GLOBAL BURDEN OF ANTIMICROBIAL RESISTANCE

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ABSTRACT

Analysis of the global burden of antimicrobial resistance may give answers to several questions important for treatment decisions: Does overall antibiotic consumption drive antibiotic resistance? Why are there differences in consumption between countries? Are there differences between penicillins, cephalosporins, and macrolides in terms of resistance induction? Antibiotic consumption appears to correlate with increases in antibiotic resistance, particularly for Streptococcus pneumoniae, and this is most clearly observable in data from the European Surveillance of Antimicrobial Consumption study in Europe. Of the various factors that influence antibiotic consumption, the physician/patient relationship is key. A patient-education campaign in Belgium to promote patient understanding of the appropriate use of antibiotics had dramatic effects on the level of prescribing. Mathematical models of antibiotic resistance demonstrate that antibiotic treatment can increase the transmission of resistant bacteria within a population, even when treated individuals have no increased risk of resistance. Antimicrobial agents that can eradicate resistant and susceptible strains have a theoretical advantage in these models, in terms of reducing the risk of transmission of resistance in the community. However, further studies are required to provide definitive data comparing different antibiotic classes. (Adv Stud Med. 2006;6(7C):S644-S651)

Analysis of the global burden of antimicrobial resistance may give answers to several important questions that help physicians to make decisions on treatment and prescribing. For example, does overall antibiotic consumption drive antibiotic resistance? Why are there differences in consumption between countries? Are there differences between penicillins, cephalosporins, fluoroquinolones, and macrolides in terms of resistance induction? This article seeks to answer these questions and uses mechanisms of emergence of resistance and antibiotic modeling to suggest appropriate prescribing practice.

ANTIBIOTIC CONSUMPTION AND ANTIBIOTIC RESISTANCE

The best data linking the overall consumption of antibiotics to the development of antibiotic resistance comes from the European Surveillance of Antimicrobial Consumption (ESAC) study. In this study, conducted in 34 countries including Turkey and Israel, consumption was reported as defined daily doses per 1000 inhabitants/day (DIDs) using wholesale sales or reimbursement data. These data are imperfect: wholesale sales data may overestimate antibiotic use in those countries that export antibiotics, whereas reimbursement data fails to capture over-the-counter sales, which are a problem in some European countries. In general, in Europe and North America, separation of dispensing and prescribing is a well-established system, whereas in Asia, hospitals and physicians relied histori-
cally on profits from drug price differences as a source of revenue. Of 26 countries for which 2002 data were available, France had the highest consumption, with 32 DIDs, and the Netherlands had the lowest at 10 DIDs.

Data from other countries show that Australia has consumption around the middle of the ESAC countries at approximately 20 DIDs. We converted US ambulatory care antibiotic use data, obtained from IMS, into DID, in accordance with the Anatomic Therapeutic Chemical (ATC) classification, and found that, in 2004, use was 21.6 DIDs (penicillins ATC J01C, 10.6 DIDs; cephalosporins ATC J01DA, 3.6 DIDs; sulfonamides/trimethoprim ATC J01E, 2.5 DIDs; macrolides/lincosamides/streptogramins ATC J01F, 1.9 DIDs; quinolones ATC J01M, 1.7 DIDs; and tetracyclines ATC J01A, 1.1 DIDs). Quinolones are the fastest growing antibiotic class, and 2002 data from IMS, expressed in prescriptions/1000 inhabitants/year, show striking worldwide differences: Japan, 231; Spain, 154; United States, 86; Germany, 63; and France, 38 prescriptions/1000 inhabitants/year. In Japan, the new “respiratory” quinolones are the most widely prescribed quinolones (127 prescriptions/1000 inhabitants/year) followed by the United States (51 prescriptions/1000 inhabitants/year). In Japan, the new “respiratory” quinolones are the most widely prescribed quinolones (127 prescriptions/1000 inhabitants/year) followed by the United States (51 prescriptions/1000 inhabitants/year). In a recent study, Suda studied antimicrobial prescribing patterns among 48,971 anti-infective prescriptions in the United States over 3 years (2001–2003), and stratified according to ICD-9s. Upper respiratory tract infections (RTIs) were found to be the major reason for outpatient antibiotic use.

Fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin, and ciprofloxacin) represented 13% of antibiotics prescribed in RTIs, in lower RTI, the proportion increased from 21% in 2001 to 35% in 2003; in upper RTI, the proportion increased from 7% in 2001 to 13% in 2003. Interestingly, 10% of RTIs were treated with ciprofloxacin. In ESAC, there was a correlation between outpatient penicillin use and the prevalence of penicillin resistance in Streptococcus pneumoniae (Figure 1). The Netherlands, which had the lowest outpatient penicillin use (3.9 DIDs), had less than 2% penicillin resistance. In France, which had the highest outpatient use of penicillin (16.3 DIDs), more than 40% of S pneumoniae isolates demonstrated penicillin resistance. Based on this figure, ambulatory care penicillin (ATC J01C group) use (10.6 DIDs in 2004) correlates nicely with S pneumoniae penicillin resistance (20.2% in 2003) in the United States. ESAC also showed a correlation between macrolide use and erythromycin resistance in S pneumoniae and (although less pronounced) in Streptococcus pyogenes.

In the United States, McCaig et al used data from the 1992 to 2000 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey to assess antibiotic use among ambulatory patients. There were 461 antibiotic prescriptions per 1000 inhabitants and 125 antibiotic prescriptions per 1000 visits in 2000, representing falls of 23% and 25%, respectively, from 1992 levels. Over the study period, there were decreases in the numbers of prescriptions per 1000 visits for amoxicillin and ampicillin (-43%), cephalosporins (-28%), erythromycin (-76%), other penicillins, tetracyclines, and trimethoprim-sulfamethoxazole, and increases in prescriptions for azithromycin and clarithromycin (+388%) and quinolones (+78%). However, this study did not examine levels of antibiotic resistance. The Tracking Resistance in the United States Today Surveillance

![Figure 1. Correlation Between Penicillin Use in 2000 and Prevalence of Penicillin-Nonsusceptible Streptococcus pneumoniae](image-url)
Program showed that the prevalence of antibiotic resistance among *S. pneumoniae* increased between winter 1998 to 1999 and winter 2001 to 2002. During this period, resistance to azithromycin rose from 22.7% to 27.5%, resistance to penicillin increased from 14.7% to 18.4%, and resistance to ceftriaxone rose from 1.2% to 1.7%.

Despite the fact that higher levels of antibiotic consumption are related to increased rates of resistance, there may be downsides to reducing antibiotic consumption. For example, a recent study showed that the incidence rate of acute mastoiditis in countries with low antibiotic use was higher than countries with high antibiotic use, albeit 2 extra cases per 100,000 children per year. A retrospective study showed recently that the reduction of antibiotic prescribing was associated with an increase in community-acquired pneumonia mortality in England and Wales, but this study suffers from serious flaws. However, prospective studies are needed to link outpatient antibiotic use and interventions that reduce prescribing with the incidence of serious complications of RTIs.

**Differences in National Consumption**

One major factor in the variety of antibiotic consumption levels in different countries is the relationship between the patient and his/her doctor. In countries where the relationship is very distant and patients feel unable to have a dialogue about their treatment with their physician, there is significantly more prescribing of antibiotics. In contrast, in countries where patients must register with a particular primary care physician and it is more difficult to change your doctor, prescribing of antibiotics is significantly lower. This may reflect the advantages of having a long-term relationship between the patient and the physician, and also makes it more difficult for patients who expect an antibiotic for a particular condition to try a number of doctors to get a prescription. Other factors affecting the level of antibiotic consumption include the number of antibiotic brands on the market and expenditure on pharmaceuticals in the particular country.

Patient education initiatives about the appropriate use of antibiotics can significantly reduce antibiotic use, as demonstrated by the response to a public awareness campaign in Belgium. The annual campaigns, which started in 2000, consist of letters to health professionals, brochures to be given to patients, and television advertisements (the fifth campaign was launched in December 2005). The campaigns had an immediate effect in terms of reducing the amount of antibiotic prescribing measured in antibiotic packs/1000 inhabitants/day, which decreased by 30% from 2000 to 2004. Face-to-face interviews with members of the public conducted between 1 and 2.5 months after the campaign showed that approximately 46% of people remembered the campaign.

Television advertising had the most impact, with 80% of subjects who remembered the campaign remembering this advertising compared to 17% and 14% remembering newspaper and radio advertising, respectively. The main message that members of the public remembered was that antibiotics are used too much, and should be used only if needed. There were also significant reductions in the numbers of patients expecting antibiotics for bronchitis, influenza, and sore throat. After the campaign, there was increased acceptance of using antibiotics less often, to limit their overuse, and preserve their efficacy. The start of the campaign in 2000 coincided with a decrease in antibiotic resistance to penicillin G, tetracycline, and erythromycin in Belgium. In addition, full penicillin resistance, which had started to rise from a baseline of close to 0% in 1997 to approximately 6% in 2000, dropped back to baseline levels in 2001 and remained low.

**Characteristics of Acute Respiratory Infections Pathogens**

Before considering the mechanisms of resistance that are relevant for acute respiratory infections (ARIs), it is appropriate to consider the characteristics of the key pathogens, such as pneumococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, and group A streptococci (GAS). Each of these organisms—with the partial exception of GAS—is primarily commensal, carried in the upper respiratory tract of a large number of human hosts, without causing disease. For such organisms, disease is a rare (and perhaps, in an evolutionary sense, an accidental) consequence of colonization, and is unnecessary for transmission. Therefore, the long-term success of such bacteria depends mainly on the success of transmission from asymptomatic host to asymptomatic host.
Indeed, it is organisms such as these, which can thrive and transmit without causing disease, that are likely to develop resistance due to misuse of antibiotics. For the same reason, it is necessary for a given treated individual to distinguish between antibiotic effects on the carried population of bacteria (in the naso- or oropharynx) and effects on the bacteria that cause disease (in the middle ear, bloodstream, lungs, etc), which may differ and may interact.14

In addition, genetic resistance to the major antimicrobial classes used to treat these pathogens generally requires the acquisition of foreign DNA, on a plasmid (as in the case of H influenzae β-lactamases), on a conjugative transposon (as in the case of some forms of macrolide and tetracycline resistance in pneumococci and streptococci), or by transformation with DNA encoding novel alleles of existing genes (as in the case of penicillin and cephalosporin resistance in pneumococci).15-17 This requirement for foreign DNA means that the appearance of a novel resistant strain in an individual colonized by drug-susceptible bacteria (emergence of resistance) occurs very rarely. This is in contrast to the situation with tuberculosis, for example, in which resistance is encoded by point mutations, and mutants resistant to any given drug are likely to be present at appreciable frequencies in most patients. The existence of such resistant subpopulations is the rationale for combination therapy of tuberculosis or HIV; however, because they are rarely present in ARI pathogens, this rationale does not apply. One important exception is the fluoroquinolone class, which is increasingly important in the treatment of some ARIs; fluoroquinolone-resistant mutants can be present in infected persons, and, not surprisingly, emergence of resistance during treatment has been documented.19

**Mechanisms of Emergence of Resistance**

Use of antimicrobial drugs can lead to increases in antimicrobial resistance by 2 main mechanisms that are relevant for ARI pathogens (for more detailed coverage see Lipsitch and Samore20). The first mechanism is the emergence of resistant mutants or, more generally, resistant subpopulations during treatment. As noted earlier in this article, single mutations cannot create resistance to most drugs used for ARIs (except fluoroquinolones). However, individuals may simultaneously carry more than 1 strain of each of these species (or may carry other bacteria that can act as donors of DNA encoding resistance). Therefore, an individual carrying a bacterial population that is mainly drug-susceptible may harbor a resistant subpopulation that can increase in numbers following drug treatment.21 Thus, following antibiotic treatment, individuals are more likely to harbor drug-resistant strains (at least at detectable frequencies) than prior to treatment.

The second mechanism is less direct, but at least as important. We now know that different strains of bacteria compete with one another to colonize individual hosts. Specifically, hosts carrying 1 strain are less likely to acquire, and/or more likely to lose, carriage of other strains. These competitive interactions certainly occur within a species, as has been demonstrated for competing strains of S pneumoniae, and also between different species (eg, between S pneumoniae and Staphylococcus aureus).22-24 As a consequence of this competition, any antimicrobial agent that clears drug-susceptible bacteria from a treated host will provide a selective advantage to resistant strains of the same species (at least) in the host population as a whole, even if no resistant strain appears in the individual receiving treatment.20,25 The reason is that each person in the population is exposed to a number of potential sources of (say) pneumococcus. Whether that person becomes colonized with a resistant or a susceptible strain depends on the relative frequency of these 2 types in the population. Treating individuals and reducing the prevalence of susceptible strains in the population makes it less likely that persons will be exposed to those susceptible strains (Figures 2 and 3). The existence of competition between strains means that any reduction in susceptible strains translates into an advantage for resistant strains, at the level of the whole host population.

Given these 2 mechanisms, one can ask what properties of an antimicrobial treatment course, including the drug used, the dose, the target pathogen, and pharmacokinetic/pharmacodynamic factors, determine its ability to promote resistance in the treated individual, and in the population as a whole.21,25 Obviously, the first mechanism of selection—the appearance of resistant strains in treated hosts—leads to a higher likelihood that the treated host will suffer from a resistant infection, and it also leads to greater transmission of resistant strains in the population. A review of clinical studies comparing colonization with penicillin-non-susceptible S pneumoniae before and after treatment...
(or in individuals who had vs had not received recent antimicrobial treatment) showed that the individual risk of carrying a penicillin-nonsusceptible strain may be increased (especially after treatment with trimethoprim-sulfamethoxazole, an oral cephalosporin, or some macrolides, and/or in the setting of an outbreak of a nonsusceptible strain), unchanged, or even reduced (especially following treatment with high-dose amoxicillin with or without clavulanic acid). To a first approximation, then, one would expect that a choice of drug and dose that reduces colonization with nonsusceptible pneumococci, such as high-dose amoxicillin, would exert less selective pressure in favor of nonsusceptible strains than one that promotes such colonization. In the next section, we update that review and consider this effect specifically for particular antimicrobial classes.

The second mechanism—the disproportionate effect of the antimicrobial agent against susceptible as opposed to resistant strains—occurs quite commonly. In cases in which a resistance mechanism confers a very large increase in minimal inhibitory concentration (MIC), as in the case of macrolide resistance, one would expect that an antimicrobial agent would have some activity (depending on dose and other factors) against susceptible strains and none against nonsusceptible strains. In this case, one expects that the more active the antimicrobial drug/dose, the greater the selective pressure in favor of nonsusceptible strains and against susceptible ones. In other cases, resistance mechanisms confer only gradual increases in MIC, such that a spectrum of strains exists, running from highly susceptible to highly resistant. In such cases, a treatment course may be active against both susceptible strains and some strains with elevated MIC, defined as nonsusceptible, but still not completely resistant to the activity of clinically achievable concentrations. This seems to occur in some cases with high-dose amoxicillin, which can retain activity at least against some penicillin-intermediate pneumococci.

**Figure 2. Primary Resistance**

<table>
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<tr>
<th>Subject with susceptible strain</th>
<th>Subject with resistant strain</th>
<th>Strain eradicated by treatment</th>
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By reducing the prevalence of susceptible bacterial strains in the community, antibiotic treatment can increase the likelihood of individuals being exposed to and colonized by resistant bacterial strains.

**Characteristics of Particular Antimicrobial Agents and Classes in Selecting for Resistance**

**Amoxicillin (With or Without Clavulanic Acid)**

As noted earlier in this article, amoxicillin, especially when administered at a relatively high dose (80–100 mg/kg/day), has been observed in a number of studies to have good activity against penicillin-susceptible strains of pneumococcus, but also to reduce colonization with penicillin-nonsusceptible strains, particularly those with MICs in the intermediate range, up to 1.0 µg/mL. This phenomenon was observed in 3 studies previously reviewed, in addition...
to 2 other studies, although in 1 study the effect was not statistically significant.\textsuperscript{16,20,21,27} Hence, the individual’s risk of carrying nonsusceptible pneumococci appears to be diminished following amoxicillin treatment. However, amoxicillin treatment is more effective against susceptible than against nonsusceptible strains, thus selection is still exerted in favor of nonsusceptible strains.

This highlights another underappreciated consequence of treatment with antimicrobial agents that are active against nonsusceptible strains. Because pneumococcal resistance to β-lactam drugs follows a spectrum ranging up to very high-level resistance (MIC \(\geq 8\) µg/mL),\textsuperscript{28} one might expect that treatments that selectively inhibit strains with, say, MIC up to 0.5 or 1 mg/L, such as high-dose amoxicillin, would ultimately lead to widespread selection of strains with even more elevated MICs. Thus, the short-term benefit of such treatments in inhibiting intermediately resistant strains must be weighed against the theoretical expectation of favoring continued increases of MIC.

**ORAL CEPHALOSPORINS**

Several studies have shown that, following treatment with various oral cephalosporins, there is a reduction in nasopharyngeal carriage of cephalosporin- (or penicillin-) susceptible strains and, in many cases, an increase in the absolute risk of carrying nonsusceptible strains.\textsuperscript{21,25,29} Thus, oral cephalosporins appear to exert selection within the treated individual, probably for outgrowth of subpopulations of nonsusceptible variants, and also to shift the balance in the population strongly in favor of nonsusceptible strains. There appears to be only 1 quantitative comparison of cephalosporins and amoxicillin, which demonstrated that cephalosporins are more potent selectors for resistance than amoxicillin.\textsuperscript{29} However, it should be noted that different oral cephalosporins may have different properties.\textsuperscript{21,29}

**AZITHROMYCIN**

The effect of azithromycin on colonization with macrolide-resistant (and in some cases penicillin-resistant) pneumococci has recently been the subject of considerable attention. Some studies have found that azithromycin treatment has no effect on the risk of being colonized with a drug-resistant strain, as in studies in Israel and the United States.\textsuperscript{21,27,30} One has found a modest tendency to eradicate resistant strains, whereas an increased risk of resistant strain carriage was found by a study in the United States and a more recent study in the same population in Israel in which no effect had been found previously.\textsuperscript{21,26,34} The reasons for this heterogeneity in study outcome are unclear. It has been suggested, and it is biologically plausible, that azithromycin treatment might promote resistant strains within treated individuals mainly in areas where the prevalence of azithromycin resistance is already high.\textsuperscript{31} This explanation is consistent with some, but not all, data.\textsuperscript{27,32}

**FLUOROQUINOLONES**

Fluoroquinolones are unusual among antipneumococcal drugs, in that resistance to fluoroquinolones occurs by mutation; hence, resistant strains can emerge during antibiotic treatment of an infection caused by a susceptible strain.\textsuperscript{19} There do not appear to be any studies of the effects of fluoroquinolones on nasopharyngeal carriage of ARI pathogens, probably because this class is not approved for pediatric use, and children are the main reservoir of carriage of most of these organisms.\textsuperscript{33} However, given the ready availability of resistant mutants in nearly any sufficiently large population of susceptible bacteria, it is reasonable to conclude that fluoroquinolones will readily select for and promote resistant variants within treated individuals, and thus will have a disproportionately large impact in selecting for resistance in the population as a whole. Indeed, fluoroquinolones fit much more closely into the model of tuberculosis described at the beginning of this article, in which monotherapy with a drug that can select resistant mutants is known to be a poor choice. This consideration suggests that widespread pediatric use of fluoroquinolones may select for very rapid increases in resistance in the population.

**CONCLUSIONS**

Greater consumption of antibiotics appears to correlate with increases in antibiotic resistance, particularly for \textit{S pneumoniae}, and this is most clearly observable in data from the ESAC study in Europe. Of the various factors that influence antibiotic consumption, the physician/patient relationship is key. Experience with a patient-education campaign in Belgium shows that promoting patient understanding of the appropriate use of antibiotics can have dramatic effects on the level of prescribing.
Models of antibiotic resistance demonstrate that antibiotic treatment can increase the transmission of resistant bacteria within a population, even when treated individuals have no increased risk of resistance. Antimicrobial agents that can eradicate resistant and susceptible strains have a theoretical advantage in these models, in terms of reducing the risk of transmission of resistance in the community; however, these agents do not exist in reality. In terms of commonly used antibiotics, there is evidence that some cephalosporins promote resistance in treated individuals. The risks associated with promotion of fluoroquinolone resistance are unlike those for the other major antibiotic classes used for ARIs, as resistance occurs by mutation rather than by acquisition of foreign DNA. Therefore, it seems likely that fluoroquinolones will readily select for and promote resistant variants within treated individuals, and have a large impact in selecting resistance in the population as a whole.

Results for azithromycin have been more heterogeneous, with some studies showing no risk, and others showing an increased risk of being colonized with resistant strains. Studies with relatively high doses of amoxicillin (80–100 mg/kg/day) have shown that treatment can reduce colonization with susceptible and some intermediate-resistant strains, suggesting that an individual’s risk of carrying nonsusceptible pneumococci would be reduced following treatment. However, further studies are required to provide definitive data comparing different antibiotic classes.

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