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Ecological antibiotic policy

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Development of resistance to antibiotics is a major problem worldwide. The normal oropharyngeal flora, the intestinal flora and the skin flora play important roles in this development. Within a few days after the onset of antibiotic therapy, resistant *Escherichia coli*, *Haemophilus influenzae* and *Staphylococcus epidermidis* can be detected in the normal flora of volunteers or patients. Horizontal spread of the resistance genes to other species, e.g. *Salmonella* spp., *Staphylococcus aureus* and *Streptococcus pneumoniae*, occurs by conjugation or transformation. An ecologically sound antibiotic policy favours the use of antibiotics with little or no impact on the normal flora. Prodrug antibiotics which are not active against the bacteria in the mouth and the intestine (before absorption) and which are not excreted to a significant degree via the intestine, saliva or skin are therefore preferred. Prodrugs such as pivampicillin, bacampicillin, pivmecillinam and cefuroxime axetil are favourable from an ecological point of view. Experience from Scandinavia supports this, since resistance to mecillinam after 20 years of use is low (about 5%) and stable.

Introduction

Global sales of antibiotics were 20.1 billion US$ in 1994 (and 25 billion US$ in 1997); 36.1% of this expenditure was on cephalosporins, 17.4% on penicillins, 14.1% on quinolones, 11.4% on macrolides, 3.4% on tetracyclines, 2.9% on aminoglycosides and 14.8% on other drugs (glycopeptides, antifungal agents, etc.).[1] If such quantities of lethal weapons were to be used against multicellular organisms, the results would be major extinction of species, similar to those which happened five times between 500 million and 65 million years ago, after the Cambrian explosion.[2] When, however, antibiotics are used against bacteria, resistance develops.[3–5] In humans, 80% of antibiotics are used in general practice (where otitis media in infants and children and urinary tract infections in women are the most common indications for treatment with antibiotics) and 20% in hospitals. Penicillin-resistant *Streptococcus pneumoniae*, β-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis*[6] and *Escherichia coli* resistant to ampicillin, sulphonamide and trimethoprim[7] are frequently isolated in areas where the consumption of antibiotics is high. In hospitals, however, methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis*, extended-spectrum β-lactamase-producing Enterobacteriaceae and vancomycin-resistant

enterococci are troublesome.[5] Recently, fluoroquinolone-resistant *Salmonella typhimurium* has raised concern.[5]

It has been reported that 20–50% of the antibiotics used to treat humans and 40–80% of those used to treat animals or for growth promotion are unnecessary or of questionable value.[8] In addition, despite improved knowledge of the pharmacodynamic and pharmacokinetic properties of antimicrobial agents, dosing is often inadequate, potentially producing suboptimal results and leading to development of resistance.[9,10] Practical guidelines for anti-infective therapy have, therefore, been published to promote optimal use for some indications.[11]

Development of resistance by interspecies recombination

It is known from clinical trials that about 4% of infecting microorganisms (occurring in 5.6% of all infections treated) become resistant upon therapy.[12] There is also a correlation between the amount of antibiotics used and the level of resistance. For instance, the prevalence of intermediate and resistant pneumococci correlates with penicillin use in different areas of Spain,[13] and a similar trend has been reported in Sweden.[6] Clones of such penicillin-resistant

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S. pneumoniae have spread locally and internationally under selective pressure, e.g. in daycare centres.[14–16]

The rapid increase in resistant strains of bacterial species in the normal flora is not as commonly acknowledged, but there is increasing evidence that the normal flora represents a pool for selection of resistance genes, which may disseminate to other species and genera by horizontal transfer by conjugation, transduction or transformation.[17,18]

The normal flora of the mouth and pharynx is exposed to antibiotics when penicillins and other oral antibiotics are swallowed and, together with excretion of antibiotics by salivary glands, suppresses the viridans group of streptococci and other components of the normal flora.[19,20] When bacteria are lysed by antibiotics such as penicillins, their DNA is released, which may promote horizontal gene transfer by transformation. Some pneumococci have become resistant to penicillin because of alterations in penicillin-binding protein 2 (PBP2), leading to decreased affinity for penicillins. There is now compelling evidence that these pneumococcal clones originated by importation of divergent regions in the PBP genes—so-called mosaic genes—that originated from *Streptococcus mitis* and other oral streptococci.[21] Similar mechanisms have been found in penicillin-resistant *Neisseria meningitidis* and *Neisseria gonorrhoeae* where the resistance genes have been derived from *Neisseria flavescens* and *Neisseria cinerea*.[21]

The normal flora of the intestine is heavily exposed to incompletely absorbed oral antibiotics and to antibiotics excreted in the bile. These antibiotics suppress the normal flora and lead to development of resistance and superinfection.[22] Work by Laufs *et al.*[23] has found that multiresistant *E. coli* containing large conjugative plasmids appeared in the intestinal flora of patients treated with oral ampicillin for 10 days. Broad-host-range plasmids are important in gene transfer in the natural environment and in clinical isolates.[18]

S. epidermidis and other bacteria in the normal skin flora are exposed to antibiotics that are used for topical treatment. Also important is the impact on the normal skin flora of antibiotics excreted into the sweat. This has been shown to lead to rapid and prolonged colonization of the skin of volunteers with multiresistant *S. epidermidis*.[24,25] This is likely to contribute to the widespread occurrence of multiresistant *S. epidermidis* in hospitals, which is associated with the amount of antibiotics used.[26,27]

The high level of *E. coli* resistant to ampicillin (30%), sulphonamides (30–40%) and trimethoprim (18%) in countries with low consumption of these drugs for medical purposes is puzzling. The prevalence of resistant isolates is similar in blood cultures and in urine cultures from hospitalized patients and those from patients treated in general practice.[7,28–30] The same high level of resistance to these drugs has also been found in *E. coli* from stools of normal persons and in *E. coli* from Danish chicken carcasses and pork, with levels of resistance in *E. coli* being

even greater in imported, than in Danish, turkey and duck.[7] The levels of resistance in *E. coli* from the faeces of vegetarians were much lower.[31] These findings indicate that zoonotic non-enteropathogenic *E. coli* are 'enterocolonizers' of humans. Enteric flora from the animals produced in the food industry pass to humans via food contaminated during the slaughtering process.

In 1997, the total consumption of antibiotics by humans in Denmark (5.1 million inhabitants) was 41 tonnes, whereas the total consumption of antibiotics for treatment of sick animals in Denmark (where, in 1998, the livestock numbers were: 2 million cattle, 11.3 million pigs, 12.5 million broilers, 3.9 million laying hens; the numbers slaughtered in 1998 were: 0.7 million cattle, 20.8 million pigs and 138 million broilers) was 56 tonnes, of which ampicillin and sulphonamides or sulphonamides/trimethoprim accounted for 6.1 tonnes and 8.3 tonnes, respectively.[7] The consumption of antibiotics used as growth promoters for animal production was 107 tonnes in Denmark in 1997; of these, only avoparcin (a glycopeptide), tylosin (a macrolide) and bacitracin were related to antibiotics used in human medicine.[7]

Discussion

Bacterial resistance problems are global.[3] Some of the major reasons for resistance are understood and possibilities for rational aproaches to improve the situations are apparent. One of the problems is the questionable appropriateness of use of 20–50% of antibiotics in humans and 40–80% of the antibiotics in animals[8] together with the observed correlation between the amount of antibiotics (e.g. penicillins) used and the level of resistance in pneumococci.[13] An ecologically sound antibiotic policy would abandon the use of growth promoters in animals and restrict the use of antibiotics for treatment of sick animals, preferably using antibiotics with limited value in human medicine. Restricting the use of antibiotics in humans is problematical in countries where over-the-counter sale of antibiotics without prescription is accepted. Banning over-the-counter sales and implementation of rapid bedside diagnostic tests for use in general practice may help to limit resistance. For instance, patients with clinical symptoms of respiratory tract infection, including otitis media, may be tested for bacterial pathogens, to avoid using antibiotics for non-bacterial causes of respiratory symptoms. Similarly, rapid tests for use in general practice for detection of the most important resistance traits in the common bacterial pathogens are needed. Reimbursement policies for such diagnostic tests should be developed to facilitate their use.

Since resistance to β-lactam antibiotics based on ever-evolving β-lactamases is a major global problem, conservative or restricted use of new generations of such antibiotics may delay further development of extended-spectrum β-lactamases.[32] Guidelines for optimal dosing regimens should be developed for community and hospital use.[9–11]

The development of resistance by horizontal transfer of resistance genes from bacterial species of the normal flora has some important implications. It is possible to develop an ecologically sound antibiotic policy that takes into account the effect of different antibiotics on the normal flora of the mouth, pharynx, intestine and skin.[19,20,22,24,25,33] Prodrugs such as pivampicillin, bacampicillin, pivmecillinam and cefuroxime axetil may be important for such a policy since their antibacterial activity is not released before the ester bond is cleaved, which normally takes place in the tissue of the intestine.[34] Thus, the use of pivmecillinam for urinary tract infections in Scandinavia for more than 20 years has not increased the low level ($\leqslant 5\%$) of resistance to this drug.[7,35] This advantage of prodrugs may, of course, be violated upon subsequent biliary excretion of the active drug. Data about the excretion of antibiotics in sweat may also facilitate the development of an ecologically sound antibiotic policy.[33]

In conclusion, the available evidence supports the introduction of an ecologically sound antibiotic policy which emphasizes: (i) a conservative approach of preferring old drugs; (ii) a restrictive approach based on rapid bedside diagnosis of offending pathogens before antibiotic treatment is initiated; (iii) an approach based on knowledge or rapid laboratory information about the antibiotic sensitivity of the offending bacteria; (iv) optimal use of pharmacokinetic and pharmacodynamic properties of the different antibiotics when dosing schedules are prescribed; and (v) selective use of antibiotics, e.g. the use of prodrugs, such as pivmecillinam, that do not interfere much with the normal flora.

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