

SESSION 16

Antibiotics in the Management of Shigellosis in Children: What Role for the Quinolones?

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In the last 20 years, epidemic bacillary dysentery due to *Shigella dysenteriae* type 1 has become an important cause of serious morbidity and death in children less than 5 years of age in a number of developing countries; in many instances the infecting strains have been resistant to many or all of the usually recommended antibiotics. Moreover, an increasing proportion of *Shigella* strains of other serotypes isolated in all parts of the world are now resistant to the most commonly used antibiotics. The new fluoroquinolones have been shown to be active against *Shigella* in vitro and effective for the treatment of shigellosis in adults, but concern about the safety of quinolones has so far prevented the evaluation of these agents for the treatment of shigellosis in young children. Two observations, however, have led a Scientific Working Group of the World Health Organization to suggest that such studies would be appropriate for the following reasons: a one- or two-dose treatment is likely to be effective, and if so the amount of drug given would be far below the doses that have been determined to be toxic in animals; and nalidixic acid, which shares all the toxicity of the fluoroquinolones, is widely recommended — and in some areas routinely used — for the treatment of shigellosis in young children without reports of significant adverse effects. In the Group's view there is an urgent need to perform carefully conducted research to determine the safety and efficacy of fluoroquinolones for the treatment of shigellosis in children.

Shigellosis is an acute inflammatory disease of the gastrointestinal tract caused by bacteria belonging to the genus *Shigella* and characterized by fever, abdominal cramping pain, and loose stools, which may contain mucus, pus, and blood; however, some patients develop only acute, nonspecific watery diarrhea. Bacillary dysentery can also be caused by other enteric pathogens, especially *Campylobacter*, enteroinvasive *Escherichia coli*, and enterohemorrhagic *E. coli*. However, the only organism causing dysentery that is frequently associated with clinically severe disease that may result in death is *Shigella*. Since visible blood in the stool generally indicates a more severe form of the disease, this symptom has generally been chosen as the marker for recognition of clinically important bacillary dysentery.

Shigellosis has a global distribution; because the infection is transmitted by the fecal-oral route, the prevalence of the disease is highest in countries where hygiene and sanitation are poor. As few as 10–100

viable *Shigella* can cause the disease in adult volunteers; this probably explains why person-to-person transmission is the most common mode of spread of this disease.

Morbidity and Mortality Due to Shigellosis

During the last 20 years, endemic shigellosis (most often due to *Shigella flexneri* or *Shigella boydii*) and epidemic shigellosis (most often due to *Shigella dysenteriae* type 1) have been recognized as important causes of morbidity and death in children <5 years of age in many developing countries. In Bangladesh, a survey of patients hospitalized at the International Center for Diarrheal Diseases Research (ICDDR,B) in Dhaka over a 14-year period showed that 21% of all patients with bacillary dysentery due to *Shigella* were <1 year old and that 44% were from 1 to 4 years old [1]. A community-based survey carried out in a rural area of Bangladesh showed that 30% of cases of culture-proven shigellosis occurred in children <5 years old and 54% in children <10 years old [2].

No data concerning mortality rates due to dysen-

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tery are available from community-based studies. However, before the widespread implementation of oral rehydration therapy (ORT) for watery dehydrating diarrhea, it was estimated that shigellosis accounted for 15% of diarrheal deaths. As the use of ORT increases and deaths due to acute dehydration decline, this percentage would inevitably rise.

In patients hospitalized for shigellosis, reported mortality rates are between 1% and 10%, depending on the epidemiologic situation [3, 4]. During the 1972–1978 epidemic due to *S. dysenteriae* type 1, the case-fatality rate at the well-equipped hospital of the ICDDR,B was ~10%; in contrast, the case-fatality rate for cholera in the same hospital was ~0.5% during the same period.

Shigellosis is more frequently severe in young children, as shown by the case-fatality rates observed in 4 years (1969, 1974, 1980, and 1982) at the ICDDR,B hospital (table 1). In fact, 87% of the deaths in patients admitted to the hospital with shigellosis occurred in children <5 years of age, and 96% in children <10 years of age [1].

Risk factors that characterize children at highest risk of death from dysentery have been identified in several studies [4, 5]. These factors are summarized as follows: (1) malnutrition—severely malnourished children (i.e., those for whom the ratio of weight for age is <60% of the median of the standards of the National Center for Health Statistics) have a three- to sevenfold increased risk of dying, compared with better nourished children; (2) age—children with shigellosis who are <1 year old have a threefold increased risk of dying compared with children who are >1 year old; (3) children who have not been breast-fed; (4) moderate or severe dehydration at presentation; (5) absence of fever at presentation; (6) presence of bacteremia; and (7) persistent diarrhea (i.e., an episode of diarrhea lasting for >2 weeks).

It has been shown that among all diarrheal epi-

sodes of known etiology, shigellosis has the greatest negative impact on linear growth [6]. It was found that diarrheal episodes due to *Shigella* lasted longer than other types of diarrhea and caused greater losses of serum protein. Moreover, the problem of protein loss is exacerbated by poor dietary intake as a result of prolonged anorexia.

From the preceding, it is apparent that prevention or effective treatment of shigellosis would not only diminish mortality due to diarrhea but should also have a significant positive impact on growth and nutritional status.

Antibiotic Resistance

When combined with appropriate dietary management, ORT, which can prevent or treat clinically evident dehydration, is the basis for effective treatment of acute watery diarrhea. In shigellosis, however, antibiotics are required. When appropriately used, antibiotics have been shown to substantially reduce the severity of the illness and to shorten its duration [8, 9].

Some of the antibacterial agents that have been used to treat shigellosis are tetracycline (single or multiple doses), ampicillin (single or multiple doses), trimethoprim-sulfamethoxazole (TMP-SMZ; multiple doses for 5 days), nalidixic acid (multiple dose for 5 days), trimethoprim alone (multiple doses for 5 days), chloramphenicol, and ceftriaxone (intravenous).

The effectiveness of these agents has, however, been seriously impaired by the widespread emergence of bacterial resistance—often to multiple antibiotics—especially in *S. dysenteriae* type 1. Tetracyclines were the first widely used effective antibiotics administered in a single dose (2.5 g) or multiple doses over a 3- to 5-day period [10]. When *Shigella* developed resistance to tetracyclines, ampicillin became the drug of choice; however, in the early 1980s ampicillin-resistant strains appeared and became widespread in Asia [11] and Africa [12]. TMP-SMZ then became the drug of choice. However, shortly after it assumed this role, resistance appeared; for example, in 1980 100% of *Shigella* strains isolated in Dhaka, Bangladesh, were sensitive to TMP-SMZ, whereas 4 years later only 45% were sensitive [11].

These changing patterns of sensitivity were well illustrated during a recent epidemic of *S. dysenteriae* type 1 in Central Africa. At the beginning of the epidemic in 1980, the first isolates were already resis-

Table 1. Case-fatality rate for children hospitalized with shigellosis.

Age group	Case-fatality rate (%)
<1 y	13.8
1–4 y	8.3
5–9 y	5.1
≥10 y	0.1

NOTE. Data are from [1].

tant to ampicillin, tetracyclines, chloramphenicol, and sulfonamides; therefore, TMP-SMZ was widely used as therapy. By 1982, resistance to TMP-SMZ had become a major problem, occurring almost equally in both epidemic and endemic strains.

The emergence of strains resistant to the three major antimicrobial agents (tetracycline, ampicillin, and TMP-SMZ) led to the use of nalidixic acid, although evidence of its efficacy, based on results of controlled studies, was scanty. Indeed, a study performed in 1973 [13] had shown that although nalidixic acid was effective *in vitro* against most strains of *Shigella*, stool cultures remained positive longer in patients who received nalidixic acid than in those who received ampicillin, and the clinical response was slower. In fact, the authors concluded that "nalidixic acid had little effect on the course of the disease." Nevertheless, nalidixic acid is now being used for the initial treatment of shigellosis in many countries where strains resistant to other antibiotics are commonly encountered (e.g., Bangladesh, India, Rwanda).

The need for more effective antimicrobial agents for the treatment of shigellosis is evident. The Diarrhoeal Diseases Control (CDD) Programme of the World Health Organization has therefore made one of its research priorities the identification of alternative antibiotics for use in the treatment of shigellosis in young children in areas where severe illness due to strains resistant to ampicillin and TMP-SMZ occurs. Some of the drugs now under consideration are as follows:

(1) *Oral gentamicin.* Nearly all *Shigella* strains are sensitive to gentamicin *in vitro*; however, this drug is not absorbed from the gastrointestinal tract, and it is not likely that therapeutic concentrations of the drug are attained in the bowel wall. In China, oral gentamicin is considered effective and widely used; however, there are no controlled studies that establish its efficacy.

(2) *Pivmecillinam.* This penicillin analogue, given orally, has been shown to be effective for the treatment of adults with shigellosis in Bangladesh [14].

(3) *Bicozamycin.* This is a nonabsorbable antibiotic with a wide spectrum of activity against gram-negative enteric organisms and no relationship to other widely used antibiotics. Despite its being nonabsorbable, bicozamycin was shown to be effective in treating diarrhea due to *Shigella* in adult travelers [15]. However, bicozamycin is not marketed at present.

(4) *Doxycycline.* A single study has shown that adults infected with tetracycline-resistant *Shigella* (resistant to 12.5 mg/L) responded adequately to treatment with a single large oral dose (2.5 g) of tetracycline [10]. The possibility that doxycycline, a long-acting tetracycline, given in a single dose may be effective even for antibiotic-resistant strains should be explored.

(5) *Fluoroquinolones.*

The Fluoroquinolones

The new quinolone antibiotics (fluoroquinolones) are closely related to nalidixic acid and have been shown to be highly effective *in vitro* against *Shigella*. The MIC₅₀ and MIC₉₀ of nalidixic acid and of five fluoroquinolones for *Shigella* are compared in table 2 [16]. This table shows that the new quinolones are highly active *in vitro* against *Shigella*. Norfloxacin and ciprofloxacin seem to be less completely absorbed from the gastrointestinal tract than are the other fluoroquinolones; these two antibiotics have also been reported to achieve a high concentration in stools (773 mg/L for norfloxacin and 891 mg/L for ciprofloxacin) [17]. In addition, 48 hours after a single 400-mg oral dose of norfloxacin, a high level of the antibiotic (>40 µg/g) remains in the feces [18].

For these reasons, norfloxacin and ciprofloxacin appear to be promising agents for use in the treatment of shigellosis. The high concentration of the drug still present in the feces 48 hours after a single 400-mg oral dose leads us to consider that single-dose therapy (or perhaps a daily dose given for 2 days) might be effective for the treatment of shigellosis. A simple treatment regimen of this type would be advantageous for the provision of effective therapy under conditions where the reliable delivery of medication for a longer period is very difficult.

Clinical studies with oral fluoroquinolones mostly

Table 2. *In vitro* activity against *Shigella* of 5-fluoroquinolones and nalidixic acid.

Compound	Concentration (mg/L)	
	MIC ₅₀	MIC ₉₀
Nalidixic acid	4.0	4.0
Norfloxacin	0.03	0.03
Ciprofloxacin	0.02	0.02
Ofloxacin	0.1	0.1
Enoxacin	0.1	0.2
Pefloxacin	0.06	0.06

concern the use of these drugs in infections of the genitourinary tract. One published study, however, compared the efficacy of norfloxacin vs. nalidixic acid in the treatment of adults with shigellosis during an epidemic in Rwanda due to *S. dysenteriae* type 1 [19]. The results of this study suggest that norfloxacin is superior to nalidixic acid with respect to clinical response and elimination of *Shigella* from the stools. However, because of the limited number of patients treated in this study and because it was not controlled, no definite conclusions could be drawn. Other studies of adults have shown that *Shigella* was eradicated within 48 hours after the administration of norfloxacin and that the clinical response in patients receiving norfloxacin was similar to that observed in patients receiving TMP-SMZ [18, 20].

As mentioned above, the new quinolones are closely related to nalidixic acid and therefore also share the toxicities of that drug, including effects on the CNS (lightheadedness, headache, drowsiness, and insomnia); cutaneous reactions (skin rash and pruritus, phototoxic reactions ranging from mild erythema in areas exposed to the sun to extensive bullous eruptions that mimic porphyria [21]); and rheumatologic symptoms (swelling and stiffness of the joints, arthralgia, myalgia [17, 21]).

However, the number of adverse effects reported to date among patients treated with fluoroquinolones appears to be low (5%–25%); therapy has been discontinued as a result of development of adverse reactions in only 1%–3% of patients [21].

Toxicity to cartilage, known to be a characteristic of nalidixic acid, has also been reported in animals treated with fluoroquinolones. This toxicity includes inhibition of the growth of juvenile cartilage; inhibition of the growth of cartilaginous limb buds in embryonic mice; and erosions of the articular cartilage, with hypertrophy and eosinophilia of the chondrocytes, in dogs given high doses of nalidixic, oxolinic, or pipemidic acids (200–350 mg/kg) [22–24].

The relationship of these experimental results to the rheumatologic symptoms observed in patients treated with nalidixic acid is still uncertain. Indeed, nalidixic acid has been used for years for the treatment of childhood infections without any report of secondary arthropathy [25, 26]. Arthropathies have been reported in patients being treated with the newer quinolones [17], but these patients were all receiving long-term therapy for chronic infection. The adverse effects, including the rheumatologic symptoms, observed with the newer quinolones all regressed

when therapy was discontinued, without any need for additional specific treatment.

However, because the toxic effect on bone and cartilage of the newer quinolones is an important concern, fluoroquinolones have not yet been recommended for routine use in pregnant women and in children <15 years of age, whose skeletal growth is incomplete.

Consideration of the Use of Fluoroquinolones to Treat Shigellosis in Young Children

Concern about the safety of fluoroquinolones has until now prevented the evaluation of these drugs for the treatment of shigellosis in young children. However, a review of available information on the safety and efficacy of these agents by the Scientific Working Group on Case Management of the WHO/CDD Programme suggests that this view may be overly cautious for the following reasons:

(1) There is an evident and urgent need for new effective antimicrobial agents for the treatment of shigellosis in young children as a result of the widespread occurrence of strains resistant to available agents.

(2) The new fluoroquinolones have been shown to be active in vitro against *Shigella* (and *Campylobacter* species, another important cause of dysentery in young children), and limited evidence suggests that they are also effective in vivo.

(3) Nalidixic acid, which shares all the cartilage toxicity of the fluoroquinolones, is licensed for use in children and is widely recommended for the treatment of shigellosis in young children without any report of major adverse effects [28].

(4) The occurrence of the rheumatologic symptoms associated with the fluoroquinolones seems to be related to the amount of drug absorbed and the duration of treatment. Because of the high concentration of the drug achieved in the feces after even one dose, the amount to be given in a single dose or even a 2-day treatment would be far below that which causes toxic signs in experimental animals. However, a careful monitoring of any adverse effect during the treatment and in the months following should be performed when using the newer quinolones in children, especially in children whose calcium metabolism or growth may be impaired by serious malnutrition.

(5) A risk-benefit analysis of the use of fluoroquinolones in children <15 years of age suggests that

the risks associated with fluoroquinolone treatment in this age group are far outweighed by the benefits that effective treatment of this life-threatening disease could provide [29].

Conclusion

It is likely that the fluoroquinolones could play an important role in the reduction of the morbidity and mortality due to shigellosis in young children infected with strains that are resistant to conventional antibiotics. Because the drug would probably be administered either as a one-dose treatment, or at most for 2 days, the amount given would be far below that which causes toxic signs in animals. Although this reasoning does not constitute a recommendation for the routine use of fluoroquinolones for the treatment of shigellosis in children, it does suggest that carefully conducted research to determine the safety and efficacy of these agents should be performed, a view also supported by the Scientific Working Group on Case Management of the WHO Programme for Control of Diarrhoeal Diseases. This group has concluded that the information derived from such studies would contribute substantially to efforts to develop better tools for the control of this important cause of morbidity and mortality in children.

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