THERAPEUTIC DILEMMA

Options for Treating Resistant *Shigella* Species Infections in Children

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Infection due to *Shigella* species remains an important public health problem, especially in developing countries where it remains the most common cause of bloody diarrhea. In the United States (US), 10,000 to 15,000 cases of shigellosis are reported each year in both children and adults. US surveillance data from 2004 has demonstrated increased resistance in *Shigella* species to first-line antibiotics such as ampicillin and trimethoprim-sulfamethoxazole, with approximately 37% of isolates demonstrating resistance to both ampicillin and trimethoprim-sulfamethoxazole. Since approximately 69% of *Shigella* infections occur in children younger than 5 years of age, it is important that alternative antibiotics other than typical first-line agents such as ampicillin and trimethoprim-sulfamethoxazole be available to treat *Shigella* infections in this population. The American Academy of Pediatrics (AAP) recommends cefixime, ceftriaxone, azithromycin, and fluoroquinolones as alternative antibiotics for the treatment of *Shigella* species infections in children. This paper will review the microbiology, susceptibility, efficacy and safety data of these alternative antibiotics with regard to the treatment of *Shigella* species infections in children, and will attempt to define the role of each of these agents in the pediatric population.

KEYWORDS antibiotics, children, infection, *Shigella* species

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TEACHING CASE

A 6-year-old, 21 kg African American girl presented to the Urgent Visit Center of a large teaching hospital with complaints of fever, vomiting, abdominal pain, and bloody diarrhea for the past 24 hours. The patient had no significant past medical history, but had been in close contact with her classmates who had recently been diagnosed with a similar illness. The patient had been feeling well until 24 hours prior to the visit, at which time she developed fever (up to 102°F at home), abdominal pain, vomiting (four episodes within the past 24 hours), and multiple bloody diarrhea bowel movements (six episodes within 24 hours). She also complained of a poor appetite and limited fluid intake over the past 24 hours. The morning of the clinic visit, the mother found the child lying on the bathroom floor in the fetal position in an attempt to alleviate the abdominal pain.

The patient was observed walking into the Urgent Visit Center bent over holding her

ABBREVIATIONS AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention; CLSI, Clinical and Laboratory Standards Institute; IM, intramuscular; MIC, Minimum Inhibitory Concentration; NARMS, National Antimicrobial Resistance Monitoring System; TMP-SMX, trimethoprim-sulfamethoxazole

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abdomen. The physical examination revealed a well developed, well nourished child in moderate distress. Her oral temperature was 101.9°F, and her exam was benign except for moderate abdominal pain both above and below her navel.

The patient was transferred to the Emergency Department for further diagnostic testing to rule out appendicitis or acute abdomen. The patient was given intravenous fluids, underwent a computed tomography scan (which revealed no significant findings), and a stool specimen was submitted for microbiologic analysis. On microscopic analysis, the stool specimen was found to contain red and white blood cells. The recent illness in her classmates was determined to be a local *Shigella* species outbreak that displayed antibiotic resistance. Therefore, the child was empirically prescribed azithromycin suspension 12 mg/kg (250 mg) po for the first day followed by 6 mg/kg po daily (125 mg) for the next 4 days. Several days later, the results of the stool culture revealed *Shigella sonnei* group D that displayed intermediate susceptibility to ampicillin (MIC 16 μg/mL), was resistant to trimethoprim-sulfamethoxazole (TMP-SMX) (MIC > 16/304 μg/mL), and was susceptible to ciprofloxacin (MIC ≤ 0.25 μg/mL). The patient was evaluated at a follow-up clinic visit with her pediatrician several weeks later, and was found to be clinically improved from her infection.

DISCUSSION

Shigella species are Gram-negative facultative bacilli of the Enterobacteriaceae family that are divided into four species based on biochemical and serological differences, namely, *Shigella dysenteriae* (serogroup A), *Shigella flexneri* (serogroup B), *Shigella boydii* (serogroup C), and *Shigella sonnei* (serogroup D). Infection due to *S sonnei* is most often associated with relatively mild illness manifested by bloody or watery diarrhea, while infection due to *S dysenteriae* type 1 is often associated with more severe infection and antimicrobial resistance.[1]

Infection due to *Shigella* species remains an important public health problem, especially in developing countries with unsafe water supplies and inadequate sanitation, where it remains the most common cause of bloody diarrhea worldwide.[1] Approximately 10,000 to 15,000 cases of shigellosis are reported each year in the US, occurring primarily in children who attend day care centers, migrant workers, travelers to developing countries, institutionalized individuals, and homosexual men.[2-4] The primary mode of transmission of *Shigella* species is by direct contact with an infected person or by eating contaminated food or drinking contaminated water, with ingestion of as few as 10 to 200 organisms required to cause infection.[1-5]

Shigella species primarily infect the colonic mucosa of humans, producing a broad spectrum of clinical symptoms ranging from a short duration of loose or watery stools to shigellosis (dysentery) manifested as fever, abdominal pain or cramps. mucoid bloody stools, and tenesmus.[1,3-6] In addition, inflammatory colitis may occur when *Shigella* species intensely invade the distal colon.[4] Constitutional clinical symptoms such as fatigue, fever, and malaise usually occur within 1 to 2 days of ingesting the organisms, which then progress to watery diarrhea and, in some cases, dysentery.

The management of a patient with infection due to *Shigella* species includes correcting fluid and electrolyte losses, administering appropriate empiric anti-infective therapy, and routine microscopy with stool culture.[1,3-5] Routine microscopy and stool culture help distinguish *Shigella* species infection from other causes of bloody diarrhea, and provide information on the antimicrobial susceptibility of the organism.[1] Although infectious diarrhea due to *Shigella* species is self-limiting in many cases, many experts believe that patients with positive stool cultures for *Shigella* species should be treated to shorten the duration of clinical symptoms and decrease fecal excretion of the organism to minimize transmission.[1,3-6] Therefore, in children with suspected *Shigella* species infection, empiric antibiotic therapy is usually administered while waiting for the stool culture and susceptibility results. Many patients often experience symptomatic relief before the results are available. Because of the emerging resistance in *Shigella* species to typical first-line antibiotics such as ampicillin and TMP-SMX, empiric antimicrobial therapy should now be selected based on local susceptibility patterns of circulating *Shigella*

species strains.

Since 1999, the National Antimicrobial Resistance Monitoring System (NARMS), supported by the Centers for Disease Control and Prevention (CDC), has been annually performing antimicrobial surveillance among enteric bacteria submitted by participating state public health laboratories in the US. During 2003 and 2004, 810 clinical isolates of *Shigella* species obtained from children and adults were submitted to NARMS for antimicrobial susceptibility testing using broth microdilution for MIC determination.[7] Most of the isolates were from stool cultures, with *Shigella sonnei* representing 83% of the *Shigella* species analyzed. The rates of resistance of these *Shigella* species to various antimicrobial agents are depicted in Table 1. Resistance to first-line antibiotics such as ampicillin and TMP-SMX remains high (77.8% and 51.4%, respectively), while resistance to fluoroquinolones, third generation cephalosporins, and gentamicin remains low. When examining the resistance patterns of the *Shigella* species isolates, 33.7% of isolates displayed resistance to both ampicillin and TMP-SMX in 2003, while 37.8% of isolates displayed resistance to both antimicrobials in 2004. This recent data heightens the awareness of the emergence of antimicrobial resistance in *Shigella* species, and supports the need for continuous surveillance of clinical isolates to ensure appropriate antibiotic therapy is utilized in the treatment of infection.

In light of the emergence of resistance to standard first-line antimicrobial agents such as ampicillin and TMP-SMX, the American Academy of Pediatrics (AAP) currently recommends antimicrobial susceptibility testing of all clinical isolates of *Shigella* species.[5] However, the antibiotics that are currently recommended by the Clinical and Laboratory Standards Institute (CLSI—formerly NCCLS) for routine susceptibility reporting against fecal isolates of *Shigella* species include ampicillin, a fluoroquinolone (ciprofloxacin or levofloxacin), and TMP-SMX. CLSI cautions laboratories not to report results for the aminoglycosides or first and second generation cephalosporins and cephamycins because these drugs are often susceptible *in vitro* but are ineffective *in vivo*.[1,8-11] The CLSI MIC and disk diffusion breakpoints for the aforementioned recommended agents (and other potentially clinically useful drugs such as third generation cephalosporins) that should be used for interpreting susceptibility for *Shigella* species are listed in Table 2.[12]

Because the majority of *Shigella* infections occur in children younger than 5 years of age, especially those in child care settings, it is important that alternatives to ampicillin and TMP-SMX are available to treat *Shigella* species infections in this population.[1,2,4,5] In the recent past, the AAP recommended ampicillin or TMP-SMX for the treatment of *Shigella* infections in pediatric patients with other agents such as azithromycin, fluoroquinolones, ceftriaxone, and cefixime recommended as alternative therapies in children with infection due to ampicillin- or TMP-SMX-resistant strains. However, because of the increasing emergence of resistance, the AAP now recommends ceftriaxone, a fluoroquinolone (such as ciprofloxacin or levofloxacin), or azithromycin for the treatment of *Shigella* species infections in pediatric patients in whom susceptibility is unknown or an ampicillin- or TMP-SMX-resistant strain has been isolated.[5] In addition, the World Health Organization currently recommends ciprofloxacin for all patients with bloody diarrhea, irrespective of age, with ceftriaxone as an alternative agent in adults and children, and azithromycin as an alternative agent in adults for the treatment of *Shigella* strains that are resistant to ciprofloxacin.[1] However, the efficacy of azithromycin in the treatment of *Shigella* species infections and the safety of fluoroquinolones in children is currently being evaluated. Additionally, nalidixic acid has been recommended as an alternative agent for the treatment of *Shigella* species infections, but is no longer commercially available in the US.

Cephalosporins for Shigella Infections

Cephalosporins have demonstrated variable efficacy for the treatment of *Shigella* species infections. First and second generation cephalosporins and oral cephalosporins appear to be less effective than third generation cephalosporins, despite apparent *in vitro* susceptibility of the infecting strains.[1,8-11]

Cefixime is an oral third generation cephalosporin that has demonstrated variable efficacy in the treatment of shigellosis in both children and adults.[13-15] Ashkenazi et al.[13]

Table 1. Percentage of *Shigella* Species Isolates Resistant to Antimicrobial Agents in the US, 2003-2004*

Antimicrobial Agent Tested (MIC Breakpoint for Interpretation of Resistance)†	Percent Resistant 2003 n = 495	Percent Resistant 2004 n = 315
Aminoglycosides		
Amikacin (MIC ≥ 64 µg/mL)	0%	0%
Gentamicin (MIC ≥ 16 µg/mL)	0%	0%
Streptomycin (MIC ≥ 64 µg/mL)	57.0%	61.0%
Aminopenicillins		
Ampicillin (MIC ≥ 32 µg/mL)	79.4%	77.8%
Amoxicillin-Clavulanate (MIC ≥ 32/16 µg/mL)	1.4%	1.6%
Cephalosporins		
Cephalothin (MIC ≥ 32 µg/mL)	9.3%	Not tested
Cefoxitin (MIC ≥ 32 µg/mL)	0%	0.3%
Ceftriaxone (MIC ≥ 64 µg/mL)	0%	0.3%
Quinolones		
Nalidixic Acid (MIC ≥ 32 µg/mL)	1.0%	1.6%
Ciprofloxacin (MIC ≥ 4 µg/mL)	0%	0%
Sulfonamides		
Sulfamethoxazole/Sulfisoxazole‡ (MIC ≥ 512 µg/mL)	33.9%	52.4%
Trimethoprim-Sulfamethoxazole (MIC ≥ 4/76 µg/mL)	38.6%	51.4%
Tetracyclines		
Tetracycline (MIC ≥ 16 µg/mL)	29.1%	49.2%
Miscellaneous		
Chloramphenicol (MIC ≥ 32 µg/mL)	8.5%	14.9%
Azithromycin (No CLSI breakpoints exist)	Not tested	Not tested

CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration

* *Data is from reference 7.*

† *MIC values were interpreted as susceptible or resistant based on Clinical and Laboratory Standards Institute (CLSI) breakpoints, when available.*

‡ *Sulfamethoxazole was tested in 2003, while sulfisoxazole was used in 2004 to represent sulfonamides.*

conducted a double-blind study evaluating the clinical and bacteriologic efficacy of 5 days of oral cefixime versus oral TMP-SMX in the treatment of childhood shigellosis. Seventy-

Table 2. CLSI Recommendations for Susceptibility Testing, Interpretation and Routine Reporting of Fecal Isolates of *Shigella* Species*

Antimicrobial Agent	Recommended for Routine Reporting of Susceptibility Results on Fecal Isolates	Recommended MIC Breakpoint for Determining Susceptibility (μg/mL) [S]	[R]
Amikacin	No	≤ 16	≥ 64
Amoxicillin-Clavulanate	No	≤ 8/4	≥ 32/16
Ampicillin	**Yes**	≤ 8	≥ 32
Azithromycin	No	Not listed	
Cefoxitin	No	≤ 8	≥ 32
Ceftriaxone	No	≤ 8	≥ 64
Cephalothin	No	≤ 8	≥ 32
Chloramphenicol	No	≤ 8	≥ 32
Ciprofloxacin	**Yes**	≤ 1	≥ 4
Gentamicin	No	≤ 4	≥ 16
Nalidixic Acid	No	≤ 16	≥ 32
Streptomycin	No	Not listed	
Sulfisoxazole	No	≤ 256	≥ 512
Tetracycline	No	≤ 4	≥ 16
Trimethoprim-Sulfamethoxazole	**Yes**	≤ 2/38	≥ 4/76

CLSI, Clinical and Laboratory Standards Institute; [R], resistant; [S], susceptible
** Data from CLSI[12]*

seven children aged 6 months to 16 years were randomized to receive cefixime 8 mg/kg orally per day divided in 2 equal daily doses (maximum 400 mg per day) or TMP-SMX 10/50 mg/kg orally per day divided in 2 equal daily doses (maximum 320 mg TMP and 1600 mg SMX) for 5 days. *S sonnei* accounted for 81% of *Shigella* species isolated, with all isolates from the cefixime-treated group and only 7 (18%) of isolates from the TMP-SMX-treated group displaying susceptibility to the antibiotic used when tested by disk diffusion. Overall, clinical cure was achieved in 34 of 38 (89%) children treated with cefixime compared to 14 of 39 (36%) children treated with TMP-SMX (P = .001). However, when evaluating clinical cure rates based on TMP-SMX susceptibility, there was no difference in the clinical cure rates between children who received cefixime (89%) and those who received TMP-SMX and had infection due to a TMP-SMX-susceptible organism (86%). Overall, bacteriologic eradication was achieved in 28 of 36 (78%) patients in the cefixime group compared to 13 of 37 (35%) in the TMP-SMX group. When evaluating bacteriologic eradication rates based on TMP-SMX susceptibility, there was no difference observed between children who received cefixime and those who received TMP-SMX that had infection due to a TMP-SMX-susceptible organism (78% versus 100%, respectively). Bacteriologic relapse was observed in one patient in each group. Children treated with TMP-SMX who had infection due to a TMP-SMX-resistant organism experienced a longer duration of symptoms and experienced lower rates of bacteriologic eradication than children in the cefixime group or TMP-SMX-susceptible group. The authors concluded that cefixime is a potentially viable treatment option for the management of shigellosis in children.

In an open, prospective, randomized study conducted in Paraguay, the efficacy of 5 days of oral cefixime (8 mg/kg per day [maximum 400 mg]) was compared with 5 days of oral azithromycin (12 mg/kg [maximum 500 mg] on the first day and 6 mg/kg daily [maximum 250mg] on days 2 through 5) in the treatment of shigellosis in 75 children aged 6 months to 5 years.[14] Eighty-seven percent of children had infection due to *S flexneri*, and all isolates were susceptible to both study drugs. Clinical success was observed in 93% of children treated with azithromycin compared to 78% of children treated with cefixime. Nine clinical failures were observed, with 7 occurring in children who received cefixime; one clinical relapse was observed in a patient who received azithromy-

cin. Bacterial eradication was achieved in 93% of azithromycin-treated children compared to 59% in cefixime-treated patients. The authors concluded that cefixime was inferior to azithromycin in terms of clinical response and bacterial eradication of *Shigella* species infections in children, possibly due to the increased isolation of *S flexneri* as a cause of infection in this study, which is often associated with more severe infection than other species.

Salam and colleagues evaluated the efficacy of cefixime and pivamdinocillin in the treatment of adult shigellosis.[15] Thirty Bangladesh men with acute dysentery due to *Shigella* species were randomized to receive cefixime 400 mg po daily for 5 days or pivamdinocillin 400 mg po every 6 hours for 5 days. The study was terminated early after an interim analysis of the first 30 evaluable patients revealed a significant difference in the clinical and bacteriologic cure rates between the two treatment groups, despite *in vitro* susceptibility of all *Shigella* species isolates to both study drugs. Clinical cure was observed in 100% of patients who received pivamdinocillin as compared to only 53% in the patients who received cefixime (P = .006), while bacteriologic success was observed in 87% of patients who received pivamdinocillin compared to only 40% in the patients who received cefixime (P = .006). The decreased clinical and bacteriologic cure rates of cefixime did not differ based on *Shigella* species isolated (50% of isolates were *S dysenteriae* type 1). The authors concluded that cefixime was markedly less effective than pivamdinocillin in the treatment of shigellosis in adults, and that this decrease in efficacy may be due to low stool and intracellular concentrations observed with cefixime.

Ceftriaxone is a parenteral third generation cephalosporin eliminated primarily by biliary excretion leading to high stool concentrations, which may contribute to its potential usefulness in the treatment of enteric infections such as shigellosis. The 2003-2004 NARMS surveillance data demonstrated only minimal resistance in *Shigella* species to ceftriaxone, with only one clinical isolate from 2004 displaying resistance.[7] There are a number of clinical studies evaluating the efficacy of ceftriaxone in the treatment of children with infections due to *Shigella* species, with the only major drawback being the requirement of parenteral administration.

Leibovitz and colleagues conducted a prospective, double-blind, double dummy, randomized, controlled trial comparing the safety and efficacy of intramuscular (IM) ceftriaxone (50 mg/kg/day [maximum 1 g daily]) and oral ciprofloxacin suspension (10 mg/kg every 12 hours) each given for 3 days in 201 children aged 6 months to 11 years with acute invasive diarrhea due to *Shigella* species and other enteropathogens.[16] Bacterial pathogens were isolated in 121 patients, yielding 127 organisms. All of the 73 *Shigella* species isolates recovered in this study displayed susceptibility to both ciprofloxacin and ceftriaxone. Clinical success was observed in 99.5% of patients, with only one clinical failure reported in a child with infection due to *S flexneri* treated with ciprofloxacin. In children infected with *Shigella* species, bacteriologic eradication rates were 100% in patients who received ciprofloxacin versus 97% in patients who received ceftriaxone. Overall, culture-negative clinical relapses for all infecting organisms occurred in 5% of children who received ciprofloxacin compared to 12% of children who received ceftriaxone.

Another prospective, randomized, open study compared the efficacy of ceftriaxone (50 mg/kg once daily [maximum 1.5 g]) and ampicillin (100 mg/kg/day divided in 4 equal doses) for 5 days in the treatment of severe shigellosis in 40 children aged 6 months to 16 years.[17] The study medications were administered intravenously for the initial 1 to 2 days of therapy, followed by IM ceftriaxone or oral ampicillin for the remainder of therapy. *S sonnei* and *S flexneri* were isolated in an equal number of patients in each treatment group (12 and 8 isolates, respectively). Overall, 11 isolates were resistant to ampicillin (4 recovered from patients treated with ampicillin) and none of the isolates were resistant to ceftriaxone using disk diffusion. Patients who received ceftriaxone experienced a significantly shorter duration of diarrhea (2.5 versus 6.75 days, respectively; P < .005), a quicker eradication of the organism from the stool (1.85 versus 4 days, respectively; P < .007), and significantly fewer diarrheal stools when compared to patients who received ampicillin. At the end of therapy, bacteriologic eradication was achieved in 12 of 20 (60%) patients who received ampicillin compared to 20 of 20 (100%) patients who re-

ceived ceftriaxone. Eight patients who received ampicillin experienced a bacteriologic relapse within 1 to 6 days of discontinuing therapy involving the same serotype of *Shigella* species that was originally cultured. The occurrence of bacteriologic relapse did not appear to correlate with pretreatment susceptibility results, and the susceptibility of relapsing organisms did not change from pretreatment results. The authors concluded that 5 days of ceftriaxone therapy produced a better clinical response and quicker, persistent bacterial eradication when compared to ampicillin in the treatment of severe shigellosis in children.

Azithromycin for Shigella Infections

Azithromycin is a macrolide antibiotic of the azalide subclass, which has been shown to display *in vitro* activity against both Gram-positive and Gram-negative aerobic bacteria. Although macrolides are most noted for their activity against Gram-positive aerobes, azithromycin has been shown *in vitro* to inhibit a limited number of Gram-negative enteric organisms, and is thought to be more potent than erythromycin against members of the Enterobacteriaceae family, including *Shigella* species.[18,19] Because azithromycin achieves high intracellular concentrations in leukocytes, colonic cells, and stool, some clinicians feel it may be particularly useful for the treatment of infections due to invasive enteric pathogens.[20,21]

Azithromycin is currently recommended by the AAP as a therapeutic option for the treatment of *Shigella* species infections in children where the susceptibility of the isolate is unknown, or when the isolate is known to be resistant to ampicillin or TMP-SMX.[5] However, microbiology laboratories do not routinely perform azithromycin susceptibility testing for *Shigella* species; CLSI does not currently recommend routine reporting of azithromycin susceptibility results for *Shigella* species; there are currently no CLSI guidelines or susceptibility breakpoints for interpretation of azithromycin susceptibility for Gram-negative bacteria including *Shigella* species; and there is limited published data on the efficacy of azithromycin in the treatment of *Shigella* species infections in children or adults.

Although there are CLSI testing guidelines and MIC and disk diffusion breakpoints for azithromycin with Gram-positive bacteria, there are currently no CLSI guidelines or susceptibility breakpoints for azithromycin for Gram-negative bacteria including *Shigella* species.[12] The *in vitro* activity of azithromycin against *Shigella* species has been evaluated in several studies, which are summarized in Table 3.[18,19,22-24] However, the correlation of *in vitro* susceptibility to clinical outcome is challenging since there are no approved breakpoints and few clinical studies to provide guidance.

Interestingly, Jain and colleagues reported difficulty in interpreting azithromycin susceptibility for *S sonnei* isolates due to a dual zone of inhibition observed using the E-test or disk diffusion.[22] The authors describe the two zones as an inner zone of complete inhibition with an outer zone of reduced growth. This dual zone of inhibition can result in an isolate being defined as susceptible using the outer zone for interpretation, but non-susceptible if the inner zone is used for interpretation. However, similar problems in determining MIC values for azithromycin have not been observed when using agar or broth dilution MIC methods.

There is limited published data on the efficacy of azithromycin in the treatment of *Shigella* species infections in children or adults. In an open, prospective, randomized study, the efficacy of 5 days of oral azithromycin (12 mg/kg [maximum 500 mg] on the first day and 6 mg/kg daily [maximum 250 mg] on days 2 through 5) and oral cefixime (8 mg/kg/day [maximum 400 mg]) was compared in the treatment of shigellosis in children aged 6 months to 5 years.[14] Seventy-five children were included in the study, with 87% of children having infection due to *S flexneri.* All isolates were susceptible to azithromycin (clear zone of inhibition of at least 17 mm by disk diffusion was used for susceptibility definition) and cefixime. Treatment was clinically successful in 93% of patients treated with azithromycin as compared to 78% of patients treated with cefixime. Seven clinical failures were observed in the children who received cefixime, and one clinical relapse was observed in a patient who received azithromycin. Bacterial eradication was achieved in 93% of azithromycin-treated children compared to 59% of cefixime-treated patients.

There is only one other published study evaluating the efficacy of azithromycin for the

Table 3. Comparative Azithromycin Susceptibility Test Data for *Shigella* Species

Reference	Method of Susceptibility Testing	Species and Number of Isolates Tested	Susceptibility Test Result
22	E-test	*S sonnei,* n = 45	Median MIC (Outer Zone) = 1.5 μg/mL (range, 0.75 to 2 μg/ml) Median MIC (Inner Zone) = 8 μg/mL (range, 4.0 to 8.0 μg/mL)
	Disk diffusion		Median MIC (Outer Zone) = 25 mm (range, 21 to 27 mm) Median MIC (Inner Zone) = 14 mm (range, 12 to 15 mm)
	Broth dilution		Median MIC = 3 μg/mL (range, 2.0 to 8.0 μg/mL)
23	Agar dilution	*Shigella* species, n = 20	MIC_{90} = 1 μg/mL (range, 0.5 to 1.0 μg/mL)
18	Broth dilution	*S flexneri,* n = 20	MIC_{90} = 2 μg/mL (range, 0.5 to 2.0 μg/mL)
	Broth dilution	*S dysenteriae*, n = 20	MIC_{90} = 2 μg/mL (range, 1 to 2 μg/mL)
	Broth dilution	*S sonnei,* n = 20	MIC_{90} = 4 μg/mL (range, 2 to 4 μg/mL)
19	Broth dilution	*S flexneri,* n = 10	MIC_{50} = 4 μg/mL MIC_{90} = 8 μg/mL (range, 2 to 16 μg/mL)
	Broth dilution	*S sonnei,* n = 10	MIC_{50} = 4 μg/mL MIC_{90} = 8 μg/mL (range, 2 to 16 μg/mL)
24	Microdilution	*S sonnei*, n = 37 *S flexneri*, n = 29 *S boydii*, n = 6 *S dysenteriae*, n = 1	MIC_{50} = 2 μg/mL MIC_{90} = 4 μg/mL (range, 0.5 to 8 μg/mL)

treatment of shigellosis, which was conducted in 70 adult Bangladesh men.[21] In this randomized, double-blind, controlled study, 34 men received oral azithromycin (500 mg on day 1 and 250 mg daily on days 2 through 5) and 36 men received oral ciprofloxacin (500 mg every 12 hours for 5 days) for the treatment of shigellosis. Half of the patients in each study group had infection due to *S dysenteriae* type 1. All *Shigella* species isolates were susceptible to both study drugs using the E-test methodology (interpretation criteria not specified), with a median azithromycin MIC of 0.5 μg/mL for *S dysenteriae* type 1 isolates and 1.5 μg/mL for other *Shigella* species serotypes. Overall clinical success was observed in 82% of azithromycin-treated patients compared to 89% of ciprofloxacin-treated patients, with higher rates of treatment failure of both drugs in patients infected with *S dysenteriae* type 1 (29% for azithromycin and 17% for ciprofloxacin). Bacteriologic success was achieved in 94% of azithromycin-treated patients compared to 100% of ciprofloxacin-treated patients. When comparing median serum concentrations to the MIC of the infecting bacteria, patients who received azithromycin achieved a median azithromycin serum concentration of 0.65 μg/mL, which was greater than or equal to the MIC of most infecting organisms; while the patients who received ciprofloxacin achieved a median ciprofloxacin serum concentration of 2.5 μg/mL, which was a median of 28 times the MIC of the infecting bacteria. Both drugs achieved high stool concentrations relative to the MIC of the infecting bacteria, with azithromycin achieving concentrations in the stool that were 432 to 680 times the median MIC.

Since azithromycin is now recommended by the AAP as a therapeutic option for the treat-

ment of *Shigella* species infections in children where the susceptibility of the isolate is unknown or is known to be resistant to ampicillin or TMP-SMX, the need for clinically validated susceptibility breakpoints and data supporting its efficacy in both children and adults is critical. Further studies are needed to define the role of azithromycin in the treatment of bacterial diarrhea due to *Shigella* species.

Fluoroquinolones for Shigella Infections

The fluoroquinolones are recommended by the AAP as a therapeutic option for the treatment of *Shigella* species infections in children when the susceptibility of the isolate is unknown or when the isolate is known to be ampicillin- or TMP-SMX-resistant.[5] In addition, the World Health Organization (WHO) currently recommends ciprofloxacin for the treatment of all patients with bloody diarrhea, irrespective of age.[1] However, there continues to be concern among some health care providers about using fluoroquinolone antibiotics in pediatric patients due to findings from early toxicology studies of fluoroquinolone-induced, dose-related cartilaginous damage and arthropathy, especially in the weight-bearing joints of juvenile animals (especially dogs).[25-27]

Numerous studies and reviews have been conducted evaluating the safety and efficacy of fluoroquinolones in children for the treatment of various infections, some of which are summarized in Table 4.[16,27-39] The clinical studies and reviews have demonstrated an overall low incidence of arthropathy and cartilaginous damage in pediatric patients who have received fluoroquinolone antibiotics for various durations of therapy. Since the occurrence of arthropathy in animals is thought to be species-dependent and dose-dependent,[25-27] many investigators and clinicians have speculated that the lower incidence of arthropathy observed in pediatric patients may be due to a higher threshold for the development of this toxicity in humans compared to animals, and because therapeutic doses administered to humans are significantly below those causing cartilaginous toxicity in animals.[28]

Although fluoroquinolones are not routinely recommended or used in children, the Food and Drug Administration approved the use of ciprofloxacin in pediatric patients exposed to inhalational anthrax in 2000 based on the following: "Because inhalational anthrax is lethal, the risk-benefit assessment indicates that use of ciprofloxacin for this indication in pediatric patients is appropriate."[40] Ciprofloxacin is also FDA-approved as an alternative agent for the treatment of complicated urinary tract infections and pyelonephritis in children aged 1 to 17 years who have not responded to other antibiotics.[36] Furthermore, the AAP recognizes the usefulness of fluoroquinolones for the treatment of infections in children in the following situations: "1) parenteral therapy is not feasible and no other effective oral agent is available; and 2) infection is caused by multidrug-resistant pathogens, such as certain *Pseudomonas* and *Mycobacterium* strains, for which there is no other effective oral agent available."[41] Therefore, possible uses of the fluoroquinolones for the treatment of infections in children include exacerbations of cystic fibrosis; chronic suppurative otitis media or malignant otitis media; acute otitis media or sinusitis due to multidrug-resistant *Streptococcus pneumoniae* in patients who have failed initial antibiotic therapy; chronic or acute osteomyelitis caused by *Pseudomonas aeruginosa*; urinary tract infections caused by *Pseudomonas aeruginosa* or other multidrug-resistant Gram-negative bacteria; mycobacterial infections known to be susceptible to fluoroquinolones; Gram-negative bacterial infections in immunocompromised children in which prolonged oral therapy is desired; and gastrointestinal tract infections caused by multidrug-resistant *Shigella* species, *Salmonella* species, *Vibrio cholerae* or *Campylobacter jejuni*.[25,26,41]

With the increasing resistance of *Shigella* species to ampicillin and TMP-SMX, the fluoroquinolones have emerged as a potential treatment option for resistant *Shigella* species infections in children. The fluoroquinolone antibiotics have retained excellent activity against clinical *Shigella* species isolates, as demonstrated in the 2003-2004 NARMS surveillance study where none of the 810 *Shigella* species isolates tested were resistant to ciprofloxacin (MIC $\geq$ 4 μg/mL).[7] In this study, less than 1% of *Shigella* species demonstrated decreased susceptibility to ciprofloxacin, defined as a ciprofloxacin MIC of $\geq$ 0.25 μg/mL. To date, there have been a limited number of reports

Table 4. Summary of Clinical Trials Evaluating the Orthopedic Safety of Fluoroquinolones in Children

Reference	Number (Age)	Therapeutic Indication	Medication and Dose	Length of Fluoroquinolone Therapy	Safety Results
28	n = 50 (1 mo-11 yr)	Unknown	Nalidixic acid 50 mg/kg/d po	10-815 days, mean 118 days	No drug-induced cartilage damage; no evidence of drug-related alterations in joint-building structures observed on radiographic examination*
29	n = 634 (3 d-17 yr)	Compassionate use for RTI (62%), skin infections (13%), UTI (8%), bacteremia (4%), etc.	Ciprofloxacin iv: 3.2-11.5 mg/kg (mean 7 mg/kg) po: 3.1-93.8 mg/kg (mean 25.2 mg/kg)	1-300 days, mean 9-22.8 days (all iv, iv and po, and all po therapy)	8 (1.3%) patients treated for acute exacerbations of CF reported transient arthralgias that resolved upon discontinuation of therapy
16	n = 95 (6 mo-11 yr)	Acute invasive diarrhea	Ciprofloxacin 10 mg/kg po bid vs. Ceftriaxone 50 mg/kg im daily	3 days	Reversible, bilateral knee arthralgia in one patient; no evidence of joint toxicity in either group†
30	n = 58 (8 mo-13 yr)	Positive Widal test‡ or blood culture positive for *Salmonella typhi*	Ciprofloxacin 15-25 mg/kg/d in 2 divided doses (mean 21 mg/kg/d)	9-16 days, mean 12.6 days	No patient developed musculoskeletal symptoms during the study period. NMR scans on 22 children revealed no evidence of joint toxicity.§
31	n = 108 (5-17 yr)	CF (acute exacerbation)	Ciprofloxacin (n = 55) 15 mg/kg po bid [max 1500 mg/d] vs. Ceftazidime plus Tobramycin	14 days	No arthropathy on ultrasound or MRI in 29 patients. Four in the ciprofloxacin group versus 6 in the ceftazidime / tobramycin group had transient joint symptoms.
32	n = 120 (2-15 yr)	Shigellosis	Ciprofloxacin (n = 60) 10 mg/kg po q 12 hr [max 500 mg/dose] vs. Pivmecillinam 15-20 mg/kg po q 8 hr	5 days	13/71 who received ciprofloxacin and 16/72 given pivmecillinam reported joint pain, which was verified on physical exam in 3 ciprofloxacin-treated and 5 pivmecillinam-treated patients. Pain resolved during the study in all but 2 patients who received pivmecillinam. Arthropathy or arthritis was not evident during the 6 months of follow-up.¶
33	n = 18 (6-24 yr)	CF	Ciprofloxacin 15 mg/kg po bid [max 750 mg/dose]	3 mo	No adverse articular events, joint effusions or changes in cartilage thickness based on clinical, laboratory, radiologic and MRI testing.

of clinical isolates of *Shigella* species with reduced susceptibility to fluoroquinolones,[7,42-44] and rare reports of resistance in Asia using current CLSI breakpoint criteria (ciprofloxacin MIC ≥ 4 μg/mL).[45-48]

A number of studies have evaluated the efficacy of fluoroquinolones in the treatment of *Shigella* species infection in children. In a

Table 4. Summary of Clinical Trials Evaluating the Orthopedic Safety of Fluoroquinolones in Children (cont.)

Reference	Number (Age)	Therapeutic Indication	Medication and Dose	Length of Fluoroquinolone Therapy	Safety Results
34	n = 11 (3 mo-9 yr)	UTI	Nalidixic acid 33-100 mg/kg/d po [median 51 mg/kg/dose, total 3.6 to 900 g]	9-600 days, median 11 days	No arthropathy observed on clinical and radiographic findings obtained via chart review.
35	n = 867 (6 mo-7 yr)	Recurrent otitis media or nonresponsive acute otitis media	Gatifloxacin 10 mg/kg/d po [max 600 mg/d]	10 days median10 days range, 1-15 days	Transient arthralgia in 1.4% of children given gatifloxacin, which resolved spontaneously within 2 wk. No abnormal physical exam or MRI findings were noted. One-year safety data on 671 children yielded no evidence of arthropathy. All gatifloxacin-treated children experienced normal growth rates based on standardized growth charts.#
36	n = 335 (1-17 yr)	Complicated UTI or pyelonephritis	Ciprofloxacin iv: 6-10 mg/kg/dose q 8 hr [max 400 mg/dose] po: 10-20 mg/kg/dose q 12 hr [max 750 mg/dose]	10-21 days median 11 days range, 1-88 days	Musculoskeletal adverse effects occurred in 9.3% (31/335) of ciprofloxacin-treated patients compared to 6.0% (21/349) of comparator-treated patients. The majority of events were mild to moderate in severity, and all resolved within 30 days of discontinuing treatment.**

BID, twice a day; CF, cystic fibrosis; im, intramuscular; iv, intravenous; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance scan; po, by mouth; RTI, respiratory tract infection; UTI, urinary tract infection

* *Safety evaluations on patients with comparable radiographic studies of the same joints were performed both shortly before and during therapy, as well as 2 years after therapy.*

† *Joint toxicity was assessed by a pediatrician or rheumatologist with examination of gait and evaluation of hips, knees, ankles, shoulders, elbows, and wrists for pain/tenderness, evidence of inflammation, and active/passive range of motion.*

‡ *Widal test is a serological test for Salmonella typhi that detects Salmonella antibodies to O-somatic and H-flagellar antigens in the blood.*

§ *Patients were monitored daily during therapy for signs of joint toxicity such as arthralgia, decreased range of motion, swelling or redness of any joint, etc. Patients were also monitored at 6-month intervals for 19 to 37 months. NMR scans were performed on right knee joints of 22 patients before the first dose of therapy and repeated between 10 and 15 days of ciprofloxacin therapy.*

¶ *Safety was assessed by evaluation of limitations in movement, difficulty walking, gait, swelling, tenderness, and pain from passive/active movement.*

\# *Arthropathy was monitored with joint evaluations at every study visit, and by a joint status/complaints diary provided to parents/legal guardians. Parents were instructed to contact the investigator at the first sign of any joint disorder. Children with joint complaints were referred to a pediatric rheumatologist or orthopedist with MRI imaging, if indicated.*

** *An independent group assessed musculoskeletal safety within 6 weeks of therapy and through one year of follow-up. Musculoskeletal adverse effects included arthralgia, abnormal gait, abnormal joint exam, joint sprain, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion.*

double-blind, randomized clinical trial, Bhattacharya and colleagues evaluated the safety and efficacy of 5 days of treatment with oral norfloxacin (20 mg/kg/day in 2 divided doses) versus oral nalidixic acid (60 mg/kg/day in 4 divided doses) in the treatment of shigellosis in 22 children.[49] Eight children received nalidixic acid and 14 children received norfloxacin. Children treated with norfloxacin demonstrated a significantly shorter duration of diarrhea (3.7 ± 0.8 days versus 2.7 ± 0.9 days, respectively) and presence of blood in the stool (2.4 ± 0.7 days versus 1.4 ± 0.6 days, respectively; $P < .05$) compared to children who received nalidixic acid. Three children who received nalidixic acid were infected with a *Shigella* species isolate

(all *S dysenteriae* type 1) that was resistant to nalidixic acid, leading to treatment failure. Therapy was successfully changed to norfloxacin therapy in these children. None of the children in this study developed arthropathy during treatment or the subsequent 4 month follow-up period.

Salam et al. compared the safety and efficacy of oral ciprofloxacin with oral pivmecillinam for the treatment of shigellosis in 120 children aged 2 to 5 years.[32] Sixty children were randomized to each group and received either oral ciprofloxacin suspension (10 mg/kg [maximum 500 mg] every 12 hours) or oral pivmecillinam tablets (15-20 mg/kg [maximum 300 mg] every 8 hours) for 5 days. All 120 *Shigella* species isolates were susceptible to ciprofloxacin (median MIC = 0.125 μg/mL), while 5 isolates were resistant to pivmecillinam. Clinical success was observed in 48 of 60 (80%) children treated with ciprofloxacin compared to 39 of 60 (65%) of those treated with pivmecillinam (P = .10), while bacteriologic success was observed in 60 of 60 (100%) treated with ciprofloxacin compared to 54 of 60 (90%) treated with pivmecillinam (P = .03). Other clinical markers such as blood-mucoid stool for greater than three days, fever for greater than 24 hours, and abdominal pain for greater than three days were similar between the two groups. In terms of safety, joint pain on physical exam was observed in 3 patients who received ciprofloxacin compared to 5 patients who received pivmecillinam, and resolved spontaneously during the study in all but 2 patients who received pivmecillinam. None of the patients had evidence of arthropathy or arthritis during the 6 month follow-up period.

Leibovitz and colleagues compared the safety and efficacy of oral ciprofloxacin suspension and IM ceftriaxone in the treatment of invasive diarrhea due to *Shigella* species, *Salmonella* species, *Campylobacter* species, or *Escherichia coli* in 201 children aged 6 months to 11 years old.[16] Children were randomized to receive a 3-day course of oral ciprofloxacin suspension (10 mg/kg every 12 hours) or IM ceftriaxone (50 mg/kg/day [maximum 1 g]). Of the 201 children enrolled, 73 (37%) had positive stool cultures for *Shigella* species. All of the *Shigella* species isolates were susceptible to both ceftriaxone and ciprofloxacin, with a ciprofloxacin MIC_{90} of 0.012 μg/mL. Clinical success was achieved in all but one patient infected with *S flexneri* who received ciprofloxacin. Overall, children who received ciprofloxacin experienced a relapse rate of 5% for all infecting organisms, compared to 12% for the ceftriaxone group. Joint examinations were normal during the study and the 21-day follow-up period.

Oral ciprofloxacin (500 mg every 12 hours for 5 days) and oral azithromycin (500 mg on the first day and 250 mg daily on days 2 through 5) were compared in a randomized, double-blind, controlled study in 70 Bangladesh men with shigellosis.[21] Thirty-four men were randomized to receive oral azithromycin and 36 men were randomized to receive oral ciprofloxacin. *S dysenteriae* type 1 was the most commonly isolated *Shigella* species from half of the patients in each study group, followed by *S flexneri*. All *Shigella* species isolates were susceptible to both study drugs using the E-test methodology, with a median ciprofloxacin MIC of 0.125 μg/mL for *S dysenteriae* type 1 isolates and 0.016 μg/ml for other *Shigella* species serotypes. Overall clinical success was observed in 82% of azithromycin-treated patients compared to 89% of ciprofloxacin-treated patients, with higher rates of treatment failure of both drugs in patients infected with *S dysenteriae* type 1 (29% for azithromycin and 17% for ciprofloxacin). Bacteriologic success was achieved in 94% of azithromycin-treated patients compared to 100% of ciprofloxacin-treated patients. When comparing median serum concentration to the MIC of the infecting bacteria, patients who received ciprofloxacin achieved a median ciprofloxacin serum concentration of 2.5 μg/mL, which was a median of 28 times the MIC of the infecting bacteria. Both drugs achieved high stool concentrations relative to the MIC of the infecting bacteria, with ciprofloxacin achieving concentrations in the stool that were 806 to 3598 times the median MIC.

CONCLUSIONS

Shigella species remain an important cause of gastrointestinal infection worldwide, primarily infecting the large intestine causing symptoms that range from loose or watery stools to fever, cramping, tenderness, or mucoid stools with or without the presence of blood.[1] The

World Health Organization endorses the importance of appropriate antibiotic selection in the treatment of infection, which is extremely important in the management of infections due to *Shigella* species in order to limit the spread of this highly contagious enteric pathogen. Recent US surveillance data has demonstrated increased resistance in *Shigella* species to both ampicillin and TMP-SMX, with approximately 37% of isolates demonstrating resistance to both ampicillin and TMP-SMX.[7] Approximately 69% of *Shigella* infections occur in children younger than 5 years of age; therefore, it is important that antibiotics other than typical first-line agents such as ampicillin and TMP-SMX be available to treat *Shigella* infections in this population.[22]

The AAP has recommended cefixime and ceftriaxone as alternative antibiotics in the treatment of *Shigella* species infections in children because of their similar or superior clinical efficacy when compared to ampicillin or TMP-SMX.[5,13,17] However, the primary limitation to the use of ceftriaxone is that it must be given parenterally.

Azithromycin is also recommended as a potential second-line agent by the AAP for the treatment of *Shigella* infections in pediatric patients. However, there are currently no CLSI guidelines for susceptibility testing of azithromycin against *Shigella* species and no breakpoints to interpret MIC or disk diffusion test results. In addition, there is currently limited clinical data on the efficacy of azithromycin in the treatment of infections due to *Shigella* species in adults and children. Therefore, further studies are needed to define the role of azithromycin in the treatment of bacterial diarrhea due to *Shigella* species.

Although the fluoroquinolones are currently contraindicated in children due to potential safety concerns, they are recommended as a potential alternative therapy by the AAP for the treatment of *Shigella* infections in pediatric patients. Fluoroquinolones retain excellent activity against *Shigella* species and have demonstrated excellent clinical efficacy in the treatment of Shigella species infections in children. In addition, multiple studies have suggested that fluoroquinolone-induced arthropathy is species-related and the prevalence of arthropathy in children is lower than that observed in early animal studies. Therefore, fluoroquinolones appear to be a potentially viable treatment option for pediatric patients with infection due to multidrug-resistant *Shigella* species.

REFERENCES

1. World Health Organization. Guidelines for the control of shigellosis, including epidemics due to *Shigella dysenteriae* type 1. Geneva, Switzerland: World Health Organization Press; 2005.
2. Centers for Disease Control and Prevention. Summary of notifiable diseases – United States, 2004. MMWR Morb Mortal Wkly Rep 2006;53:1-79.
3. Oldfield EC, Wallace MR. The role of antibiotics in the treatment of infectious diarrhea. Gastroenterol Clin North Am 2001;30:817-36.
4. Niyogi SK. Shigellosis. J Microbiol 2005;43:133-143.
5. American Academy of Pediatrics Committee on Infectious Diseases. Section 3: Summaries of Infectious Diseases: *Shigella* Infections. In: Red Book: 2006 Report of the Committee on Infectious Diseases, 27th Edition. Accessed online via StatRef on December 6, 2006.
6. Phavichitr N, Catto-Smith A. Acute gastroenteritis in children: What role for antibacterials? Paediatr Drugs 2003;5:279-290.
7. Centers for Disease Control and Prevention. National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Final Report, 2004. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC, 2007.
8. Nelson JD, Haltalin KC. Comparative efficacy of cephalexin and ampicillin for shigellosis and other types of acute diarrhea in infants and children. Antimicrob Agents Chemother 1975;7:415-20.
9. Nelson JD, Haltalin KC. In vitro effectiveness of four cephalosporins against shigellae and clinical ineffectiveness of cephaloglycan. Chemotherapy 1972;17:40-60.

10. Orenstein WA, Ross L, Overturf GD, et al. Antibiotic treatment of acute shigellosis: Failure of cefamandole compared with trimethoprim/sulfamethoxazole and ampicillin. Am J Med Sci 1981;282:27-33.
11. Prado D, Lopez E, Liu H, et al. Ceftibuten and trimethoprim-sulfamethoxazole for treatment of *Shigella* and enteroinvasive *Escherichia coli* disease. Pediatr Infect Dis J 1992;11:644-647.
12. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Eighteenth Informational Supplement, M100-S18, Wayne, PA. January 2008; 27: 98-101.
13. Ashkenazi S, Amir J, Waisman Y, et al. A randomized, double-blind study comparing cefixime and trimethoprim-sulfamethoxazole in the treatment of childhood shigellosis. J Pediatr 1993;123:817-821.
14. Basualdo W, Arbo A. Randomized comparison of azithromycin versus cefixime for treatment of shigellosis in children. Pediatr Infect Dis J 2003;22:374-377.
15. Salam MA, Seas C, Khan WA, et al. Treatment of shigellosis: IV. Cefixime is ineffective in shigellosis in adults. Ann Intern Med 1995;123:505-508.
16. Leibovitz E, Janco J, Piglansky L, et al. Oral ciprofloxacin vs. intramuscular ceftriaxone as empiric treatment of acute invasive diarrhea in children. Pediatr Infect Dis J 2000;19:1060-1067.
17. Varsano I, Eidlitz-Marcus T, Nussinovitch M, et al. Comparative efficacy of ceftriaxone and ampicillin for treatment of severe shigellosis in children. J Pediatr 1991;118:627-632.
18. Jones K, Felmingham D, Ridgway G. In vitro activity of azithromycin (CP-62,993), a novel macrolide, against enteric pathogens. Drugs Exp Clin Res 1988;14:613-615.
19. Neu HC, Chin NX, Saha G, et al. Comparative in vitro activity of the new oral macrolide azithromycin. Eur J Clin Microbiol Infect Dis 1988;7:541-544.
20. Gladue RP, Bright GM, Isaacson RE, et al. In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanisms of delivery and release at sites of infection. Antimicrob Agents Chemother 1989;33:277-282.
21. Khan WA, Seas C, Dhar U, et al. Treatment of shigellosis: comparison of azithromycin and ciprofloxacin: a double-blind, randomized, controlled trial. Ann Intern Med 1997;126:697-703.
22. Jain SK, Gupta A, Glanz B, et al. Antimicrobial-resistant *Shigella sonnei*: Limited antimicrobial treatment options for children and challenges of interpreting in vitro azithromycin susceptibility. Pediatr Infect Dis J 2005;24:494-497.
23. Gordillo ME, Singh KV, Murray BE. In vitro activity of azithromycin against bacterial enteric pathogens. Antimicrob Agents Chemother 1993;37:1203-1205.
24. Stock I, Wiedemann B. Natural antibiotic susceptibility of *Escherichia coli, Shigella, E. vulneris,* and *E. hermannii* strains. Diagn Microbiol Infect Dis 1999;33:187-199.
25. Jafri HS, McCracken GH Jr. Fluoroquinolones in paediatrics. Drugs 1999;58(Supp 2):43-48.
26. Grady R. Safety profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis J 2003;22:1128-1132.
27. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. Clin Infect Dis 1997;25:1196-1204.
28. Adam D. Use of quinolones in pediatric patients. Rev Infect Dis 1989;11(Supp 5):S1113-1116.
29. Chysky V, Kapila K, Hullmann R, et al. Safety of ciprofloxacin in children: worldwide clinical experience based on compassionate use. Emphasis on joint evaluation. Infection 1991;19:289-296.
30. Pradhan KM, Arora NK, Jena A, et al. Safety of ciprofloxacin therapy in children: magnetic resonance images, body fluid levels of fluoride and linear growth. Acta Paediatr 1995;84:555-560.

31. Richard DA, Nousia-Arvanitakis S, Sollich V, et al. Oral ciprofloxacin vs. intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety with ultrasonography and magnetic resonance imaging. Cystic Fibrosis Study Group. Pediatr Infect Dis J 1997;16:572-578.
32. Salam MA, Dhar U, Khan WA, et al. Randomised comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis. Lancet 1998;352:522-527.
33. Schaad UB, Stoupis C, Wedgwood J, et al. Clinical, radiological and magnetic resonance monitoring for skeletal toxicity in pediatric patients with cystic fibrosis receiving a three-month course of ciprofloxacin. Pediatr Infect Dis J 1991;10:723-729.
34. Schaad UB, Wedgwood-Krucko J. Nalidixic acid in children: retrospective matched controlled study for cartilage toxicity. Infection 1987;15:165-168.
35. Pichichero ME, Arguedas A, Dagan R, et al. Safety and efficacy of gatifloxacin therapy for children with recurrent acute otitis media (AOM) and/or AOM treatment failure. Clin Infect Dis 2005;41:470-478.
36. Bayer Pharmaceutical Corp. Cipro (ciprofloxacin) prescribing information. West Haven, CT, December 2005.
37. Jick S. Ciprofloxacin safety in a pediatric population. Pediatr Infect Dis J 1997;16:130-134.
38. Hampel B, Hullmann R, Schmidt H. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use – safety report. Pediatr Infect Dis J 1997;16:127-129.
39. Yee CL, Duffy C, Gerbino PG, et al. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. Pediatr Infect Dis J 2002;21:525-529.
40. Food and Drug Administration Talk Paper. Approval of Cipro for use after exposure to inhalational anthrax. Available at: http://www.fda.gov/bbs/topics/ANSWERS/ANS01030.html Accessed January 12, 2007.
41. American Academy of Pediatrics Committee on Infectious Diseases. Section 4: Antimicrobial Agents and Related Therapy: Fluoroquinolones. In: RedBook: 2006 Report of the Committee on Infectious Diseases, 27th Edition. Accessed online via StatRef on January 12, 2007.
42. Horiuchi S, Inagaki Y, Yamamoto N, et al. Reduced susceptibilities of *Shigella sonnei* strains isolated from patients with dysentery to fluoroquinolones. Antimicrob Agents Chemother 1993;37:2486-2489.
43. Sarkar K, Niyogi SK, Bhattacharya SK. *Shigella dysenteriae* type 1 with reduced susceptibility to fluoroquinolones. Lancet 2003;361:785.
44. Hirose K, Terajima J, Izumiya H, et al. Antimicrobial susceptibility of *Shigella sonnei* isolates in Japan and molecular analysis of *S. sonnei* strains with reduced susceptibility to fluoroquinolones. Antimicrob Agents Chemother 2005:49:1203-1205.
45. Bhattacharya SK, Sarkar K, Nair BG, et al. Multidrug-resistant *Shigella dysenteriae* type 1 in south Asia. Lancet Infect Dis 2003;3:755.
46. Naheed A, Kalluri P, Talukder KA, et al. Fluoroquinolone-resistant *Shigella dysenteriae* type 1 in northeastern Bangladesh. Lancet Infect Dis 2004;4:607-608.
47. Pazhani GP, Ramamurthy T, Mitra U, et al. Species diversity and antimicrobial resistance of *Shigella* spp. isolated between 2001 and 2004 from hospitalized children with diarrhoea in Kolkata (Calcutta), India. Epidemiol Infect 2005;133:1089-1095.
48. Talukder KA, Khajanchi BK, Islam M, et al. Fluoroquinolone resistance linked to both *gyrA* and *parC* mutations in the quinolone-resistance determining region of *Shigella dysenteriae* type 1. Curr Microbiol 2006;52:108-111.
49. Bhattacharya SK, Bhattacharya MK, Dutta D, et al. Double-blind, randomized clinical trial for safety and efficacy of norfloxacin for shigellosis in children. Acta Paediatr 1997;86:319-320.