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A review of the role of antibiotic policies in the control of antibiotic resistance

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The optimal antibiotic control measures remain to be described and probably vary between institutions. Nevertheless, various control measures have been shown to be useful in reducing costs of therapy and total amounts of prescribing, while maintaining quality of care. More recently, interest has turned to whether antibiotic policies can reduce the spread of resistance and even reverse current high levels. Early studies indicated this was feasible, but mathematical models and the recent discovery of the role of transposons and integrons in multi-drug resistance have both cast doubt on likely future success in this area. Nevertheless, there have been some major successes in recent studies, both in the community and hospital. While cross-infection is a major impediment to control of resistance, there is little doubt that careful antibiotic prescribing can curtail the emergence and reduce the prevalence of resistance.

Introduction

Antibiotic resistance is a direct consequence of antibiotic use. Both continue to escalate despite many calls for moderation of antibiotic use, in the hospital and in the community.[1–4] Much has been written on antibiotic policies and other control measures. Despite the lack of properly controlled studies, which would be very difficult to perform, there is no doubt that policies can be efficacious in reducing costs[5] and levels of use[6] without being detrimental to patient care. The costs of control measures can be recouped several times over in savings and quality of prescribing can also be improved. There are, however, many barriers to the success of individual control measures[7,8] and each institution will need to adapt these measures to their own needs. Timely information and education are crucial[9] and efforts certainly need to be continuous to maintain effect.[1] We all have experience of fruitless individual efforts in this area and they are no substitute for on-the-ward clinical liaison.

The emphasis in the area of antibiotic policies has now turned to their impact on antibiotic resistance. McGowan & Tenover[9] have summarized the pathways by which resistance can be introduced, selected, maintained and spread in health institutions and describe six basic mechanisms:

(i) Introduction of a few resistant organisms into a population where resistance previously was not present, usually by transfer from another healthcare system but also from the community.

(ii) Acquisition of resistance by a few previously susceptible strains through genetic mutation in reservoirs of high organism concentration such as an abscess.

(iii) Acquisition of resistance by a susceptible strain through transfer of genetic material, for example in the gut or on the skin.

(iv) Emergence of inducible resistance that is already present in a few strains in the bacterial population, usually from direct selection by antibiotic prescribing.

(v) Selection of a small resistant subpopulation of organisms, again by antibiotic prescription.

(vi) Dissemination of inherently resistant organisms locally within the specific setting due to poor infection control procedures.

It is evident that while antibiotic resistance determinants are much older than the modern era of chemotherapy, their maintenance and spread in our healthcare institutions are dependent on the unrestrained antibiotic prescribing that is prevalent.[9,10] Much attention is now directed towards establishing whether or not antibiotic control measures can reduce current levels of resistance rather than just halting its spread.[10,11] A review of the literature suggests that guarded optimism is justified in this area also.

Clinical studies

Early studies in various hospitals showed rapid reversal of major clinical problems of resistance to chloramphenicol,

erythromycin and tetracycline in *Staphylococcus aureus* on withdrawal of these antibiotics from clinical use.[12–14] The study by Price & Sleigh[15] nearly 30 years ago is a milestone. They showed that complete cessation of all antibiotic prescribing on a neurosurgical intensive care unit (ICU) was necessary to control an outbreak of multiply-resistant klebsiella infection, after all attempts at antibiotic restriction and infection control had failed.[15] Notably, in this study, not only did the multiply-resistant klebsiellae disappear, but the rate of infection with other organisms also decreased and there were no deaths from infection during the study period. Also in the UK at about this time, an outbreak of gentamicin-resistant *Pseudomonas aeruginosa* on a burns unit was controlled only when a ban on topical gentamicin was put in place.[16]

In the community, outbreaks of erythromycin-resistant Group A streptococci and penicillin-resistant pneumococci have been controlled by major reductions in prescribing of erythromycin and penicillin, respectively; firstly in Japan[17] and Hungary[18] and, more recently, in Finland[19] and Iceland.[20]

Many studies have also been published on the control of multiply-resistant Gram-negative bacteria and the role played by reducing the prescribing of third-generation cephalosporins.[21–24] Cephalosporins certainly have a bad reputation, not only for selecting extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and stably derepressed mutants of inducible Enterobacteriacea, but also enterococci, methicillin-resistant *S. aureus* (MRSA), *Clostridium difficile* and yeasts.[25,26] While not all studies have shown benefits of decreased cephalosporin use, many have shown a reduction in the incidence, if not complete eradication, of problem organisms.

Many of the above studies have also involved complex epidemiological situations and the use of upgraded infection control efforts at the time of outbreaks, which makes it difficult to attribute cause and effect entirely to the antibiotic withdrawal, but several authors have attributed success specifically to antibiotic control measures.[12,13,15,23] I believe that the two measures (infection control and antibiotic control) are so crucially interrelated that it is unrewarding and unnecessary to separate them. McGowan[10] and others[1] have discussed these confounding factors in detail (Table I).

Theoretical considerations

Mathematical models as well as consideration of epidemiology and specific mechanisms of resistance help in understanding where, when and how antibiotic policies are likely to control resistance. It is worth considering four interacting areas: the patient, the organism, the drug and the environment (Figure 1).

The patient

Factors likely to be relevant to the development of resistance in individual patients include a large inoculum infection, which increases the potential for pre-existing resistant mutants.[27] Any process that lowers drug concentrations at the site of infection is also more likely to select out resistance, as will slower eradication of infection due to a foreign body or a compromised immune system.[27] While the normal flora is usually forgotten about, or ignored, when treating specific infections, its exposure to the antibiotic is inevitable. Development of resistance in normal flora is probably of great significance clinically, as this resistance may spread to more pathogenic organisms.[28,29] Eradication of resistant pathogens by the use of selective digestive decontamination (SDD) regimens has proved

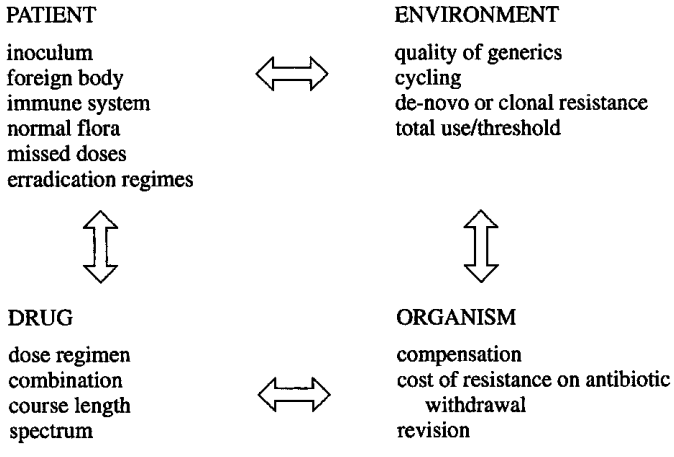

Figure 1. The dynamics of resistance. The patient, the drug(s), the microorganism(s) and the environment interact. It is difficult to identify any one factor as crucial on its own.

Table I. Factors that may increase antimicrobial resistance in hospitals (after reference 1)

Greater severity of illness of hospitalized patients
More severely immunocompromised patients
Newer devices and procedures in use
Increased introduction of resistant organisms from the community
Ineffective infection control and isolation practices and compliance
Increased empirical polymicrobial antimicrobial therapy
High antimicrobial usage for geographical area per unit time

disappointing.[30] While colonization by resistant organisms has occasionally been eradicated by SDD[31] my experiences with this approach (unpublished) are not encouraging and I do not believe that this holds a bright future. Decolonization does, however, have a proven role in eradication of MRSA carriage.[9]

The organism

Whether resistant survivors revert to full sensitivity on removal of antibiotic selective pressure depends on several factors. On rapid removal of selective pressure, reversion to sensitivity will probably occur, although taking longer than the initial process of development of resistance. We know, however, that genetic compensation for the cost of resistance can occur, i.e. the resistant survivors can undergo separate mutations over several hundred generations that favour maintenance of the resistant gene.[32,33] Clearly this seems to have happened with MRSA and vancomycin-resistant enterococci (VRE). By mathematical modelling, compensation can be shown to be more likely than reversion.[33] Many factors must be considered, such as prevalence and rates of transfer of resistance factors, the disease and the conditions for maintenance of plasmid, transposon and phage. Based on rates of transfer it seems that plasmids cannot be maintained in the absence of at least occasional selection by antibiotic use.[32] However, where induction or adaptive resistance has occurred on exposure, this probably reverts quickly[34] unless this adaption is mutational.[35]

The most complex situation is where multiple resistance mechanisms occur. The worst scenario is the presence of an integron, a type of transposon, which can accommodate not only many resistant determinants (cassettes), including the *mecA* gene, but also the genes for their chromosomal integration and expression. However, linked resistance is complex, as shown many years ago in transposon-mediated resistance to both amoxycillin and trimethoprim, where declining use of amoxycillin, even in the presence of increased trimethoprim use, led to a decline in trimethoprim resistance.[36] In other situations it is likely that use of any antibiotic, the resistance determinant for which is coded on an integron, will select for maintenance of resistance to all agents represented on that integron.[37] Transposons can also code for active efflux of many different classes of antibiotics (the 'sump-pump' resistance mechanism). The fluoroquinolones are known to be able to activate this resistance mechanism.[38]

The drug

The antibiotic itself is likely to be important regarding development of resistance. Narrow-spectrum agents should be beneficial as they have less effect on normal flora than broad-spectrum agents. In this context, excretion of drugs into the gut lumen and skin has been little studied.[28,29] White *et al.*[39] graded several β-lactams recently, according to whether resistance developed during use (Table II), but made the point that patterns of use of multiple agents need to be studied to gauge the relative importance of individual agents. In a previous review, only aminoglycosides were noted to be particularly prone to selection of resistance and this was associated with a higher incidence of treatment failure.[38] Dose regimen is also likely to be important. Higher doses, which will achieve higher drug concentrations at the site of infection, are less likely to select for resistance although the effects of this strategy on the normal flora are unknown.[39,40] Finally, antibiotic combinations are well proven, both in HIV[41] and tuberculosis[42], as a means of preventing resistance. The role of combinations in prevention of resistance during the treatment of other infections is not clear-cut, although they probably do work in some situations.[38] Mathematical models favour them as the best method of preventing both de-novo emergence and clonal spread of resistance.[40]

Table II. Rank order of various antibiotics in respect of frequency of association of drug use with resistance in Gram-negative aerobes (after reference 39)

Antibiotic	Frequency of resistance
Piperacillin	high
Cefotaxime	↕
Ticarcillin/clavulanate	↕
Aztreonam, ceftazidime	↕
Imipenem	↕
Ceftriaxone	↕
Ticarcillin	low

The environment

The final interactive area is the environment which covers, most importantly, the hospital as well as the nursing home, institution or community. Clearly the situation differs, depending on whether there is clonal spread or de-novo emergence of resistance. With clonal spread, cross-infection and environmental contamination are also important and can defeat attempts to contain resistance by antibiotic restriction.[10] Levy[43] has introduced the concept of 'total use threshold' as an important factor in the development of resistance. Certainly there is not always a clear-cut relationship between use and resistance, which may not develop to detectable levels until a 'threshold' of use has been reached. Reduction of use below this 'threshold' may then be successful in reducing resistance. In crucial areas like the ICU a clearer, more direct relationship between level of use and resistance is often seen, e.g. ceftazidime use and resistant *Enterobacter*

cloacae and *P. aeruginosa*, or MRSA and anti-staphylococcal penicillins and first-generation cephalosporins.[44]

Finally, the concept of using antibiotic rotation to control resistance (recently termed cycling) has re-emerged. The little published evidence there is in its support mostly concerns rotation of aminoglycosides,[45–51] usually gentamicin and amikacin. Recently C. C. Saunders (personal communication) has proposed a scheme (Figure 2) for empirical use, although gathering evidence for its efficacy is likely to be difficult.[9] Two-month periods of use seem rather frequent but are proposed to prevent any resistant mutants becoming established. Perhaps rotation on an individual patient basis is just as practical, although this may not always be feasible. If possible, therapy should always be designed to give the least chance for selection of resistant strains.

New evidence

Several recent studies confirm the ability of policies to reduce antibiotic use (both at a national level and also in individual hospitals) and the beneficial effect this has had on resistance rates.

In two large community-based studies in Iceland[20] and Finland,[19] the problem of penicillin-resistant pneumococci and erythromycin-resistant *Streptococcus pyogenes* was addressed. In Iceland the problem followed the increased use of a wide range of antibiotics. Consumption in defined daily doses (DDD)/1000 inhabitants/day reached a high of 23.2 in 1990. This was associated with a peak in penicillin resistance of 20% in 1992. By 1995 consumption was down to 20.2 DDD/1000 inhabitants/day, mainly through reduction in penicillin and co-trimoxazole use, and reduction in penicillin resistance to 15%. Antibiotic use in those surveyed had been 15.5% in the preceding 6 months in 1992 and 9.2% in 1995. The problem was particularly prevalent in young children in daycare centres and was associated with clonal spread of a strain (serotype 6B) from Spain. In Finland, a trebling of community prescribing of erythromycin in the late 1980s and early 1990s, to treat Group A streptococcal throat and skin infections, led to an increase in erythromycin resistance from 5% in 1988 to 19% in 1993. A subsequent 50% reduction in erythromycin consumption then led to resistance rates falling to 8.6% in 1996. This seems to be another example of a 'critical threshold' being breached, in that resistance rates declined without total removal of the antibiotic, probably by reduced selection allowing suppressed, sensitive strains to become more dominant.

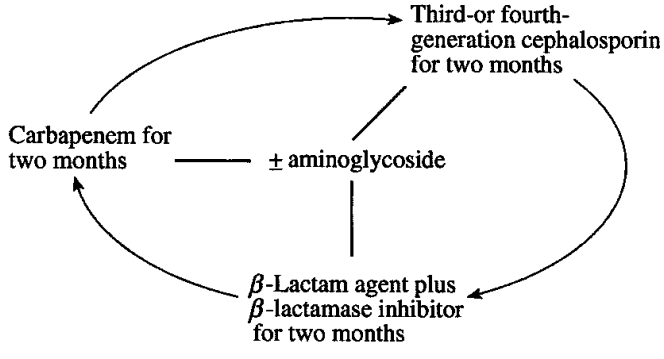

Figure 2. Suggested scheme for cycling of empirical treatment of serious sepsis in units where there are no major, established resistance problems that would prevent the first-line use of one of the three main categories of β-lactams. Aminoglycosides should be used in combination where there is clinical severity or a particular need to prevent emergence of resistant mutants. The period of cycling suggested is 2 months, which should be short enough to prevent emergence of major resistance problems. Fluoroquinolones should be reserved for treatment failure, β-lactam allergy or aminoglycoside toxicity. Individualize glycopeptide use within local guidelines: avoid oral vancomycin as far as possible. Adapted from C. C. Sanders, personal communication.

Recent studies in France have demonstrated reduced prevalence of gentamicin-resistant MRSA on reducing gentamicin prescribing.[52,53] Early reports suggest that decreasing vancomycin use is helpful in controlling VRE.[54,55] Roghmann *et al*.[56] also found a positive association between anti-anaerobic drug use (metronidazole and clindamcycin) and VRE infection and a negative association with use of all three generations of cephalosporins, illustrating the complexities of some resistance problems and the need for a considered approach when planning control strategies.

Continuing work in Greece,[57] updated at the 1997 International Congress of Antimicrobial Agents and Chemotherapy (ICAAC), shows that an 80% reduction in quinolone use was associated with decreased resistance rates amongst various Gram-negative bacilli ($P < 0.001$). In another study,[58] implementation of management protocols in an ICU cut antibiotic use by half and length of ICU stay decreased overall from 3.7 to 2.6 days ($P < 0.001$). There were also trends in improvements in clinical outcome and resistance.

Frank *et al.*[59] recently described an antibiotic prescribing improvement programme which substantially reduced the use of 'most' broad-spectrum agents over a 2 year period. There were significant decreases in the rates of nosocomial bacteraemia ($P = 0.016$), selected Gram-negative bacteraemia ($P = 0.015$), MRSA colonization or infection ($P < 0.0001$) and *Stenotrophomonas maltophilia* colonization or infection ($P = 0.019$). The decreases could not be attributed to changes in infection control practices, number of outbreaks or patient demographics.

Finally, a notable study has recently been reported from America.[6] In response to an outbreak of multiply-resistant *Acinetobacter* sp. infection, which was not controlled by infection control procedures, a restrictive antibiotic policy was introduced requiring approval for certain key drugs

Table III. Percentage of isolates susceptible to restricted antibiotics during the 12 month periods immediately before (January–December 1993) and after (July 1994 to June 1995) full implementation of a prior-authorization requirement for antimicrobials[6]

	No. of isolates		Ticarcillin/ clavulanate		Imipenem		Aztreonam		Ceftazidime	
Organism, patient location	before	after	before	after	before	after	before	after	before	after
Escherichia coli										
inpatient	1289	1252	88	98[a]	97	99[a]	96	99[a]	97	99[a]
ICU	162	148	77	97[a]	98	99	87	99[a]	81	99[a]
P. aeruginosa										
inpatient	447	533	83	89[a]	83	95[a]	70	88[a]	76	92[a]
ICU	334	300	70	87[a]	65	83[a]	63	81[a]	66	88[a]
Klebsiella pneumoniae										
inpatient	399	332	80	93[a]	84	98[a]	92	95	91	93
ICU	161	126	84	94[a]	96	100	85	98[a]	86	93

[a]Increases were statistically significant ($P \leqslant 0.01$).

including amikacin, aztreonam, ceftazidime, imipenem, ciprofloxacin and ticarcillin/clavulanate. Over the following 6 months there was a significant decrease ($P < 0.01$) not only in the resistant acinetobacter but also in resistance to the key antibiotics amongst many Enterobacteriaceae (Table III). Clinical outcome data showed no detrimental effect on survival, time to discharge, length of ICU stay or time to receive appropriate antibiotics, despite the restrictive policy. There was no change in infection control procedures during the period of the study. Costs of implementing the policy were less than US$150,000 per year and projected savings US$900,000 per year. The authors conclude that it is no longer a question of whether antibiotic use should be controlled, but only which controls are optimal for a particular healthcare system.

Conclusions

While it is true to say that there is no absolute proof of a causative association between antibiotic use and resistance, most authorities believe the association to be 'virtually certain'.[1] Given this and the impossibility of controlling for all compounding factors in prospective trials, a pragmatic approach to control of antibiotic resistance is essential. Given the recent worldwide escalation in resistance and the overwhelming evidence of much over-use of antibiotics (and thus unnecessary resistance), the pragmatic and essential approach to the control of antibiotic resistance is to control antibiotic use. The important question is how, not whether. Much research is still needed in this area. To a large extent, local problems are best addressed by local solutions, but, there has been no shortage of National Guidelines on this topic, both in Europe and the USA. The recent Strategic Goals statement from the USA[1] may be a step in the right direction but will need modifying for different countries: a recent meeting in Scotland has started to address this issue, for example. Better diagnostic and therapeutic protocols are also likely to be important. A Europe-wide Working Group of the European Society for Clinical Microbiology and Infectious Diseases has recently been set up to address the role of antibiotic policies and other measures to control antibiotic misuse.

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