Steering an appropriate course: principles to guide antibiotic choice

O. Cars

Swedish Institute for Infectious Disease Control, Solna, Sweden

The prevalence and degree of antibacterial resistance in common respiratory pathogens are increasing worldwide. The health impact of resistance is not yet fully understood. However, once the impact of resistance becomes measurable, it may be too late to apply interventions to reduce resistance levels and regain previous quality and cost of care. We should address resistance now, before patient care is irreversibly compromised. The association between antibiotic consumption and the prevalence of resistance is widely assumed. However, evidence suggests that there is a more complex, multifactorial relationship between antibiotic use and resistance. It is also assumed that there is an adaptive fitness cost for bacterial resistance mutations. However, in some cases, bacteria are able to acquire 'compensatory genes' negating any negative impact of resistance mutations. Mathematical modeling indicates that the timescale for the emergence of resistance is typically shorter than the decay time following a decline in antibiotic consumption. Against this background, a general principle is proposed: to maximize patient outcome whilst minimizing the potential for selection and spread of resistance. This may be achieved through the use of agents that fulfill defined pharmacodynamic and pharmacokinetic parameters and elicit rapid eradication of the bacterial population, including emerging resistant mutants, from the site of infection. The choice of agent may not be the same in all regions, as selection will depend on local resistance patterns and disease etiology; however, the application of this principle may help to preserve the benefits of antibiotic therapy.

Key words: antibiotic resistance; antibiotic usage; appropriate prescribing; rational prescribing; reversal of resistance; transient hypermutation.

Introduction

The high prevalence of antibiotic resistance has now become a global public health concern (1). Many species and strains of bacteria that are pathogenic to humans have developed resistance to both well-established and newer antibiotics. Multiply-resistant organisms (e.g. drug-resistant Streptococcus pneumoniae, DRSP) give particular cause for concern. These bacteria are responsible for increased numbers of infections in both hospitals and the community (see Garau, 'Clinical failures: the tip of the iceberg?', this issue).

Resistant pathogens compromise the bacteriological and clinical efficacy of common antibiotic regimens (see Garau, 'Clinical failures: the tip of the iceberg?', this issue). As the prevalence and degree of resistance increases, the choice of effective antibiotic therapy becomes more restricted. The failure of antibiotic therapy also has cost implications. For example, a recent study found that when the choice of antibiotic therapy matched the susceptibility results for an episode of lower respiratory tract infection, the mean cost of therapy was almost US$ 6000 lower than when therapy did not match the pathogen susceptibility (P = 0.02) (2).

With few exceptions, the introduction of an antibiotic is followed by an increase in the prevalence of resistance. In general, resistance tends to be more prevalent in closed environments (e.g. daycare centers, intensive care units) and in countries with high antibiotic exposure. Antibiotic resistance can emerge following a spontaneous chromosomal mutation or through the introduction of foreign genetic material, e.g. through plasmids. Under selective antibiotic pressure, isolates carrying resistance genes may persist, leading to continued carriage and spread of the resistant strains throughout the community. Examples showing reversibility of antibiotic resistance in the community by modifying the volume and patterns of antibiotic usage are scarce, and bacteria may overcome the biological cost of resistance by molecular adaptation (3).

This paper will address three specific issues—first, the quantitative and temporal relationships between antibiotic use and resistance, second, whether or not resistance is reversible and, third, whether the rate at which resistance develops can be reduced through improved pharmacological strategies.
Antibiotic use and resistance—quantitative and temporal relationships

At present, it is difficult to establish a precise quantitative relationship between the frequency of resistance to a defined antibiotic and the volume of drug use, because of the scarcity of longitudinal studies which record resistance and drug use patterns and the often multifactorial aspect of emergence of resistance (4). However, mathematical models have been shown to be useful tools in examining the effects of various patterns of antibiotic drug use at the population level. Models are based on available data and assume that the major selective pressure driving changes in the frequency of resistance is the volume of drug use. Such models indicate that the higher the level of antibiotic consumption, the faster the emergence of resistance (4) (Fig. 1).

Despite the apparently clear correlation predicted from mathematical modeling, there is no one simple relationship between antibiotic consumption and bacterial resistance in nature. Factors influencing this relationship include variable epidemiology, regional differences, co-selection (where multiple resistance is present an antibiotic of one class can increase resistance to an antibiotic of another class), cross-infection, clonal spread as well as differences in the pharmacokinetics/pharmacodynamics (PK/PD) of antibiotics and their ecological impact on the normal flora.

For example, the impact of co-selection on antibiotic resistance was described in a study conducted in Iceland involving 919 children (<7 years of age) (5). In this study, a high prevalence of resistant pneumococci was found, most of which (80%) were multiresistant (5). Analysis indicated that the odds ratio for co-trimoxazole or erythromycin being associated with penicillin-resistant pneumococcal (PRP) carriage was twice that for β-lactams in association with three or more courses of antibiotic treatment. Thus, in this case, penicillin resistance was more likely to be related to the use of co-trimoxazole and erythromycin than to the use of β-lactams (5).

Is antibiotic resistance reversible?

HOW DO BACTERIA RESPOND TO ANTIBIOTICS?

Exposure to an antibiotic acts as a physiological ‘stress’ on bacteria. However, they possess a range of adaptive mechanisms to ensure their continued survival. The rate of spontaneous mutation or the rate of transfer of genetic material between organisms may increase. For example, Oliver et al. described transient hypermutation in Pseudomonas aeruginosa under environmental stress (6). The investigators determined the spontaneous mutation rate in 128 P. aeruginosa isolates from 30 patients with cystic fibrosis (CF). Mutator strains were found in 36% of patients. These strains persisted for years in most patients, and had a frequency of antibiotic resistance roughly twice that of non-mutator isolates (6). Hypermutation is a state in which bacteria mutate at a much more rapid rate than normal due to alterations in the DNA mismatch repair process. It is thought that this process increases the adaptive diversity of the bacterial population, presumably allowing them to overcome rapidly changing conditions or exploit newly emerging environmental niches. The lungs of CF patients are chronically infected with P. aeruginosa. These organisms must continually adapt to limitations in specific growth factors, dehydration, deteriorating lung tissue etc., as well as to frequently changing and prolonged (over a period of years) antibiotic therapy (6).

ADAPTIVE COSTS OF ANTIBIOTIC RESISTANCE

It is widely believed that the development of antibiotic resistance imposes some biological (fitness) cost on the bacterium. Data from in vitro studies indicate that resistance encoded by chromosomal mutations, i.e. primarily by the modification of drug target molecules, imposes some cost to fitness. However, mutants with no measurable adaptive cost have also been observed (3).

If the acquisition of chromosomal resistance does impose an adaptive cost, e.g. a slower growth rate, there are two possibilities for addressing this deficit in fitness: (i) by reverting to the susceptible state (‘true reversion’—very rare) or (ii) through the acquisition of compensatory (intragenic or extragenic) mutations (Table 1) (3). For example, the fitness cost of the point mutation conferring resistance in Salmonella typhimurium can be compensated for by intragenic or extragenic mutations that have no impact on the resistance status of this pathogen.

Resistant mutants that cannot overcome any fitness loss by reversion or compensatory mutation will presumably be at a competitive disadvantage compared with susceptible isolates once the antibiotic pressure has been removed. In this situation, the prevalence of resistance would be expected to fall. However, mathematical models indicate that the emergence of resistance is typically far more rapid than the decline (4) (Fig. 2).
TABLE 1. Compensatory evolution and amelioration of fitness losses. Adapted from (3)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Resistance mutation</th>
<th>Compensatory mutation</th>
<th>Resistance maintained</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella typhimurium</em></td>
<td><em>rpsL</em> (streptomycin)</td>
<td>Intragenic, <em>rpsL</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><em>rpsL</em> (streptomycin)</td>
<td>Extragenic, <em>rpsD/E</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><em>gyrA</em> (nalidixic acid)</td>
<td>Intragenic, <em>gyrA</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><em>rpoB</em> (rifampicin)</td>
<td>Intragenic, <em>rpoB</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><em>fusA</em> (fusidic acid)</td>
<td>True reversion, <em>fusA</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td><em>fusA</em> (fusidic acid)</td>
<td>Intragenic, <em>fusA</em></td>
<td>Often</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td><em>fus</em> (fusidic acid)</td>
<td>Intragenic, <em>fus</em></td>
<td>Yes/no</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td><em>rpsL</em> (streptomycin)</td>
<td>Extragenic, <em>rpsD/E</em></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><em>rpoB</em> (rifampicin)</td>
<td>Intragenic, <em>rpoB</em></td>
<td>Yes</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td><em>katG</em> (isoniazid)</td>
<td>Extragenic, <em>anpC</em></td>
<td>Yes</td>
</tr>
</tbody>
</table>

![Graph](image1.png)

**Fig. 2.** Emergence of resistance is typically more rapid than decline. ---: time taken for resistance to increase from 1 to 10%; - - -: time taken for resistance to decrease following reductions in antibiotic consumption of 25, 50, 75 and 100%; DDDs: defined daily doses. Reproduced with permission (4).

![Graph](image2.png)

**Fig. 3.** Reduction in the frequency of erythromycin resistance among group A streptococcal isolates in Finland, following nationwide recommendations to restrict the use of macrolide antibiotics for outpatients with skin or respiratory tract infections. Reproduced with permission (8).

**EVIDENCE OF REVERSAL OF RESISTANCE**

There is some evidence that resistance can be reduced by reducing antibiotic selective pressure in the hospital environment. For example, interventions in a Greek hospital attempted to reduce the high level (around 30%) of quinolone resistance that was observed in Gram-negative pathogens (*Pseudomonas aeruginosa*, *Klebsiella* spp. and *Proteus mirabilis*) (7). Between the beginning of 1995 and the end of 1996, there was a six-fold reduction in quinolone use and a significant fall in the prevalence of resistance among these pathogens—*P. aeruginosa* (34% to 18%), *Klebsiella* (26% to 6%) and *P. mirabilis* (30% to 16%) (7).

There are only scarce reports of resistance reversal in the community—one from Finland (8) and another from Iceland (9). In one report from Finland, during the early 1990s, there was an increase in erythromycin resistance among group A streptococci (8). In order to address this concern, nationwide recommendations were issued for a reduction in the use of erythromycin for outpatients with respiratory tract (RTI) or skin infections. From 1991 to 1992, the consumption of macrolides decreased from 2.40 defined daily doses (DDD) per 1000 inhabitants to 1.38 (P = 0.007), with a concomitant steady decrease in the frequency of erythromycin resistance among group A streptococci, from 16.5% in 1992 to 8.6% in 1996 (Fig. 3) (8). Another report, from Iceland, comes from a study published in 1998, which evaluated the impact of reducing antibiotic consumption on PRP carriage (9). The incidence of penicillin-non-susceptible pneumococci (PNSP) had been increasing in Iceland since the late 1980s, and a policy was implemented to reduce antimicrobial use, particularly for upper respiratory tract infections in children. The particular risk associated with trimethoprim-sulfamethoxazole use was emphasized. From 1990, the overall national antibiotic consumption was reduced by 10%, though the consumption of trimethoprim-sulfamethoxazole and erythromycin were reduced by 30%. Although the incidence of PNSP...
reached a peak in 1993 (19.8%), it fell, thereafter, reaching just 12.9% in 1997 (9). Thus, for these two examples, a reduction in consumption of an individual antibiotic or antibiotic class seemed to result in a reduction in the frequency of resistance. However, spontaneous disappearance of resistance clone(s) due to acquired herd immunity after antibiotic exposure may also be a partial explanation. For example, in a study by Leach et al. (10), there was a reduction in resistance to azithromycin over time that coincided with the average time that pneumococci clones are carried in the nasopharynx. Similarly, in a study by Arason et al. (5), the impact of previous antibiotic exposure on resistance decreased after 2 months, probably reflecting immunological eradication of the carriage of resistant clones.

In southern Sweden, there has also been concern over the high prevalence of resistant pneumococci, which increased to 15% during the early 1990s though the corresponding figures for the rest of Sweden remained at lower levels (11). A national expert committee was formed, and discussions soon focused on the spread of resistant pneumococci in small children, especially those attending daycare centers. A restriction on antibiotic consumption was imposed while, alongside this policy, a measure was initiated where children with positive cultures for PNSP were not allowed to attend daycare centers until they had two consecutive negative tests. Parents staying at home with these children were reimbursed by the social security system. Since then, there has been a substantial reduction in the use of outpatient antibiotic use, particularly macrolides and broad-spectrum penicillins. As yet, this dual strategy has not led to a significant reduction in PNSP—the prevalence remains at around 10%—though there is a trend towards fewer index cases, i.e. individuals first identified with PNSP. The effect of these measures on contact cases (close contacts of the index case) are not yet clear, though are likely to become apparent as the study continues (11).

These studies illustrate that, though in many cases resistance may well be reversible, once detected, there is a need for early action. In addition, strategies to bring about a reversal of resistance, particularly in the community, are likely to be multi-faceted, extensive, protracted and potentially costly.

Can improved pharmacological strategies limit the rate at which resistance develops?

One way to reduce the rate of development of resistance is to ensure that the dose and activity of an antibiotic will minimize the risk for selection of resistant mutants. Early use of highly active and rapidly bactericidal antibiotics will reduce the ancestor bacterial population, decrease the possibility of emerging resistant strains and avoid the selection of low-level mutants which may be considered as ‘stepping stones’ for high level resistance. The use of PK/PD parameters in defining optimal antibiotic therapy is discussed by Craig, ‘Re-evaluating current antibiotic therapy’, this issue.

SUB-OPTIMAL ANTIBIOTIC REGIMENS AND RESISTANCE—CAUSE AND EFFECT?

Several studies have described a possible relationship between the use of sub-optimal antibiotic dosages and the emergence of resistance in S. pneumoniae. Baquero (12) described that during the early 1990s in France, there was a shift from the use of oral aminopenicillins towards oral cephalosporins for the treatment of RTIs. Correspondingly, there was an increase in penicillin resistance in S. pneumoniae—a key respiratory pathogen (Fig. 4). It is possible to explain this shift in the resistance pattern in France by the differences in PK/PD parameters between the two drug classes. For cephalosporins, serum concentrations above MIC for at least 49% of the dosing interval is thought to be required for effective antimicrobial treatment. However, the serum concentrations of many of the oral cephalosporins being used increasingly in France at this time fail to meet this parameter for S. pneumoniae with reduced penicillin susceptibility. Use of these agents would, therefore, be expected to result in a poor level of bacterial eradication and the persistence and spread of resistant strains (12).

Another example is the correlation observed between the use of new, long-acting macrolides (e.g. azithromycin and clarithromycin) and the emergence of macrolide resistance in S. pneumoniae (13) (Fig. 5). The long half-lives of these agents, combined with serum concentrations which do not exceed the MIC throughout the dosing interval, may be driving the selection of macrolide resistance in S. pneumoniae. There was no correlation observed between the increase in macrolide resistance and the use of older, short-acting macrolides, such as erythromycin (13). Recently, a similar correlation between the use of azithromycin and emergence of macrolide/penicillin-resistant S. pneumoniae has been reported from Denmark (14).

![Fig. 4. Relationship between a shift in the use of oral aminopenicillins and oral cephalosporins and the emergence of penicillin resistance in S. pneumoniae. ■: penicillin resistance in S. pneumoniae; ○: ratio of aminopenicillins: cephalosporins per 1000 inhabitants in France. Reproduced with permission (12).](image-url)
Treatment duration is another factor to consider, though it is not yet clear how important this is in relation to the development of resistance, and there is little clinical information on the subject. One clinical study, carried out in a group of French children, indicated that the nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* was associated with low dose (lower than clinically recommended) and long duration β-lactam therapy (>5 days) (15). Although this study was small, it does suggest that there is some connection between treatment duration and resistance. Logically, shorter treatment times should be advantageous. However, it is also likely that some bacteriological efficacy would be lost if treatment times were shortened. Further studies are required to define the point at which this optimal balance is achieved.

Improved pharmacological strategies may, indeed, help to limit the rate at which resistance develops. Such strategies will, however, require the use of evidence-based treatment guidelines derived from clinical trial data. One of the limiting factors in the development of such guidelines, however, is the way in which clinical trials are currently designed and conducted. Vital data are often either not reported or not collected, for example, efficacy rates versus placebo, optimal dose regimens, bacteriological eradication rates, the ecological impact of the antibiotic and the selection of resistance in normal flora.

**Conclusion—have we reached the point of no return?**

There is no certainty that the current extent of resistance can be reversed—the point of no return may already have been reached for certain antibiotic–bacterial combinations. Antibiotic resistance tends to go unnoticed and unmeasured for long periods of time—at least, as long as there is no clinical impact. Once resistance does begin to affect clinical efficacy—as it has now (see Garau, *Clinical failures: the tip of the iceberg?*, this issue)—then it may, indeed, be already too late to implement measures which may make a difference.

What is clear is that to limit the further development and spread of resistance there must be judicious use of antibiotics, with reductions in unnecessary and inappropriate use. Antibiotic use must be 'appropriate', that is limited to appropriate circumstances, and optimal dose regimens should be defined according to specific PK/PD principles, particularly for new agents. Agents with the greatest potential for rapid eradication of susceptible bacteria and more resistant sub-populations should be chosen as first-line therapy. Agents to be avoided are those with sustained, low concentrations at the site of infection and those that have the greatest effect on the normal flora. Whilst the choice of antibiotic may not be the same in all regions and will depend on local resistance patterns and disease etiology, the application of these principles may help to preserve the benefits of antibiotic therapy through maximization of clinical outcomes and minimizing the potential for selection and spread of resistance.

**References**


