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 resistance-coding 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 $\geqslant$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 ciprofloxacin 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 definite 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 *N*-methyl-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 $\geq$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.

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