Microbiological resistance promoted by misuse of antibiotics: a public health concern

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The introduction of penicillin in the mid-1940s marked one of the major medical breakthroughs in the twentieth century. At almost a single stroke, diseases that had often been fatal, such as meningitis, pneumococcal pneumonia and systemic group A streptococcus infections, became curable. Resistance to penicillin was detected soon after its first clinical use, but this caused little concern at the time as the pharmaceutical industry was rapidly succeeding in producing new antimicrobials which could circumvent the resistance mechanisms while remaining microbiologically active.

This situation has changed dramatically in the past 10 years: the frequency of resistance of most common pathogens is increasing with alarming speed. For example, 2–10% of pneumococci were penicillin resistant in South Africa and Spain in the mid-1980s, while rates of 50–80% are now reported from Greece, Spain, Eastern Europe and South East Asia.1 These pneumococci are still susceptible to expensive drugs such as carbapenems, newer fluoroquinolones and glycopeptides. However, some enterococci are now resistant to all antibiotics available — and the genes coding for these resistance mechanisms can be transmitted to many other Gram positive bacteria. The pharmaceutical industry has produced some antibiotics which have activity against these ‘superbugs’, but there are increasing difficulties in developing new antimicrobials.

WHAT HAS GONE WRONG?

There are no simple explanations as to what has gone wrong, but we are gathering knowledge and experience which will enable us to intervene before it is too late - if we start now.

First, resistance develops whenever antibiotics are used and there is a fairly high correlation between the amount used and the frequency of resistance. Some types of antibiotics are worse than others; for example tetracycline is particularly prone to select for resistance, often coupled to resistance genes for other antibiotics on the same conjugative plasmids.2 Thus, the geographical distribution of antimicrobial resistance is generally a reflection of the antibiotic use in that region. Second, resistant bacteria can spread, between individuals in a family, in children’s institutions, or in the hospital ward, but also by means of people (patients or tourists) moving between countries; the spread of penicillin-resistant pneumococci from Spain to Iceland is a good example.3

An issue of ongoing controversy has been the public health effects of antibiotic usage in agriculture, notably the risk of transmission of resistant bacteria and bacterial resistance genes from animals to man via the food chain. Although not all questions have been answered, there is a consensus of opinion that resistance develops in zoonotic bacteria, such as salmonella and campylobacter, primarily as a consequence of antibiotic usage in livestock.4 The recent emergence and rapid spread of the multi-resistant Salmonella typhimurium DT104 on several continents, with some having reduced susceptibility to quinolones, has shown that development of resistance in one region can quickly spread, probably through the animal and food trade, affecting hundred of millions of consumers. The rapidly growing use of fluoroquinolones for treatment and prophylaxis in livestock has been of particular concern because these are candidate drugs for treatment of human gastrointestinal infections in most regions of the world. Reduced susceptibility to fluoroquinolones by salmonella and campylobacter has been associated with the use of fluoroquinolones for animals.3

Of great concern is the recent development of resistance and its subsequent spread in last-resort antibiotics such as glycopeptides (vancomycin) and streptogramins (synercid) in enterococci, which has been associated with the use of similar classes of antibiotics as growth enhancers in livestock.6 It may be argued that, from an animal welfare perspective, all classes of antimicrobials should be made available to the veterinarian for treatment of disease. However, there is no valid argument supporting the use of these important last-resort antibiotics for food animal growth promotion, as at the same time we are losing their benefits for life-threatening infections in humans.

INTERVENTION IS POSSIBLE

There are several examples from departments, hospitals and even countries that reducing the amount and range of antibiotics reduces the frequency of resistance. An example is Denmark, where a country-wide epidemic of methicillin resistant Staphylococcus aureus (MRSA) o-
cured in the late 1960s and early 1970s, with up to 40% of all S. aureus bacteremia isolates methicillin resistant. A number of measures were implemented: meticulous and continuing monitoring and registration of all S. aureus isolates from hospitals including phage typing, susceptibility testing, reduction of the use of broad-spectrum antibiotics such as tetracycline and streptomycin, improvement of infection control policies in hospitals, improved education of physicians in prudent use of antibiotics etc. Denmark now has the lowest antibiotic use in Scandinavia as measured in defined daily doses per capita and, since 1975, the frequency of MRSA has remained below 0.5%. As a predominantly extra-nosocomial example, Finland experienced an epidemic increase in erythromycin-resistant Streptococcus pyogenes, which correlated closely with a rapid increase in macrolide use in Finland during the preceding years. Again, reduction in use of macrolides mostly in general practice resulted in decreasing rates (from 16–17% to 8–9%) in a few years. In Denmark, banning the use of the glycopeptide avoparcin as a growth promoter for animals has resulted in a reduction of carriage rate of vancomycin resistant Enterococcus faecium in broilers from 80 to 10% in the period between 1995 and 1998. Furthermore, the total consumption of therapeutic antibiotics by animals was reduced from nearly 90,000 kg in 1994 to approximately 44,000 kg in 1995 essentially by removing the economical incentives for veterinarians to prescribe. Intervention thus primarily involves several elements. Reduce the amount of antibiotics used and substitute broad spectrum antibiotics with narrow alternatives whenever possible. Identify emerging problems by monitoring antibiotic resistance in important pathogens and indicator organisms such as coagulase-negative staphylococci and enterococci. Relate the resistance pattern to the use of antibiotics and detect the important culprits. Reduction of use can be accomplished by many different means: via regulatory measures including strict rules for prescription of antibiotics, education of physicians (and patients), guidelines for use of antibiotics and good quality clinical microbiology with dependable susceptibility testing. Reduced use of antibiotics also depends on reducing indications for non-therapeutic use such as growth promotion in animal husbandry and unsubstantiated prophylactic use in veterinary practice. On a global scale the use of antibiotics for these purposes probably greatly surpasses the human use. Their use in growth promotion has no other reason than the apparent economic benefit from obtaining a greater weight increase per unit of fodder. We have grave concerns that the economical benefits in the long run will be outweighed by the public health consequences.

DEVELOPING NEW ANTIBIOTICS

What can be done to speed up the development of new antibiotics? The pharmaceutical companies complain that it is too expensive to market new drugs due to regulatory barriers concerning toxicity studies and large and expensive phase 1, 2 and 3 studies. And when the drug finally makes it to the market after 8–10 years, patent rules leave a relatively short interval to recover expenditures on the drug. Authorities should review these regulations carefully and if possible change them in such a manner so that there is no disincentive to produce relevant new antibiotics. On the other hand, the pharmaceutical industry must realize, that part of the responsibility for the present misuse of antibiotics — both for humans but certainly also for animals — can be traced back to the industry. It has not, in general, spared any effort to promote all new broad spectrum antibiotics knowing that their indiscriminate use would lead to development of resistance. The use of antibiotics cannot simply be left to the market but instead require regulation and close monitoring by relevant authorities. This is in the long term interests of the industry but even more so of the public.

LOOKING AHEAD

Bacterial resistance to antibiotics respects no national boundaries. Restrictive antibiotic policies within a country will be beneficial not only to that country, but also to its neighbours. From a public health point of view, a true international approach will be needed to combat this threat to human health.

It is thus comforting that in May 1998 the World Health Assembly adopted Resolution WHA51.17 ‘Emerging and other communicable diseases: antimicrobial resistance’ in which member countries and WHO were urged to prevent the further spread of bacterial resistance through a combination of legislative, monitoring and educational means. The Director Generals of Health of the EU countries and applicant countries will further discuss this issue at a conference in Copenhagen in September 1998, coinciding with the publication of this editorial.

REFERENCES


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