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Leading article

Rethinking options for the treatment of shigellosis

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Shigellosis remains a major cause of death of children in developing countries. It also causes substantial morbidity in developed countries, especially among children in day care centres, residents of custodial institutions, and those living in impoverished communities, and is a common cause of travellers' diarrhoea (Bennish & Wojtyniak, 1991). Effective antimicrobial therapy of shigellosis can reduce both the severity and duration of diarrhoea, and the incidence of potentially lethal complications (Salam & Bennish, 1991). For the past 25 years either ampicillin or co-trimoxazole have been the drugs of choice for treating shigellosis (Salam & Bennish, 1991). These two drugs have several attributes that make them ideal agents to treat shigellosis. Both drugs attain sufficient concentrations in the serum and gut lumen to inhibit the growth of *Shigella* spp.; they can be safely used in children; they are inexpensive; both have been found effective in controlled clinical trials; and until recently almost all strains of *Shigella* spp. were susceptible to one or both of these agents.

Although most reference textbooks continue to recommend one of these two agents as first line therapy for shigellosis (Dupont, 1990), an increasing proportion of shigella infections (indeed probably the majority of those occurring worldwide) are caused by strains that are resistant to both drugs. In the early 1980s strains of *Shigella dysenteriae* type 1 resistant to both ampicillin and co-trimoxazole were identified (Malengreau *et al.*, 1983; Bennish *et al.*, 1985; Frost *et al.*, 1985; Panhotra, Desai & Sharma, 1985); subsequent studies have reported an increasing prevalence of resistance to these two agents among all species of *Shigella* (Table). Most reports of multiresistant infections have come from developing countries in Asia, Africa, and Latin America (Chun *et al.*, 1984; Jegathesan, 1984; Chugh *et al.*, 1985; Frost *et al.*, 1985., Huq *et al.*, 1987; Centers for Disease Control, 1991; Vibulbandhitkit & Poonyarit, 1991; Bennish *et al.*, 1992*a*). Because of this increase in the prevalence of strains resistant to both ampicillin and co-trimoxazole, neither agent can be used with confidence in developing countries as empirical therapy for shigellosis. Except for endemic multi-resistant *Shigella flexneri* in isolated communities, such as a Navajo reservation in the USA (Griffin *et al.*, 1989), and limited outbreaks of multi-resistant *Shigella sonnei*, also in the USA (Centers for Disease Control, 1986, 1987), most multi-resistant shigella infections in Northern Europe and North America occur in persons who have recently travelled to a developing country (Gross, Thomas & Rowe, 1979); Heikkilä *et al.*, 1990; Tauxe *et al.*, 1990).

The quinolone agents are the primary alternatives to ampicillin and co-trimoxazole for the treatment of shigellosis. When therapy for shigellosis was last reviewed in a leading article in this journal in 1987, the quinolones appeared to be promising agents for the treatment of shigellosis, but had been little studied (Jewes, 1987). Since then the quinolones have been both extensively evaluated and used in the treatment of shigellosis. Nalidixic acid, an agent now rarely if ever used in developed countries, has become the drug of choice for treating patients with shigellosis in Bangladesh and many other developing countries (Salam & Bennish, 1988). Five days therapy with nalidixic acid produces a more rapid decrease in the frequency of diarrhoea than ampicillin, although bacteriological resolution is slower (Salam & Bennish, 1988). Nalidixic acid is inexpensive and available as an elixir for use in children, among whom the majority of shigella infections occur. Unfortunately, resistance to nalidixic acid appears relatively rapidly. For instance, nalidixic acid was introduced for the treatment of shigellosis in Bangladesh in 1986; by 1990 58% of *S. dysenteriae* type 1 isolates obtained from patients at the Diarrhoea Treatment Centre of the International Centre for Dirrhoeal Disease Research, Bangladesh in Dhaka were resistant (Bennish *et al.*, 1992*a*). Resistance to nalidixic acid among other

Table. Prevalence of ampicillin and co-trimoxazole resistant *Shigella* spp. in eight countries

Author	Country	Year isolates obtained	*S. dysenteriae* number of isolates	% resistant to Amp	% resistant to Co-tr[a]	*S. flexneri* number of isolates	% resistant to Amp	% resistant to Co-tr[a]	Other *Shigella* species number of isolates	% resistant to Amp	% resistant to Co-tr[a]
Uwaydah & Osseiran (1981)	Ethiopia	1980	7	29	15	66	32	6	29	3	31
Chun *et al.* (1984)	Korea	1980–81	6	17	17[b]	338	87	92[b]	65	3	97[b]
Jegathesan (1984)	Malaysia	1980–81	—	—	—	351	84	49	54	22	85
Chugh *et al.* (1985)	Kuwait	1982–83	7	57	43	99	62	39	47	64	42
Huq *et al.* (1987)	Saudi Arabia	1983–84	59	53	17	173	70	56	342	29	25
Griffin *et al.* (1989)	USA (Navajo Reservation)	1985	—	—	—	207	40	20	102	85	21
Tauxe *et al.* (1990)	USA	1985–86	2	0	0	88	19	9	162	39	7
Lolekha *et al.* (1991)	Thailand	1988	46	22	70	1280	98	88	219	38	65
Bennish *et al.* (1992*a*)	Bangladesh	1983	4732	54	85	8537	46	23	2084	18	21

[a]The disc-diffusion method was used to determine susceptibility in all studies except that of Chun *et al.* (1984) in which a plate-dilution method was used.
[b]Susceptibility determined only to the trimethoprim component.
Amp, Ampicillin; Co-tr, co-trimoxazole.

species of *Shigella* remains uncommon, with only 3% of isolates obtained in Dhaka being resistant (Bennish *et al.*, 1992*a*).

Virtually all shigella strains, including nalidixic acid resistant strains, currently remain susceptible to the newer, fluorinated quinolones. Five day courses of ciprofloxacin, norfloxacin, and enoxacin, have been evaluated in controlled clinical trials for the treatment of shigellosis, and found effective (Rogerie *et al.*, 1986; De Mol *et al.*, 1987; Bennish *et al.*, 1990). Because many of the newer quinolones have relatively long half-lives, and their in-vitro activity against shigella is much greater than for other orally administered agents, they are ideal candidates for short course therapy. Single dose courses of both norfloxacin and ciprofloxacin have been evaluated for the treatment of shigellosis in controlled clinical trials (Gotuzzo *et al.*, 1989; Bennish *et al.*, 1992*b*). Both are effective in the treatment of infections caused by species other than *S. dysenteriae* type 1. The relative lack of efficacy of single dose regimens for treatment of *S. dysenteriae* type 1 infections may have been due to the higher concentrations of quinolones required to inhibit growth of *S. dysenteriae* type 1 strains when compared to other *Shigella* species, or because *S. dysenteriae* type 1 infected patients had more severe disease when they presented for care (Bennish *et al.*, 1992*b*).

Despite the proven efficacy of the newer quinolones in the treatment of shigellosis, and the almost universal susceptibility of *Shigella* spp. to them, there are at least three factors limiting the routine use of these agents. One factor is the uncertainty with regard to the safety of these agents in children (Douidar & Snodgrass, 1989). All quinolones, including nalidixic acid, cause arthropathy in selected species of juvenile animals. Most national drug regulatory agencies have approved nalidixic acid for use in children older than three months. This approval was given in the 1960s, long before information concerning quinolone induced cartilaginous toxicity in animals became available. The newer quinolones, in contrast, have not been approved for use in children. Because of these concerns there has been little effort to evaluate the newer quinolones in children, and elixir preparations are not currently available. Before the newer quinolones can be widely recommended for the treatment of shigellosis, further information on their safety in children, and on the pharmacokinetics of any elixir preparations, will be required.

A further limitation to the use of quinolones in the treatment of shigellosis, especially in developing countries, is cost. A five day course of either ampicillin or co-trimoxazole costs less than 50 pence in most developing countries. Single doses of the newer quinolones in the USA and most other developed countries are four to eight times higher (Leading article, 1988). If priced similarly in developing countries, where per capita income is often less than 50 pence per day, many will not be able to afford it. A third concern is that indiscriminate use could lead to the rapid development of resistance, as has occurred with nalidixic acid. Although the frequency with which Enterobacteriaceae develop resistance *in vitro* to the newer quinolones is lower than for nalidixic acid (Sanders *et al.*, 1984), if selective pressure is great enough then it is likely that fluoroquinolone resistant strains of shigella will emerge. The identification of quinolone-resistant strains of *Campylobacter jejuni* following therapy with ciprofloxacin provides cause for concern in this regard (Petrucelli *et al.*, 1992).

Pivmecillinam and ceftriaxone are the only drugs, other than the new quinolones, that have been shown to be effective for the treatment of shigellosis in controlled clinical trials, and to which the majority of multi-resistant strains remain susceptible (Kabir *et al.*, 1984; Varsano *et al.*, 1991). Although pivmecillinam is not widely marketed, it is safe for use in children, and can be given as an oral suspension. The usefulness of ceftriaxone, especially in field settings in developing countries, is limited by the need to administer it parenterally. Evaluation of the effectiveness of oral third-generation cephalosporins, most of which have good in-vitro activity against multi-resistant strains of *Shigella* spp., is now under way. Should these agents prove effective they will provide an additional alternative to pivmecillinam and the quinolones for treating multi-resistant shigella infections.

Given the problems posed by the emergence of *Shigella* spp. resistant to ampicillin and co-trimoxazole, what are the current options for antimicrobial therapy of shigellosis? For patients in developed countries, unless there is a history of recent travel to a developing country, it is likely that the infecting strain will continue to be susceptible to either ampicillin or co-trimoxazole. Although standard treatment regimens call for five days therapy, the practical advantages of single dose therapy in adults with a newer quinolone, or with ampicillin (which has been shown effective when

given as a single 2 g dose (Gilman *et al.*, 1981)) are considerable. Children should continue to be treated with five days of either ampicillin or co-trimoxazole.

The treatment of shigellosis in developing countries is complicated by the high prevalence of resistant strains, and the need to treat most patients empirically, since diagnostic laboratory services are usually not available. Unless there is recent microbiological data indicating that the majority of *Shigella* spp. in the community remain susceptible to either co-trimoxazole or ampicillin, it should be assumed that the infecting isolate is resistant to these two agents. Nalidixic acid has been the preferred alternative therapy. If *S. dysenteriae* type 1 infection is suspected, however, and nalidixic acid resistant strains of *S. dysenteriae* type 1 have been identified, pivmecillinam should be given. If nalidixic acid is given as initial therapy, patients should be re-evaluated in 48 h. Those without substantial clinical improvement should be treated with pivmecillinam or a newer quinolone.

In developing countries newer quinolone agents should currently be held in reserve for treatment of strains resistant to nalidixic acid and pivmecillinam. If the newer quinolone agents prove safe for use in children, and if they become less expensive, they will most probably supplant other agents and become the treatment of choice for shigellosis.

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References

Bennish, M., Eusof, A., Kay, B. & Wierzba, T. (1985). Multiresistant *Shigella* infections in Bangladesh. *Lancet ii*, 441.

Bennish, M. L., Salam, M. A., Haider, R. & Barza, M. (1990). Therapy for shigellosis. II. Randomized, double-blind comparison of ciprofloxacin and ampicillin. *Journal of Infectious Diseases* **162**, 711–6.

Bennish, M. L., Salam, M. A., Hossain, M. A., Myaux, J., Haque, E., Chakraborty, J. *et al.* (1992*a*). Antimicrobial resistance of *Shigella* isolates in Bangladesh, 1983–1990; increasing frequency of strains multiply resistant to ampicillin, trimethoprim-sulfamethoxazole, and nalidixic acid. *Clinical Infectious Diseases* **14**, 1055–60.

Bennish, M. L., Salam, M. A., Khan, W. A. & Khan, A. M. (1992*b*). Treatment of shigellosis, III. Randomized, blinded comparison of one- or two-dose ciprofloxacin with standard 5 day therapy. *Annals of Internal Medicine*, in press.

Bennish, M. L. & Wojtyniak, B. J. (1991). Mortality due to shigellosis: community and hospital data. *Reviews of Infectious Diseases* **13**, *Suppl. 4*, S245–51.

Centers for Disease Control. (1986). Multiply resistant shigellosis in a day-care center—Texas. *Morbidity and Mortality Weekly Report* **35**, 753–5.

Centers for Disease Control. (1987). Nationwide dissemination of multiply resistant *Shigella sonnei* following a common-source outbreak. *Morbidity and Mortality Weekly Report* **36**, 633–4.

Centers for Disease Control. (1991). *Shigella dysenteriae* type-1—Guatemala, 1991. *Morbidity and Mortality Weekly Report* **40**, 421, 427–8.

Chugh, T. D., Suheir, A., Mahboob, A. G., Neil, L. & El-Bishbishi, E. (1985). Plasmid-mediated drug resistance of shigellae in Kuwait. *Antonie van Leeuwenhoek* **51**, 241–7.

Chun, D., Cho, D. T., Seol, S. Y., Suh, M. H. & Lee, Y. C. (1984). R plasmids conferring multiple drug resistance from shigella isolated in Korea. *Journal of Hygiene* **92**, 153–60.

De Mol, P., Mets, T., Lagasse, R., Vandepitte, J. Mutwewingabo, A. & Butzler, J. P. (1987). Treatment of bacillary dysentery: a comparison between enoxacin and nalidixic acid. *Journal of Antimicrobial Chemotherapy* **19**, 695–8.

Douidar, S. M. & Snodgrass, W. R. (1989). Potential role of fluoroquinolones in pediatric infections. *Reviews of Infectious Diseases* **11**, 878–89.

DuPont, H. L. (1990). Shigella species (bacillary dysentery). In *Principles and Practice of Infectious Diseases*, 3rd edn (Mandell, G. L., Douglas, R. G. & Bennett, J. E., Eds), pp. 1716–22. Churchill Livingstone, New York.

Frost, J. A., Willshaw, G. A., Barclay, E. A., Rowe, B., Lemmens, P. & Vandepitte, J. (1985). Plasmid characterization of drug-resistant *Shigella dysenteriae* 1 from an epidemic in Central Africa. *Journal of Hygiene* **94**, 163–72.

Gilman, R. H., Spira, W., Rabbani, H., Ahmed, W., Islam, A. & Rahaman, M. M. (1981). Single-dose ampicillin therapy for severe shigellosis in Bangladesh. *Journal of Infectious Diseases* **143**, 164–9.

Gotuzzo, E., Oberhelman, R. A., Maguiña, C., Berry, S. J., Yi, A., Guzman, M. *et al.* (1989).

Comparison of single-dose treatment with norfloxacin and standard 5-day treatment with trimethoprim-sulfamethoxazole for acute shigellosis in adults. *Antimicrobial Agents and Chemotherapy* **33**, 1101–4.

Griffin, P. M., Tauxe, R. V., Redd, S. C., Puhr, N. D., Hargrett-Bean, N. & Blake, P. A. (1989). Emergence of highly trimethoprim-sulfamethoxazole-resistant *Shigella* in a native American population: an epidemiologic study. *American Journal of Epidemiology* **129**, 1042–51.

Gross, R. J., Thomas, L. V. & Rowe, B. (1979). *Shigella dysenteriae, Sh. flexneri*, and *Sh. boydii* infections in England and Wales: the importance of foreign travel. *British Medical Journal ii*, 744.

Heikkilä, E., Siitonen, A., Jahkola, M., Fling, M., Sundström, L. & Huovinen, P. (1990). Increase of trimethoprim resistance among *Shigella* species, 1975–1988: analysis of resistance mechanisms. *Journal of Infectious Diseases* **161**, 1242–8.

Huq, M. I., Al Ghamdi, M. A., Haider, K. & Alim, A. R. M. A. (1987). Antimicrobial susceptibility pattern of the clinical isolates of *Shigella* sp. in the eastern province of Saudia Arabia. *Asian Medical Journal* **30**, 228–34.

Jegathesan, M. (1984). Serotype prevalence and antibiotic susceptibility of *Shigella* strains isolated in Malaysia during 1980 and 1981. *Journal of Diarrhoeal Diseases Research* **2**, 102–4.

Jewes, L. A. (1987). Antimicrobial therapy of non-typhi salmonella and shigella infection. *Journal of Antimicrobial Chemotherapy* **19**, 557–60.

Kabir, I., Rahaman, M. M., Ahmed, S. M., Akhter, S. Q. & Butler, T. (1984). Comparative efficacies of pivmecillinam and ampicillin in acute shigellosis. *Antimicrobial Agents and Chemotherapy* **25**, 643–5.

Leading article. (1988). Ciprofloxacin. *Medical Letter on Drugs and Therapeutics* **30**, 11–3.

Lolekha, S., Vibulbandhitkit, S. & Poonyarit, P. (1991). Response to antimicrobial therapy for shigellosis in Thailand. *Reviews of Infectious Diseases* **13**, *Suppl. 4*, S342–6.

Malengreau, M., Molima-Kaba, Gillieaux, M., de Feyter, M., Kyele-Duibone & Mukolo-Ndjolo. (1963). Outbreak of *Shigella* dysentery in Eastern Zaire, 1980–1982. *Annales de la Société Belge de Médecine Tropicale* **63**, 59–67.

Panhotra, B. R., Desai, B. & Sharma, P. L. (1985). Nalidixic-acid-resistant *Shigella dysenteriae* I *Lancet i*, 763.

Petruccelli, B. P., Murphy, G. S., Sanchez, J. L., Walz, S., DeFraites, R., Gelnett, J. *et al.* (1992). Treatment of traveler's diarrhea with ciprofloxacin and loperamide. *Journal of Infectious Diseases* **165**, 557–60.

Rogerie, F., Ott, D., Vandepitte, J., Verbist, L., Lemmens, P. & Habiyaremye, I. (1986). Comparison of norfloxacin and nalidixic acid for treatment of dysentery caused by *Shigella dysenteriae* type 1 in adults. *Antimicrobial Agents and Chemotherapy* **29**, 883–6.

Salam, M. A. & Bennish, M. L. (1988). Therapy for shigellosis. 1. Randomized, double-blind trial of nalidixic acid in childhood shigellosis. *Journal of Pediatrics* **113**, 901–7.

Salam, M. A. & Bennish, M. L. (1991). Antimicrobial therapy for shigellosis. *Reviews of Infectious Diseases* **13**, *Suppl. 4*, S332–41.

Sanders, C. C., Sanders, W. E., Goering, R. V. & Werner, V. (1984). Selection of multiple antibiotic resistance by quinolones, β-lactams, and aminoglycosides with special reference to cross-resistance between unrelated drug classes. *Antimicrobial Agents and Chemotherapy* **26**, 797–801.

Tauxe, R. V., Puhr, N. D., Wells, J. G., Hargrett-Bean, N. & Blake, P. A. (1990). Antimicrobial resistance of *Shigella* isolates in the USA: the importance of international travelers. *Journal of Infectious Diseases* **162**, 1107–11.

Uwaydah, M. & Osseiran, M. (1981). Susceptibility of recent *Shigella* isolates to mecillinam, ampicillin, tetracycline, chloramphenicol, and cotrimoxazole. *Journal of Antimicrobial Chemotherapy* **7**, 619–22.

Varsano, I., Eidlitz-Marcus, T., Nussinovitch, M. & Elian, I. (1991). Comparative efficacy of ceftriaxone and ampicillin for treatment of severe shigellosis in children. *Journal of Pediatrics* **118**, 627–32.