Antibiotic and Antiparasitic Therapy in Chronic Diarrhea

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Chronic and recurrent diarrheal illnesses are common in malnourished populations, particularly in young children, and contribute significantly to malabsorption and undernutrition. There is a vast array of infectious causes of these illnesses, parasitic, bacterial, fungal, and viral, which present major problems in prevention, control, and treatment of childhood diarrheal diseases in developing countries.

It is risky to suggest rigid rules about antibiotic and antiparasitic therapy in chronic diarrheas. Regional variations in patterns of bacterial and parasitic gut infections can be vastly different depending on local environmental and geographic conditions. In most places where malnutrition and chronic diarrhea are endemic, the facilities available for adequate clinical diagnosis are usually lacking or too expensive to be able to be applied except to the elite. The subject is often complicated by multiple pathology on an individual or community basis, and multiple infections are the rule rather than the exception. There is a complex relationship between infecting organisms in the gastrointestinal tract. For example, invasive amebiasis is more common in children with Trichuris (whipworm) infection, and patients infected with whipworm who develop bloody diarrhea with mucus should be suspected of having coexisting amebiasis (1). Strongyloides stercoralis (roundworm) lives in the tissues of the small intestine, is often associated with eosinophilia, sometimes causes bloody diarrhea with mucus, can cause malabsorption, and may also predispose to amebiasis.

EPIDEMIOLOGY OF CHRONIC CHILDHOOD DIARRHEA

This subject of bacterial and parasitic gut infections is bedeviled by inadequate epidemiological information. There is a great need for carefully planned, comprehensive studies to help fill this gap in knowledge to help devise better forms of treatment.

We have recently completed a prospective study of almost 1,000 children with diarrhea, compared with the same number of matched controls, to determine
the major bacterial causes of diarrhea in children in our community and the possible role of viral infections. Particular emphasis was given to the role of enterotoxigenic Aeromonas hydrophila as a cause of bacterial diarrhea because in the summer of 1979 we found these organisms without other enteric pathogens in a group of children with diarrhea. Although there have been many reports of acute diarrhea associated with Aeromonas sp. in fecal samples (2), Aeromonas sp. have not become generally accepted as enteric pathogens. This may be because incorrect laboratory identification has led to failure to isolate Aeromonas sp. in patients with diarrhea, whereas strains isolated from patients without diarrhea have not been tested for enterotoxigenicity. The study included all patients who had fecal specimens examined in our hospital between September 1980 and September 1981.

Overall, 24% of patients with diarrhea and only 2% of patients without diarrhea had bacterial pathogens isolated from their stools. In contrast, almost 13% of children with diarrhea and 11% of those without diarrhea had rotavirus, identified by ELISA, in their stools. Four children with diarrhea (0.4%) had adenovirus identified in their stools using electron microscopy. There were almost 33% of patients with diarrhea in whom bacterial pathogens, rotavirus, or adenovirus were identified.

Multiple isolations were common. Isolation associated with one or more bacterial pathogens or rotavirus was found with 24.5% of enterotoxigenic Aeromonas sp. isolated from patients with diarrhea, and one nonenterotoxigenic strain isolated from the control group. This strain was associated with isolation of a Salmonella. Of Salmonella sp. isolated from children with diarrhea, almost 30% were found with other bacterial pathogens or rotavirus. In the control group, there was only one multiple isolation, in association with Aeromonas hydrophila. In children with diarrhea, almost one-quarter of Shigella sp. isolated and one-fifth of Campylobacter sp. were associated with other bacterial pathogens or rotavirus. Shigella sp. was not isolated from the control group, and there were no multiple isolations that included Campylobacter sp. in these patients. With enterotoxigenic E. coli (ETEC), more than half of the isolates from children with diarrhea and the single isolate from the nondiarrheal group were associated with isolation of other bacterial pathogens or rotavirus. This emphasizes the importance of multiple infections in association with ETEC. Rotavirus was detected in association with bacterial pathogens in one-sixth of the identifications from children with diarrhea and in only one instance from the control group.

The first objective of the study was to define the importance of Aeromonas sp. in childhood gastroenteritis. We found Aeromonas to be the most common bacterial cause of gastroenteritis in children in our community (10% of patients with diarrhea), and it is a markedly seasonal infection, peaking in summer (3), and was most important between the ages of 6 months and 2 years.

Giardia lamblia is endemic in our community and is particularly common in groups with poor hygiene, e.g., aboriginal communities. Its role as a cause of diarrhea and malabsorption is not universally accepted, and it seemed unimportant in this study since it was as common in control subjects without
diarrhea as it was in the patients with diarrhea. Fecal specimens only were examined in this study, and since diagnosis is much improved if upper intestinal fluid is examined (4), it is difficult to know how this factor may have affected results. However, investigation of small bowel contents was not possible in this study, particularly in the control group. The pathogenesis of changes in small bowel function related to *Giardia lamblia* is not defined and may be modified considerably by interaction with the host (5). Thus, the finding of *Giardia lamblia* trophozoites in feces may not always indicate the presence of a significant effect on the small bowel.

The findings of this study also question the importance of viruses as a cause of sporadic gastroenteritis in children. Almost 13% of patients with diarrhea and 11% of subjects without diarrhea had rotavirus isolated. This rate of isolation of viruses in patients with diarrhea is similar to reports from other studies from North America (6), Africa (7), and Southeast Asia (8).

Our study did not include identification of organisms such as *Clostridium difficile*, *Yersinia* sp., *Bacillus cereus*, and other enterotoxigenic enterobacteriaceae (e.g., *Klebsiella*), which have recently become recognized as diarrhea-producing agents. Yet, 30% of our patients had bacterial causes found for their diarrheal illnesses; a more comprehensive investigation including the agents above would, no doubt, have identified even more. One of the most important findings was the frequency of multiple infections, especially with enterotoxigenic *Aeromonas* sp., *Salmonella*, *Campylobacter*, and rotavirus. This greatly complicates approaches to antibiotic therapy.

**INTESTINAL MICROFLORA IN CHILDHOOD DIARRHEA**

There is evidence of significant alteration of the upper gastrointestinal microflora in malnourished children with chronic diarrhea (9), and it has been linked causally with tropical enteritis (10). As discussed elsewhere (M. Gracey, *Chapter 11, this volume*), bacterial contamination of the upper gut results in a spectrum of clinical consequences including diarrhea and malabsorption, which have deleterious effects on nutritional state. The major underlying defects in these patients are:

1. Bacterial contamination of the proximal small bowel and impaired bacterial clearance.
3. Abnormal electrolyte and water flux with net transmucosal fluid accumulation.
4. Disruption to the integrity of the upper intestinal epithelium.

**ANTIBIOTICS AND THE UPPER GUT FLORA**

Gorbach and his colleagues showed clearance of predominantly coliforms colonizing the upper gut in 80% of adults with tropical malabsorption (10), and
this was accompanied by improved intestinal absorption. Antibiotic therapy has been accepted as effective in tropical sprue (11). Antibiotics have been used with some benefit in treating malnourished children (12), and Gorbach (10) has drawn the analogy with their use in animal husbandry to suggest that long-term, small-dose antibiotic treatment (e.g., in a food supplement) might have a place alongside wider strategies to combat childhood malnutrition. Others take an opposite view. Jon Rohde (13), working in Indonesia, found no benefits to a group of 100 children given antibiotics compared to the same number who were not and strongly discourages their use without specific indications. Without readily demonstrable benefits, the numerous well-documented disadvantages of antibiotic usage, including side effects, transferable drug resistance among bacteria and throughout communities, and their considerable expense, should limit their use to situations in which they are specifically indicated.

**ANTIBIOTICS IN GASTROENTERITIS**

Antibiotics often have to be used systemically in ill infants because of suspected underlying systemic infections such as meningitis or septicemia. Nonabsorbable antibiotics can also be used to try to prevent cross infection in nurseries, but this is often unsuccessful in serious outbreaks (14), and they should not be used in this situation unless other recognized methods to prevent cross infection cannot be effectively instituted.

There is little good evidence that antibiotics are useful even when specific bacterial causes of diarrhea have been found. This is not surprising in view of the diversity of mechanisms that might be involved in causing diarrhea; in ordinary clinical circumstances, particularly in developing countries, this information is unavailable to the medical attendant. However, Boyer et al. (15) found that nonabsorbable antibiotics appeared to help infants in a nursery outbreak of diarrhea caused by the enterotoxigenic *E. coli* O142:K86:H6, suggesting that therapy might have helped by reducing the numbers of toxin-producing bacteria within the intestinal lumen. Another report about *E. coli* gastroenteritis (16) suggests that toxigenic diarrheas might respond to antibiotics such as co-trimoxazole and mecillinam. A more recent study by the same workers in Sweden (17) showed that antibiotics were required (or used) in only four out of almost 100 consecutive patients with gastroenteritis; two of these had *Yersinia* infections, and one had *Campylobacter* enteritis. Despite this, our expanding knowledge of bacterial diarrheas has given added therapeutic options in those severely ill patients who will benefit from appropriate treatment, e.g., those with blood diarrhea and mucus in *Campylobacter* enteritis, who usually respond to erythromycin.

**Novel Antibacterial Processes**

Keusch (18) has discussed antibacterial therapy in a range of strategies to control the bacterial diarrheas. He points out that antibiotics have produced
problems of their own, e.g., in not shortening the clinical course of Salmonella gastroenteritis and prolonging its convalescent excretion, so causing an additional public health problem (19). The situation is different in shigellosis, and most authorities agree with the use of antibiotic treatment in Shigella enteritis, although the problem of transmitted multiple drug resistance is of increasing concern and in some places Sh. sonnei is often drug resistant (20). Keusch comments further on prospects for other approaches to antibacterial therapy, including methods that might be developed to immunologically inactivate virulence mechanisms, e.g., by neutralizing toxin binding at the mucosal surface or by devising antiadherence factors.

**Practical Applications**

For the present, however, antibiotic therapy has to be based on available antibacterial agents. Their use should be limited to those individuals who, on clinical grounds, will not improve without therapeutic intervention or who are suspected of having serious associated disease requiring antibiotics. In shigellosis, symptomatic treatment is usually adequate for mildly ill patients. In more seriously ill patients an appropriate antibiotic, e.g., ampicillin, can be used, and for children the dose is 50 mg/kg per day. Trimethoprim-sulfamethoxazole can be used if the organism is resistant to ampicillin. Typhoid fever is a gastrointestinal infection for which there is little argument that antibiotics should be used; chloramphenicol has the advantages of being quick acting, having few side effects, and being inexpensive in developing countries. Its disadvantages include drug resistance and bone marrow depression. Co-trimoxazole and amoxicillin are acceptable alternatives (20). For other Salmonella infections the decision to treat or not often depends on the severity of the illness and the presence or absence of disseminated infection or complicating disease. The choice of antibiotic to be used depends on local patterns of infection, epidemiology, and antibiotic sensitivities. This applies for other bacterial diarrheas, e.g., E. coli gastroenteritis, and hard and fast rules that are valid everywhere cannot be set down. Local decisions must be based on local knowledge.

**PARASITIC GUT INFECTIONS**

As with antibiotic therapy for bacterial diarrheas, decisions about treating parasitic infections of the gut should be based on local knowledge of the parasites, their response to alternative forms of treatment, and the availability of different drugs in different parts of the world. The comments that follow apply in my community but are not necessarily applicable elsewhere.

**Giardiasis**

Giardiasis and amebiasis are recognized as causes of mild to severe gastrointestinal disease in Australians, particularly in Aboriginals because of their gen-
erally inadequate standards of housing and community hygiene. Metronidazole (Flagyl®) has been used to good effect and with few side effects for many years (dose: 5 mg/kg t.d.s. for 7 days), and the older forms of treatment, e.g., mepacrine (known as quinacrine or atabrine in some places), are no longer used because of their unwelcome side effects, which include skin reactions, toxic psychosis, gastrointestinal upsets, and yellowing of the skin. Mepacrine could still be tried for infections resistant to the newer drugs. Metronidazole is usually given in a 7-day course of treatment, which has problems of noncompliance, particularly in groups such as the Aboriginals, who rarely complete courses of treatment without very close supervision. Tinidazole (Fasigyn®) is a more recent 5-imidazole drug that has been shown to be effective in metronidazole-resistant giardiasis. It has the additional appeal of being effective in a single-dose regimen and can be used against *Giardia lamblia* or *Entamoeba histolytica* (21). A recent study in an Aboriginal community in Queensland showed that tinidazole effectively cleared *Giardia lamblia* and *Entamoeba histolytica* from stool of Aboriginal children when given in a single dose of 1 to 1.5 g on three consecutive days (22). Furazolidine (Furoxone®) can also be used and has the advantage of being available in a liquid formulation (dose: 5–8 mg/kg per day for 7 days), but it appears to be less effective than the other drugs (23).

**Amebiasis**

Gastrointestinal infection with *Entamoeba histolytica* is very common in the tropics, and, contrary to common belief, infections are not uncommon between 1 and 2 years of age when acute intestinal amebic infection and acute liver abscess are common and carry a high morbidity and mortality (24). Metronidazole (35–50 mg/kg in three divided doses) can be used, but this and similar regimens may not eliminate the parasite from the gut lumen, and diloxanide furoate (Furamide®) can be used for this (20 mg/kg in divided doses for 10 days). Emetine or dehydroemetine is sometimes used for severely ill patients. Tinidazole (50 mg/kg per day for 3–5 days) has been used effectively in amebic dysentery (25) and liver abscess (26). In chronic and dysenteric amebiasis, it is recommended that two types of drugs be used to (a) act against the invading parasites in the tissues and (b) eradicate the parasites in the lumen by attacking them directly. The imidazole derivatives (e.g., metronidazole or tinidazole) are used for the former; the emetines, given parenterally (e.g., emetine or dehydroemetine), for the latter.

**Ascariasis**

*Ascaris lumbricoides* (roundworm) is a very common intestinal helminth which lives in the gut lumen and will respond to most antihelmintics such as pyantel pamoate, mebendazole, levamisol, or piperazine.
Trichuriasis

*Trichuris trichiura* (whipworm) can cause serious infections in malnourished children but usually responds well to treatment with mebendazole (100 mg b.d. for 3 days) or oxantel pamoate (10 mg/kg b.d. for 3 days).

The hookworms *Ancylostoma duodenale* and *Necator americanus* are common in the tropics, particularly in wet, monsoonal coastal environments. They are a major cause of severe anemias in Aboriginal children in tropical parts of Australia, and in our experience mebendazole (e.g., 100 mg b.d. for 3 days) is usually effective. Other drugs, e.g., pyrantel pamoate or bitoscanate can be used.

Strongyloidiasis

The small roundworm *Strongyloides stercoralis* is common in many environments and invades the tissues of the small intestine. It enters the body the same way as hookworm, through the skin, and goes through the heart and lungs and then via the airways to the upper gut. The only effective drug for this infection is thiabendazole at a dose of 25 mg/kg b.d. for 3 days. The drug should be taken after meals to lower its side effects.

REFERENCES