus vaccine should have been administered by age 8 months and 0 days.[62]Effective vaccines against ETEC and *Shigella* are under development. In our country however, rotavirus vaccination is not yet routinely done for children for it is not yet introduced into our free routine National Programme for Immunization schedule.[63]However, child carers and parents that can afford it can get for their children at the rate of about 20,000NGN for both doses. The question is, how many Nigerians can afford that, with as high as 62% of the population living below the international poverty datum line of US$ 1.25 per day.[64]

CONCLUSION

Diarrhoea contributes greatly to under-5 morbidity and mortality globally. Effective control and management can be achieved through breast-feeding promotion, improved weaning practices, personal hygiene, domestic hygiene promotion, oral rehydration therapy with additional L-glutamine, zinc supplementation coupled with vaccination against childhood infectious diseases like

rotavirus, measles and cholera. An aluminmagnesium silicate, Smectite®has been suggested to be of potential benefit in the management of diarrhoea.

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