The Battle against Emerging Antibiotic Resistance: Should Fluoroquinolones Be Used to Treat Children?

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Inappropriate use of antibiotic drugs in humans and animals has led to widespread resistance among microbial pathogens. Resistance is the phenotypic expression corresponding to genetic changes caused by either mutation or acquisition of new genetic information. In some cases, multidrug resistance occurs. *Streptococcus pneumoniae* is one of the most important respiratory pathogens, playing a major role in both upper and lower respiratory tract infections. Pneumococcal resistance to antimicrobials may be acquired by means of horizontal transfer followed by homologous recombination of genetic material from the normal flora of the human oral cavity or by means of mutation. Resistance to penicillins and macrolides has been increasing for some time, but, recently, fluoroquinolone resistance has become an issue as well. We are concerned that, if fluoroquinolones are approved for use in children, their widespread use will result in rapid emergence of pneumococcal resistance, because children are more often colonized in the nasopharynx with high-density populations of pneumococci than are adults.

DISCOVERY OF ANTIBIOTICS AND EMERGENCE OF MICROBIAL RESISTANCE

The development of antimicrobials is considered among the most important medical advances of the twentieth century [1]. However, penicillin G had barely been released when reports of penicillinase-producing isolates of *Staphylococcus aureus* appeared, raising a note of caution [2]. We believe it is important to review the history

and biology of antibiotic resistance, to comment on contemporary issues relating to emerging resistance, and, most importantly, to argue against the unnecessary use of fluoroquinolones to treat children, a development that may exacerbate this phenomenon.

Antimicrobial agents are used extensively around the world, and many drugs, including fluoroquinolones, are used for growth promotion and prophylaxis in animal husbandry. Unfortunately, there is a correlation between the total amount of drug use and the appearance and dissemination of resistant microbial strains [3]. Societal expectations, coupled with physicians' intrinsic desire to help patients, have contributed to widespread abuse of antibiotics. A recent survey highlighted

this, showing that, although only 22% of patients seeking medical care had an infection diagnosed, 67% were given antibiotics as a result of their physician visit [4].

Bacteria have developed ingenious strategies to protect themselves against antimicrobials, which they themselves often produce. For example, aminoglycoside-inactivating enzymes are produced by strains of *Streptomyces* that also produce an aminoglycoside [5], and the *van* gene cluster that codes for high-level vancomycin resistance recently has been found in the glycopeptide-producing microorganisms [6] as well as in a bacterium that is present in a widely distributed biopesticide [7]. It is postulated that resistance genes escaped from soil microorganisms and, after pas-

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sage and remodeling in other bacteria, entered human pathogens [8]. Bacterial isolates displaying resistance to tetracycline and streptomycin have been isolated from stool samples obtained from Solomon Islanders who have never been exposed to antibiotics [9]. These are but a few examples in which microbes that have not been exposed to antibiotics have been found to have the genetic machinery to resist antimicrobial agents.

The phenotypic expression of resistance corresponds to genetic alterations that result either from horizontal acquisition of genetic information from other organisms or from adaptive mutations in the microbial genome. Compounding the problem of emerging resistance is the appearance, relatively recently, of organisms with multidrug resistance. This occurs when the organisms acquire resistance genes carried by plasmids or transposons. In certain bacteria, such as Streptococcus pneumoniae, resistance may even be acquired by direct incorporation and remodeling of DNA from closely related oral commensal bacteria, by the process of natural transformation [10]. It is only recently that we have begun to appreciate the complexity of the mechanisms in which the "normal" human flora develops resistance; when humans are treated unnecessarily or treated with inappropriate regimens, invading pathogens can acquire resistancecoding DNA from colonizing microflora [11]. Although both clinical practice and environmental conditions may help to enhance the growth of select bacteria with newly acquired resistance genes, it is clear that the selection pressure generated by the use of antibiotics is one of the critical factors in the emergence and dissemination of bacteria resistant to antimicrobial agents [3, 12, 13].

DRUG DEVELOPMENT AND EMERGENCE OF ANTIMICROBIAL RESISTANCE

Bacteria can manifest resistance by a variety of mechanisms. For the penicillin-

resistant pneumococcus, however, the only significant mechanism demonstrated to date is alteration in the penicillin-binding proteins (PBPs), the target site for β lactams. This alteration is accomplished by remodeling of DNA through the unique mechanism of natural transformation [14]. The PBPs themselves are transpeptidase and carboxypeptidase enzymes involved in bacterial cell wall synthesis and are the primary target sites for all β -lactams. It is not surprising, therefore, that penicillin-resistant pneumococci also exhibit varying degrees of resistance to other penicillins and, occasionally, to cephalosporins. The situation is further complicated by the fact that certain strains are resistant to third-generation cephalosporins but susceptible to penicillin G [15, 16].

Analysis of the sequence of the structural genes for PBPs indicated that, although the genes of susceptible S. pneumoniae are conserved, those of resistant strains have a mosaic structure composed of blocks, some of which are similar to and some of which are different from their counterparts in susceptible strains [17]. The "diverged regions" are acquired from other bacterial species that are part of the normal flora of the human oral cavity, such as Streptococcus mitis or Streptococcus oralis (viridans group streptococci), by means of horizontal transfer (transformation) followed by homologous recombination of genetic material [14, 18].

"Multidrug resistance" refers to resistance to ≥3 antimicrobials that have different mechanisms of action. This resistance is due to the stable coexistence in the bacterial genome of mutations in various housekeeping genes or of assortments of acquired foreign genes, each of which confers resistance to a class of antibiotics [19]. Multidrug-resistant *S. pneumoniae*, first reported in South Africa in 1977, have now been recovered in a number of countries [20–22]. One type of resistance of particular concern to clinicians is that mediated by the *ermB* gene. This confers resistance not only to the macrolide class

but to lincosamides and streptogramin B compounds as well [23, 24]. For unknown reasons, some multidrug-resistant *S. pneumoniae* clones have disseminated worldwide and account for the observed coresistance to various drug classes [25].

Recently there has been a marked increase in the percentages of pneumococcal isolates that are penicillin resistant. Most worrisome is the propensity for pneumococcal resistance to penicillin G to be associated with reduced susceptibility to other drugs, such as macrolides, lincosamides, and streptogramins; tetracyclines; chloramphenicol; and trimethoprim-sulfamethoxazole. In the United States, 58.9% of pneumococcal isolates recovered from blood that are penicillin resistant are also macrolide resistant (D. Sahm, personal communication). Fluoroquinolone resistance in pneumococci has also been reported recently [26], and an association between penicillin and fluoroquinolone resistance in the pneumococcus has been suggested [27, 28].

Fluoroquinolone resistance is not limited to S. pneumoniae and has been documented in other pathogens as well, including those responsible for urinary, respiratory, and gastrointestinal tract infections, skin and soft-tissue and bone and joint infections, sexually transmitted diseases, and ulcers. The microorganisms include gram-positive and gram-negative cocci, such as methicillin-susceptible and methicillin-resistant S. aureus and Neisseria gonorrhoeae, respectively; gram-negative rods, such as Pseudomonas aeruginosa and Serratia marcescens; Mycobacterium tuberculosis and atypical mycobacteria; and Campylobacter jejuni and Helicobacter pylori [29-36].

The critical question, however, is whether in vitro resistance necessarily means that treatment will result in clinical failure. This question is important, because *S. pneumoniae* causes infection in a number of sites that are not only anatomically distinct but functionally and biologically distinct as well. Otitis media is, essentially, a closed-space infection, and

meningitis treatment is complicated by the presence of the blood-brain barrier.

For penicillin therapy of pneumococcal pneumonia, no bacteriologically confirmed treatment failures have been reported for infections caused by organisms with penicillin MICs of <4 mg/L [37–39]. For strains with MICs of ≥4 mg/L, data are conflicting regarding the occurrence of treatment failure [40–45].

There are also data regarding the relevance of macrolide-resistant *S. pneumoniae*. A recent paper described 4 patients with infection caused by *S. pneumoniae* with low-level macrolide resistance who failed to respond to outpatient oral therapy with either azithromycin or clarithromycin [46]. Pharmacodynamic principles suggest that macrolide-resistant strains with MICs of ≥8 mg/L should not respond to macrolide therapy, and >20 cases have now been documented of pneumococcal bacteremia due to such macrolide-resistant strains that occurred after macrolide therapy [46–50].

In vitro evidence suggests that fluoroquinolones, such as moxifloxacin and trovafloxacin, are superior to older agents, such as ciprofloxacin and levofloxacin, in that they do not permit subpopulations of bacteria with single mutations to survive after exposure to drug concentrations that exceed their MICs and are, thus, less likely to select for resistant mutants [51]. Clinical data also support this observation: for example, gatifloxacin was compared with levofloxacin in a prospective, blinded trial, and the only culture-proven treatment failures for cases of pneumonia caused by S. pneumoniae (3 cases) or S. aureus (2 cases) occurred in the levofloxacin arm [52].

It would appear, therefore, that the problem of fluoroquinolone resistance is solved and that 2 new fluoroquinolones, moxifloxacin and gatifloxacin, that have potent antipneumococcal activity are now available for use. Unfortunately, the problem is far from solved. A disturbing article reported that 2 of 29 pneumococcal isolates were resistant not only to ciproflox-

acin but to moxifloxacin and trovafloxacin as well—2 of the very potent "newer quinolones" that were under development and had not seen widespread clinical use at the time of publication [53]. Furthermore, a case-control study from Hong Kong demonstrated that a key risk factor for acquisition of fluoroquinolone-resistant S. pneumoniae was prior treatment with ofloxacin, levofloxacin, or ciprofloxacin (OR, 10.7) [54]. These findings clearly raise concerns that use of earlier fluoroquinolones poses the risk of infection with organisms with resistance to newer, more potent agents. The study showed that pneumococcal resistance to fluoroquinolones is essentially a class effect [54], and, by extrapolation from past experience, it seems clear that overuse of one member of this class may weaken the effectiveness of structurally related drugs.

ADVERSE DRUG REACTIONS

A detailed discussion of adverse drug reactions is beyond the scope of this article. However, discussion of fluoroquinolones would be incomplete without some mention of drug-related toxicity. As a result of initial concerns about potential toxicity in children, there are few data on the experimental use of these agents in pediatric practice, and most of our information derives from animal experiments, experimental and clinical use to treat adults, and use to treat children as part of compassionate-use programs.

The description of cartilage lesions in weight-bearing diarthrodial joints of juvenile animals that occurred following exposure to fluoroquinolones led to the moratorium on the use of fluoroquinolones to treat children. Arthropathy is a class effect, and virtually all fluoroquinolones tested have induced changes in immature cartilage in all animals studied [55–57]. The lesions typically are fissures, blisters, and erosions resulting from necrosis of the chondrocytes and disruption of the extracellular matrix [55]. The precise mechanism is unknown, and no def-

inite relationship has been established between fluoroquinolone structure and this adverse event. It is thought, however, that the fluoroquinolones chelate magnesium ions, resulting in disruption of the signal transduction from the chondrocyte surface integrin receptors that are thought to play a role in maintaining the integrity of the cartilage matrix [58]. To date, there is no evidence categorically linking fluoroquinolone use to arthropathy in humans, and the long-standing restrictions on fluoroquinolone use appear to be lifting [59].

Other adverse reactions that occur in adults also will be of potential concern in children, if these drugs are released for general use. They are seizures; cardiotoxicity, in the form of QT interval prolongation and malignant arrhythmias; and phototoxicity. CNS effects, which rarely include seizures, occur either as the result of direct action of a drug on CNS receptors or as the result of an interaction between the fluoroquinolone and another pharmacologic agent. Direct actions are further divided into the blocking of the γ -aminobutyric acid receptor and primary excitatory effects mediated by the Nmethyl-D-aspartate adenosine receptor [60, 61].

The main area of interest related to cardiotoxicity is prolongation of the QT interval [62]. This phenomenon has been well described with other agents, including the macrolides, and it may be a class effect for the fluoroquinolones. The precise mechanism is not known, but it is likely multifactorial. It is generally thought that fluoroquinolones should not be given to patients known to have QT interval prolongation nor to patients receiving concomitant therapy with agents that might increase the QT interval and induce bradycardia or torsades de pointes.

Phototoxicity may occur if the dose of a photolabile drug and exposure to UV light are sufficiently high. Certain fluoroquinolones can cause the formation of toxic monovalent oxygen radicals after such exposure, and these, in turn, may attack cellular lipid membranes, resulting, ultimately, in the clinical manifestations of phototoxicity [63]. Halogenation at the C-8 position is one of the main determinants of such an adverse event [64].

CURRENT DILEMMA AND FUTURE PROBLEMS

Evidence is accumulating that multidrug resistance in pneumococci is related to prescription of antimicrobial agents to a critically important reservoir for these organisms: children. This likely occurs because children, more often than adults, are colonized with high-density populations of pneumococci in the nasopharynx, which increases the potential for resistance development and, thus, raises the specter of rapidly accelerating development of resistance to antimicrobial drugs, including fluoroquinolones, should this class of antimicrobials be overused among children, as they have been among adults. Supporting this concern are studies of day care and pediatric chronic care centers that have found a very high prevalence of nasopharyngeal carriage of drug-resistant strains of S. pneumoniae [65, 66]. Overcrowding facilitates the transmission of resistant strains from colonized to susceptible infants and children who, in turn, serve as a source for further transmission to family members and, ultimately, to the general population [67]. Investigators also found high rates of pneumococcal carriage (50%) among children [68] and found that prior receipt of antibiotics significantly increased the risk of harboring a drug-resistant strain [68, 69]. However, rather than suggesting that new antimicrobials were needed for the treatment of children, the authors of the study recommended reducing unnecessary use of antimicrobials in the community as the most appropriate course of action, particularly because most of the infections treated with antimicrobials are viral [69]. Finally, the prevalence of macrolide resistance among pneumococci doubled in the United States between 1995 and 1999, during which time use of macrolides remained stable in the population ≥5 years of age but increased by 320% in the population <5 years of age [70].

A new concern about widespread use of fluoroquinolones to treat children, as well as adults, is the recent recognition of horizontal transfer of fluoroquinolone resistance from viridans group streptococci (such as S. oralis and S. mitis) to S. pneumoniae [10, 11]. Once resistance mutations develop in these naturally commensal organisms as a result of fluoroquinolone exposure (even in the absence of pathogenic pneumococci), any subsequent pneumococcal infection carries the risk that the infecting strain of S. pneumoniae will readily acquire fluoroquinolone resistance-determining DNA regions when antimicrobial therapy is instituted. These fluoroquinolone-resistant S. pneumoniae can then be easily spread from child to parent, followed by widespread dissemination to the adult population.

The dangerous triad of antibiotic misuse, a reservoir of resistance genes, and a closed-space pneumococcal infection (otitis media) would come together if fluoroquinolones were approved for general use in the pediatric population. The odds of the appearance and dissemination of resistant strains through the emergence of de novo resistance and clonal spread would likely increase dramatically. Fluoroquinolone resistance has already been observed in globally distributed clones of multidrug-resistant pneumococci [71]. These clones are encapsulated and belong to the serotypes most commonly found among children. Resistant isolates already exist and, under the influence of enhanced selection pressure, will rapidly disseminate themselves or their resistance genes. Our previous experience with the spread of penicillin resistance allows us to predict that such spread will occur with other drug classes. It is likely that, shortly after their approval for use in pediatric practice, fluoroquinolones will be as widely used as they are in the adult population, and any advantages of using them will dissipate quickly. As already mentioned, pneumococci have cross-resistance, albeit at various levels, to fluoroquinolones. For strains that are more resistant to the less active drugs [19], the most active agents will likely select for clones that are resistant to both the older and newer drugs. Thus, inappropriate and unnecessary use of the new fluoroquinolones will exert the selection pressure required for clonal dissemination of the most-resistant isolates.

This brings us to the heart of the matter. Do we really need fluoroquinolones for general use in pediatric practice? The broad spectrum of many of the fluoroquinolones, coupled with their ease of use (once-daily dosing for many patients), makes them appealing to physicians and patients alike. There is no question that fluoroquinolones are valuable for treatment of selected pediatric patients. However, we propose that their use to treat children be limited to those specific infections complicated by special conditions for which the benefit of these drugs is clear and for which no alternative safe and effective antibiotic therapy is available [72, 73]. To date, potential pediatric indications for fluoroquinolones include pseudomonal bronchopulmonary exacerbation in cystic fibrosis [74–76], complicated urinary tract infection [77, 78], invasive gastrointestinal infection [79, 80], and chronic ear infection [81]. For these 4 specific infections, results of controlled clinical trials have shown similar efficacy for the fluoroquinolones and conventional regimens [74-81]. Preliminary experience with pediatric patients also indicates that the fluoroquinolones are effective and safe for the eradication of nasopharyngeal carriage of meningococci [82] and for treatment of selected patients with febrile neutropenia [80, 83, 84] or invasive infection caused by multidrug-resistant pathogens [85, 86]. Such limited use certainly does not require that the regulatory authorities approve fluoroquinolones for general use in the pediatric population.

The selection of antibiotic-resistant pneumococci, however, is likely to occur

more rapidly among children than among adults, because nasopharyngeal colonization with high-density populations of pneumococci is more common among children [87]. Fluoroquinolones have not been widely prescribed for children because of potential toxicity problems; therefore, there are no data on the effect of such drugs on the selection of resistant pneumococcal mutants in the nasopharynx of children, whereas there are such data for adults [88]. Thus, although this class of drugs is able to eradicate meningococcal carriage in children, it would be prudent to conduct studies of selection for resistant mutants, as a matter of urgency, before use of the new fluoroquinolones to treat children is considered.

There is no compelling need to extend regulatory approval for use of these important agents in persons aged <16 years. Pichichero et al. [89] recently documented that >75% of pediatric patients who visited a physician for acute respiratory tract infection did not require antimicrobial therapy at the first office visit. The ideal was to prescribe antimicrobials only for those patients who clearly needed them. It is of interest that there were more return visits related to the initial infection among children who were given antibiotics than among children who were not [89]. The authors of this commentary are unanimous in their desire for more prudent use of fluoroquinolones to treat adult patients and in their objection to the approval of fluoroquinolones for use in pediatric patients and the subsequent widespread use of these drugs [89]. Hooper [90] raised a similar note of caution in his recent review of the fluoroquinolones. He suggests that avoidance of their routine administration may play a significant role in limiting the spread of pneumococcal resistance to these drugs.

Multiple alternatives are usually available for treatment of most infections in the pediatric population. Reserving the fluoroquinolones for treatment of adults, in whom their efficacy and safety are clear and well documented, is one step we can

all take to extend the period of utility of the fluoroquinolone class.

References

- Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1990–1999. MMWR Morb Mortal Wkly Rep 1999; 48:241–3.
- Abraham EP. Chain E: an enzyme from bacteria able to destroy penicillin. Nature 1940; 146:837–9.
- Austin DJ, Kristinsson KG, Anderson RM.
 The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Proc Natl Acad Sci USA 1999; 96:1152–6.
- Baquero F. Antibiotic resistance in Spain: what can be done? Task Force of the General Directions for Health Planning of the Spanish Ministry of Health. Clin Infect Dis 1996; 23: 819–23.
- Benveniste R, Davies J. Aminoglycoside antibiotic-inactivating enzymes in actinomycetes similar to those present in clinical isolates of antibiotic-resistant bacteria. Proc Natl Acad Sci USA 1973; 70:2276–80.
- Marshall CG, Lessard IAD, Park IS, Wright GD. Glycopeptide antibiotic resistance genes in glycopeptide-producing organisms. Antimicrob Agents Chemother 1998; 42:2215–20.
- Patel R, Piper K, Cockerill FR III, Steckelberg JM, Yousten AA. The biopesticide *Paenibacil-lus popilliae* has a common vancomycin resistance gene cluster to the enterococcal *vanA* vancomycin resistance gene cluster. Antimicrob Agents Chemother **2000**; 44:705–9.
- Levy SB. Antibiotic resistance: microbial adaptation and evolution. In: The antibiotic paradox: how miracle drugs are destroying the miracle. New York: Plenum Press, 1992: 67–103.
- Gardner P, Smith DH, Beer H, Moellering RC. Recovery of resistance factors from a drugfree community. Lancet 1970; 1:301.
- 10. Gonzalez I, Georgiou M, Alcaide F, Balas D, Liñares J, de la Campa AG. Fluoroquinolone resistance mutations in the *parC*, *parE*, and *gyrA* genes of clinical isolates of viridans group streptococci. Antimicrob Agents Chemother **1998**; 42:2792–8.
- Ferrándiz MJ, Fernoll A, Liñares J, de La Campa AG. Horizontal transfer of parC and gyrA in fluoroquinolone-resistant clinical isolates of Streptococcus pneumoniae. Antimicrob Agents Chemother 2000; 44:840–7.
- Tenover FC, Hughes JM. The challenges of emerging infectious diseases: development and spread of multiply-resistant bacterial pathogens. JAMA 1996; 275:300–4.
- Cohen M. Epidemiology of drug resistance: implications for a post-antimicrobial era. Science 1992; 257:1050–55.
- 14. Lorenz MG, Wackernagel W. Bacterial gene transfer by natural genetic transformation in

- the environment. Microbiol Rev **1994**; 58: 563–602.
- Figueiredo AMS, Connor JD, Severin A, Vaz Pato MV, Tomasz A. A pneumococcal clinical isolate with high-level resistance to cefotaxime and ceftriaxone. Antimicrob Agents Chemother 1992; 36:886–9.
- Dowson CG, Johnson AP, Cercenado E, George RC. Genetics of oxacillin resistance in clinical isolates of *Streptococcus pneumoniae* that are oxacillin resistant and penicillin susceptible. Antimicrob Agents Chemother 1994; 38:49–53.
- Dowson CG, Hutchison A, Brannigan JA, et al. Horizontal transfer of penicillin-binding protein genes in penicillin-resistant clinical isolates of *Streptococcus pneumoniae*. Proc Natl Acad Sci USA 1989; 86:8842–6.
- Dowson CG, Coffey TJ, Kell C, Whiley RA. Evolution of penicillin resistance in *Streptococcus pneumoniae*: the role of *Streptococcus mitis* in the formation of a low affinity PBP2B in *S. pneumoniae*. Mol Microbiol 1993; 9: 635–43.
- Courvalin P, Trieu-Cuot P. Minimizing potential resistance: the molecular view. Clin Infect Dis 2001; 33(Suppl 3):S138–46.
- 1997 ASCP Susceptibility Testing Group. United States geographic bacteria susceptibility patterns. Diagn Microbiol Infect Dis 1999; 35:143–51.
- Jacobs MR, Koornhof HJ, Robbins-Browne RM, et al. Emergence of multiply resistant pneumococci. N Engl J Med 1978; 299: 735–40.
- 22. McDougal LK, Facklam R, Reeves M, et al. Analysis of multiply antimicrobial-resistant isolates of *Streptococcus pneumoniae* from the United States. Antimicrob Agents Chemother 1992; 36:2176–84.
- Courvalin P, Carlier C. Transposable multiple antibiotic resistance in *Streptococcus pneu-moniae*. Mol Gen Genet 1986; 205:291–7.
- Leclercq R, Courvalin P. Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. Antimicrob Agents Chemother 1991; 35:1273–6.
- McGee L, McDougal L, Zhou J, et al. Nomenclature of major antibiotic-resistant clones of *Streptococcus pneumoniae* defined by the Pneumococcal Molecular Epidemiology Network. J Clin Microbiol 2001; 39:2565–71.
- Ho PL, Yung RW, Tsang DN, et al. Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: results of a Hong Kong multicentre study in 2000. J Antimicrob Chemother 2001; 48:659–65.
- 27. Chen DK, McGeer A, De Azavedo JC, Low DE. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N Engl J Med **1999**; 341:233–9.
- Goldsmith CE, More JE, Murphy PG, Ambler JE. Increased incidence of ciprofloxacin resistance in penicillin-resistant pneumococci in Northern Ireland. J Antimicrob Chemother 1998; 41:420–1.
- 29. Greenberg RN, Kennedy DI, Reilly PM, et al.

- Treatment of bone, joint, and soft tissue infections with oral ciprofloxacin. Antimicrob Agents Chemother **1987**; 31:151–5.
- Fass RJ. Treatment of skin and soft tissue infections with oral ciprofloxacin. J Antimicrob Chemother 1986; 18(Suppl D):153–7.
- 31. van der Willigen AH, van der Hoek JCS, Wagenvoort JHT, et al. Comparative double-blind study of 200- and 400-mg enoxacin given orally in the treatment of acute uncomplicated urethral gonorrhea in males. Antimicrob Agents Chemother 1987; 31:535–8.
- Wolfson JS, Hooper DC. Fluoroquinolone antimicrobial agents. Clin Microbiol Rev 1989; 2:378–424.
- Tsukamura M, Nakamura E, Yoshii S, Amano H. Therapy effect of a new antibacterial substance ofloxacin (DL8280) on pulmonary tuberculosis. Am Rev Respir Dis 1985; 131: 352–6.
- 34. Wallace RJ Jr, Bedsole G, Sumter G, et al. Activities of ciprofloxacin and ofloxacin against rapidly growing mycobacteria with demonstration of acquired resistance following single-drug therapy. Antimicrob Agents Chemother 1990; 34:65–70.
- Goodman LJ, Trenholme GM, Kaplan RL, et al. Empiric antimicrobial therapy of domestically acquired acute diarrhea in urban adults. Arch Intern Med 1990; 150:541–6.
- Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. N Engl J Med 1991; 324: 384–94.
- Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group. Arch Intern Med 2000; 160:1399–408.
- Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000; 31:347–82.
- 39. Mandell LA, Marrie TH, Grossman RF, et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Canadian Community-Acquired Pneumonia Working Group. Clin Infect Dis 2000; 31:383–421.
- Choi E, Lee H. Clinical outcome of invasive infections by penicillin-resistant *Streptococcus* pneumoniae in Korean children. Clin Infect Dis 1998; 26:1346–54.
- Deeks SL, Palacio R, Rinsky R, et al. Risk factors and course of illness among children with invasive penicillin-resistant *Streptococcus* pneumoniae. Pediatrics 1999; 103:409–13.
- Feikin D, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. Am J Public Health 2000; 90:223–9.
- Turrett GS, Blum S, Fazal BA, Justman JE, Telzak EE. Penicillin resistance and other predictors of mortality in pneumococcal bacter-

- emia in a population with high HIV sero-prevalence. Clin Infect Dis **1999**; 29:321–7.
- Buckingham SC, Brown SP, Joaquin VH. Breakthrough bacteremia and meningitis during treatment parenterally with cephalosporins for pneumococcal pneumonia. J Pediatr 1998; 132:174–6.
- Dowell SF, Smith T, Leversedge K, Snitzer J. Pneumonia treatment failure associated with highly resistant pneumococci. Clin Infect Dis 1999; 29:462–3.
- Kelley MA, Weber DJ, Gilligan P, Cohen MS. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. Clin Infect Dis 2000; 31: 1008–11.
- Klugman KP, Koornhof HJ, Kuhnle V, Miller SD, Ginsberg P, Mauff AC. Meningitis and pnuemonia due to novel multiply resistant pneumococci. BMJ 1986; 292:730.
- 48. Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. Clin Infect Dis **2002**; 35:556–64.
- Gootz DG, Brighty KE. Chemistry and mechanism of action of the quinolone antibacterial.
 In: Andriole VT, ed. The quinolones. 2nd ed.
 London: Academic Press, 1998:29–80.
- Schut RL, Peterson LR, Shanholtzer CJ, Janoff EN. Development of erythromycin-resistant pneumococcal endocarditis in a patient receiving erythromycin for communityacquired pneumonia. Infect Dis Clin Pract 1994; 3:108–10.
- 51. Beyer R, Pestova E, Millichap JJ, Stosor V, Noskin GA, Peterson LR. A convenient assay for estimating the possible involvement of efflux of fluoroquinolones by *Streptococcus* pneumoniae and *Staphylococcus aureus*: evidence for diminished moxifloxacin, sparfloxacin, and trovafloxacin efflux. Antimicrob Agents Chemother 2000; 44:798–801.
- Sullivan JG, McElroy AD, Honsinger RW, et al. Treating community-acquired pneumonia with once-daily gatifloxacin vs once-daily levofloxacin. J Respir Dis 1999; 20(Suppl): S49–59.
- Wise R, Brenwald N, Gill M, Fraisc A. Streptococcus pneumoniae resistance to fluoroquinolones [letter]. Lancet 1996; 348:1660.
- Ho PL, Tse WS, Tsang KWT, et al. Risk factors for acquisition of levofloxacin-resistant *Strep-tococcus pneumoniae*: a case-control study. Clin Infect Dis 2001; 32:701–7.
- Stahlmann R, Merker HJ, Hinz N, et al. Ofloxacin in juvenile non-human primates and rats: arthropathia and drug plasma concentrations. Arch Toxicol 1990; 64:193–204.
- Linseman DA, Hampton LA, Branstetter DG. Quinolone-induced arthropathy in the neonatal mouse: morphological analysis of articular lesions produced by pipemidic acid and ciprofloxacin. Fundam Appl Toxicol 1995; 28: 59–64.
- 57. Burkhardt JE, Hill MA, Carlton WW, Kester-

- son JW. Histologic and histochemical changes in articular cartilages of immature beagle dogs dosed with difloxacin, a fluoroquinolone. Vet Pathol **1990**; 27:162–70.
- Hynes RQ. Integrins: versatility, modulation and signaling in cell adhesion. Cell 1992; 69: 11–25.
- Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. Clin Infect Dis 1997; 25:1196–204.
- Takayama S, Hirohashi M, Kato M, Shimada H. Toxicity of quinolone antimicrobial agents.
 J Toxicol Environ Health 1995; 45:1–45.
- Schmuck G, Schurmann A, Schluter G. Determination of the excitatory potencies of fluoroquinolones in the central nervous system by an in vitro model. Antimicrob Agents Chemother 1998; 42:1831–6.
- Ball P. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. J Antimicrob Chemother 2000; 45:557–9.
- Ball P, Tillotson GS. Tolerability of fluoroquinolone antibiotics: past, present and future. Drug Saf 1995; 13:343–58.
- Domagala JM. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. J Antimicrob Chemother 1994; 33:685–706.
- 65. Yagupsky P, Porat N, Fraser D, et al. Acquisition, carriage, and transmission of pneumococci with decreased antibiotic susceptibility in young children attending a day care facility in southern Israel. J Infect Dis 1998; 177:1003–12.
- Mannheimer SB, Riley LW, Roberts RB. Association of penicillin-resistant pneumococci with residence in a pediatric chronic care facility. J Infect Dis 1996; 174:513–9.
- 67. Kronenberger CB, Hoffman RE, Lezotte DC, Marine WM. Invasive penicillin-resistant pneumococcal infections: a prevalence and historical cohort study. Emerg Infect Dis 1996: 2:121–4
- 68. De Lencastre H, Kristinsson KG, Brito-Avo A, et al. Carriage of respiratory tract pathogens and molecular epidemiology of *Streptococcus pneumoniae* colonization in healthy children attending day care centers in Lisbon, Portugal. Microb Drug Resist **1999**; 5:19–29.
- 69. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross-sectional prevalence study. BMJ 1996; 313:387–91.
- Hyde TB, Gay K, Stephens DS, et al. Macrolide resistance among invasive *Streptococcus pneu-moniae* isolates. JAMA 2001; 286:1857–62.
- McGee L, Goldsmith CE, Klugman KP. Fluoroquinolone resistance among clinical isolates of *Streptococcus pneumoniae* belonging to international multiresistant clones. J Antimicrob Chemother 2002; 49:173–6.
- 72. Schaad UB, Salam MA, Aujard Y, et al. Use of fluoroquinolones in pediatrics: consensus report of an International Society of Che-

- motherapy commission. Pediatr Infect Dis J 1995; 14:1–9.
- Schaad UB. Use of the quinolones in pediatrics. In: Andriole VT, ed. The quinolones.
 3rd ed. London: Academic Press, 2000: 455-75
- Schaad UB, Wedgwood J, Ruedeberg A, et al. Ciprofloxacin as antipseudomonal treatment in patients with cystic fibrosis. Pediatr Infect Dis J 1997; 16:106–11.
- Church DA, Kanga JF, Kuhn RJ, et al. Sequential ciprofloxacin therapy in pediatric cystic fibrosis: comparative study vs ceftazidime/tobramycin in the treatment of acute pulmonary exacerbations. Pediatr Infect Dis J 1997; 16:91–105.
- 76. Richard DA, Nousia-Arvanitakis S, Sollich V, et al. Oral ciprofloxacin versus intravenous ceftazidime plus tobramycin in pediatric cystic fibrosis patients: comparison of antipseudomonas efficacy and assessment of safety using ultrasonography and magnetic resonance imaging. Pediatr Infect Dis J 1997; 16:572–8.
- Van Wijk JAE, de Jong TPVM, Van Gool JD, et al. Using quinolones in urinary tract infections in children. Adv Antimicrob Antineopl Chemother 1992; 11(Suppl 2):157–61.
- 78. Fujii R, Meguro H, Arimasu O, et al. Evaluation of norfloxacin in the pediatric field. Pe-

- diatric Study Group for Norfloxacin. Jpn J Antibiot 1990; 43:181–215.
- Salam MA, Dhar U, Khan WA, Bennish ML. Randomised comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis. Lancet 1998; 352:522–7.
- 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: 1060–7.
- Lang R, Goshen S, Raas-Rothschild A. Oral ciprofloxacin in the management of chronic suppurative otitis media without cholesteatoma in children: preliminary experience in 21 children. Pediatr Infect Dis J 1992; 11: 925–9.
- Cuevas LE, Kazembe P, Mughogho GK, et al. Eradication of nasopharyngeal carriage of Neisseria meningitidis in children and adults in rural Africa: a comparison of ciprofloxacin and rifampicin. J Infect Dis 1995; 171:728–31.
- Patrick CC. Use of fluoroquinolones as prophylaxis agents in patients with neutropenia. Pediatr Infect Dis J 1997; 16:135–9.
- Freifeld A, Pizzo P. Use of fluoroquinolones for empirical management of febrile neutropenia in pediatric cancer patients. Pediatr Infect Dis J 1997; 16:140–6.

- Bannon MJ, Stutchfield PR, Weindling AM, et al. Ciprofloxacin in neonatal *Enterobacter cloacae* septicaemia. Arch Dis Child 1989; 64: 1388–91.
- 86. Krcmery V, Filka J, Uher J, et al. Ciprofloxacin in treatment of nosocomial meningitis in neonates and in infants: report of 12 cases and review. Diagn Microbiol Infect Dis 1999; 35: 75–80.
- 87. Ekdahl K, Ahlinder I, Hansson HB, et al. Duration of nasopharyngeal carriage of penicil-lin-resistant *Streptococcus pneumoniae*: experiences from the south Swedish pneumococcal intervention project. Clin Infect Dis 1997; 25: 1113–7.
- Ball P, Mandell L, Niki Y, Tillotson G. Comparative tolerability of the newer fluoroquinolone antibacterials. Drug Safety 1999; 21: 407–21.
- Pichichero ME, Green JL, Francis AB, Marsocci SM, Murphy ML. Outcomes after judicious antibiotic use for respiratory tract infections in a private pediatric practice. Pediatrics 2000; 105:753–9.
- Hooper DC. New uses for new and old quinolones and the challenge of resistance. Clin Infect Dis 2000; 30:243–54.