

General Policy Topics

Socially-responsive development of medicines

Never has it been more important, during the evolution of modern medicine, to take stock of the challenges ahead. In two short decades, confidence that infections and transmissible disease could be effectively contained has been replaced by apprehension about the emergence of new infections and of multidrug-resistant organisms.

The antibiotic era may be in irreversible decline. Defensive strategies that embrace both public and private sector interests need to be developed as a matter of urgency.

The following commentary is part II of a series on different aspects of the underlying situation.

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WHO Drug Information

II. Antibiotics in eclipse

Bacterial resistance in the hospital environment

The basis of concern

Throughout the early decades of this century, infectious bacterial disease was the principal cause of death in every country. Hospitals were populated with patients, young and old, many of whom were to die from acute bacterial infections including diphtheria, pneumonia, meningitis, typhoid fever, septicaemia, endocarditis and miliary tuberculosis. Others were admitted with tertiary syphilis, rheumatic heart disease and other delayed, terminal complications of bacterial infections.

All of this changed as living standards improved, public health services developed and, most reassuringly, as these infections became immediately responsive to antibiotics. UN statistics indicate that, over the past half century, public health and socioeconomic development has resulted in an unprecedented increase in life expectancy. In Europe, this has risen from 65 to 74 years, in South America from 51 to 65 years, in Asia from 41 to 65 years, and in Africa from 38 to 52 years. Much of this improvement has been attributed to reduction of deaths from infectious disease — a success that has been described as

the single most significant public health achievement of the past century (1).

Within the developed world, there is already a whole generation of clinicians for whom acute bacterial disease has posed little, if any, therapeutic challenge. With the advent of the first generation of antibiotic preparations in the 1940s, many infections — previously potentially lethal — became curable with an immediacy that invited complacency (2). It was inevitable that the impressive efficacy and safety of antibiotics should come to be taken for granted. The consequences of this attitude are manifest. Antibiotics have become widely and often inappropriately used in community practice to treat minor intercurrent infections (3). They are intensively used in hospitals both to treat and protect patients against nosocomial infections. Outside the sphere of human medicine, they are used in enormous quantities to support intensive stock rearing in farms and fisheries (4, 5).

By 1983, the total world market in antibiotics was estimated to approach US\$ 9 billion annually (6), and the projection that these costs will rise some fivefold by the turn of the century may already have been exceeded (7). Within the United Kingdom, for example, the total cost of antibiotics prescribed within the national health service rose fourfold to the equivalent of some US\$ 600 million between 1980 and 1991 (8). Much of this rise reflects increasing use of recently-developed, highly-

expensive antibiotics. This trend, in turn, has been driven by recognition that widespread and intensive use of first-line antibiotic agents has favoured the emergence of resistance to these less-costly products.

For too long the assumption has been commonly held by clinicians — and often fostered by manufacturers — that resistance might be countered indefinitely by the development of new generations of antibiotic substances. This complacent view no longer holds any vestige of legitimacy. Over the past few years, strains of many highly pathogenic species resistant to all widely-available antibiotics have emerged and proliferated at rates that were never envisaged (9–13).

Bacteria have evolved with a diversity that has secured their success in virtually every environment capable of supporting life. It seems prudent, given this capability, to accept the worst case hypothesis — that natural selection of resistant strains is an inevitable corollary to sustained antimicrobial pressure — and to plan accordingly. It is still not generally appreciated, even within the scientific community, that organisms commonly responsible for respiratory infections, diarrhoea, urinary infections and sepsis are now often resistant to all widely-available first-line antibiotics. Meanwhile, newly developed alternative products remain prohibitively expensive for public sector use in many countries. In the United States alone, the cost of treating hospital-acquired drug-resistant infections is now estimated to add as much as US\$ 4.5 billion annually to the cost of health care (14, 15).

Mechanisms of bacterial resistance

Antibiotics are essentially substances produced and extruded by bacteria that inhibit the growth of microbes competing in their natural habitat. By common usage, however, the definition has been extended to include systemically-administered synthetic antimicrobial substances, including the sulfonamides, quinolones, trimethoprim, and several anti-tuberculosis drugs.

The unifying characteristic of all medicinal antibiotics is that, whereas they disrupt specific metabolic processes vital to the growth of bacteria, they are largely innocuous to higher forms of life. At the same time, they are highly diverse in the mechanisms by which they inactivate susceptible bacteria. Penicillins, cephalosporins and the glycopeptide antibiotics (vancomycin and teicoplanin) kill

bacteria by disrupting the integrity of the outer cell wall. Most other widely-used antibiotics prevent bacterial growth by inhibiting one or more vital steps in protein synthesis.

Inherent, genetically-determined resistance to antibiotics is common among bacterial species. By definition, a narrow-spectrum antibiotic is lethal to relatively few pathogenic species. The remainder are inherently resistant for a variety of reasons (16). They may lack receptor configurations to which the antibiotic can attach; they may be relatively impermeable to the antibiotic or actively extrude it; they may inactivate it by producing a detoxifying enzyme; or they may lack a metabolic pathway that is the prime target of the antibiotic.

The emergence of newly-resistant strains

The facility with which many initially susceptible bacteria can acquire one or more mechanisms of resistance to a widely-used antibiotic is now all too evident. Indeed, it seems probable that all bacteria possess an inherent flexibility that enables them, sooner or later, to evolve genes rendering them resistant to any antibiotic (13). The emergence of resistant strains results from the operation of "selection pressure" — or the preferential survival of resistant variants within the population of bacteria exposed to the antibiotic. The time frame of such events varies considerably but, once formed, such strains tend to spread rapidly within the species.

Within a few years of the introduction of penicillin in the 1940s, resistant isolates of *Staphylococcus aureus* and *Neisseria gonorrhoeae* had become widespread (17, 18). In contrast, penicillin resistance was not described in *Haemophilus influenzae* or *Streptococcus pneumoniae* until three to four decades later (19–21). As yet, group A beta-haemolytic streptococci remain fully sensitive to penicillin. However, recently reported erythromycin-resistant strains have created a recognition that penicillin resistance could emerge in these potentially highly dangerous species at any time (22).

Initially, it was assumed that resistant strains emerge simply as a result of chromosomal mutation or inductive expression of a latent chromosomal gene. However, mutational change could not account for the sudden and simultaneous acquisition of resistance to several different antibiotics, which has been observed repeatedly over the past decade in many bacterial species. The ominous

explanation is that genes determining resistance to one or several antibiotics can be transferred from organism to organism — and sometimes from species to species — packaged in extrachromosomal structures known as plasmids (23, 24) or in loops of DNA called transposons that move reversibly between plasmids and chromosomes (25).

Although assumptions were initially made that plasmid-mediated resistance would be unstable, experience now suggests otherwise. Indeed, multidrug-resistant strains of pneumococci have been shown to remain stable *in vitro* over hundreds of generations (26). Nor is there persuasive evidence to support the view that the genetic load implicit in the acquisition of multiple resistance genes attenuates pathogenic virulence (11). Susceptible and resistant strains of staphylococci, for example, have been reported to be fully capable of producing toxin and of causing disease (27).

The practical implications of this knowledge have been succinctly summarized in the following way (13): "Once a resistant strain emerges, there are mechanisms by which such an advantageous change may be passed on to subsequent generations and to unrelated bacteria. Indeed, when a new type of drug resistance is noticed through a patient failing to respond to drug treatment, it is unlikely that the resistance will have evolved in that patient. The initial mutation may well have occurred elsewhere, often in a different type of bacterium, and the new gene may have become quite widespread throughout the bacterial world by the time it is detected" (28).

Prevalence of resistant strains in hospitals

Because it is in hospitals that antibiotics are most intensively used, it is here that resistance is most highly prevalent. Estimates applicable to the United States (29) and the United Kingdom (30) indicate that 5–10% of patients acquire an infection during an admission to hospital. During 1992, some two million such infections were recorded in the United States alone (31). Most of these infections are caused by widely-distributed commensal organisms, notably staphylococci, enterococci, enterobacteria, streptococci, and *Klebsiella* species.

Increasingly, these hospital-acquired (or nosocomial) infections are caused by drug-resistant strains of bacteria that are difficult to control. In the

USA, such organisms are claimed to be responsible for 60 000 to 70 000 deaths each year (31, 32). Initially, they were found only in larger regional and teaching hospitals. They are now widespread in smaller units and nursing homes (33) where methicillin-resistant strains of *Staphylococcus aureus* are proving particularly difficult to eradicate (34, 35).

Staphylococcal disease

Drug-resistant strains of *S. aureus* are now among the most life-threatening organisms in the hospital environment. They are a foremost cause of skin and wound infections, and of bacteraemias; they are responsible for many lower respiratory tract infections, for infections arising around indwelling catheters and prosthetic devices, and for cases of menstrual toxic shock.

When antibiotics first became widely available in the early 1950s, staphylococci were fully susceptible to penicillin, tetracycline and erythromycin. Within a decade, however, strains resistant to each of these substances were widespread. First to emerge were beta-lactamase-producing isolates of *Staphylococcus aureus*. The enzymes produced by these organisms inactivated the beta-lactam nucleus of naturally-occurring penicillins and the early broad-spectrum derivatives (16). The situation was temporarily assuaged during the 1970s as a result of the introduction of methicillin and other semi-synthetic penicillins containing a modified beta-lactam nucleus which was not a substrate for beta-lactamases (36). Within a decade, however, strains resistant to methicillin, resulting from the expression of cell-wall binding proteins with a low affinity for penicillin, became widespread both in Europe and North America (37–39).

Several distinct strains of *Staphylococcus aureus* have developed this mechanism of resistance, which is of considerable importance because it is operative against all beta-lactam antibiotics including penicillins, cephalosporins, carbapenems and penems (40). In some of the strains now epidemic, the responsible gene is chromosomal rather than plasmid-borne, and these are presumed to be highly stable. Moreover, other resistance genes frequently carried on the same chromosome extend this spectrum of resistance to other antibiotics including erythromycin, tetracyclines, minocycline, streptomycin, spectinomycin, sulfonamides and fusidic acid (16). In the United Kingdom, it is estimated that some two-thirds of *S. aureus* outbreaks in hospitals now involve multi-resistant strains of this nature (41).

The only agents now reliably effective against these organisms are the two glycopeptide antibiotics, vancomycin and teicoplanin, which block the synthesis of bacterial cell walls by binding to the terminus of peptide stems (42). In the United States, many large hospitals now spend 10–15% of their total pharmaceutical budget on vancomycin alone (11, 15). If vancomycin-resistant strains were to emerge and spread — a highly tangible risk that is ever present — some of the most prevalent nosocomial infections would become virtually untreatable. It is ominous that widespread use of this vital antibiotic has already resulted in the emergence of vancomycin-resistance in enterococci (43–45) — particularly since vancomycin resistance in *Enterococcus faecium*, which is plasmid-mediated, has been transferred by conjugation in the laboratory to Gram-positive cocci (46). Vancomycin resistance could thus well spread by this mechanism not only to *S. aureus*, but to other major pathogens including group A and B streptococci and *Streptococcus pneumoniae* (13).

Enterococci

Enterococci were once recognized simply as commensals prominent in the gut flora. In recent years they have become — after *S. aureus* and *Escherichia coli* — the third most prevalent cause of hospital-acquired infections in the United States (11, 47). *Enterococcus faecalis* — and to a lesser extent *E. faecium* — account for many cases of endocarditis and of urinary tract, wound, abdominal and pelvic infections. Because enterococci have pronounced inherent resistance to many antibiotics, these infections have always been difficult to treat. The standard regimen has been a synergistic combination of a penicillin and an aminoglycoside: penicillin increases the permeability of the bacterium to the aminoglycoside, which can then accumulate in lethal amounts within the periplasmic space (16).

Increasingly, however, hospital isolates have become resistant to beta-lactam antibiotics, tetracycline, chloramphenicol, aminoglycosides and fluoroquinolones. Vancomycin, held in reserve to treat these resistant strains, remained reliably effective until the 1980s. Within the past decade, infections resulting from strains resistant not only to penicillin and aminoglycosides but also to vancomycin have been reported which are essentially untreatable (48). Thus far, these multidrug-resistant strains are uncommon, but death rates exceeding 30% have been reported in outbreaks of bacteraemic infections in which they have been implicated (11).

Enterobacteria

Among the aerobic Gram-negative enterobacteria, *Escherichia coli* remains the most prevalent single cause of urinary tract infections, pyelonephritis, and hospital-acquired bacteraemia. More recently, *Klebsiella*, *Serratia*, *Proteus* and *Enterobacter* have emerged as important causes of hospital-acquired infections, and many strains are now resistant to multiple antibiotics (38).

Strains of *E. coli* clinically resistant to ampicillin and cephalosporins commonly contain a gene which strongly promotes expression of beta-lactamase. Although this gene is chromosomal in its location, its structure suggests that it may initially have been transmitted from *Shigella* (49). Some of these strains are resistant to ampicillin, even in the presence of one of the specific beta-lactamase inhibitors, clavulanate or sulbactam (16). Moreover, they have become so widely distributed in developed and developing countries that first-line antibiotics are now seldom useful in urinary tract and other infections attributed to *E. coli* (16).

The beta-lactamases generated by other Gram-negative organisms are usually plasmid-mediated (50). The most prevalent of these enzymes confers resistance to penicillins and second generation cephalosporins, but not to the broad-spectrum cephalosporins, cefamycins, monobactams and carbapenems. However, a more recently identified and widely dispersed variant commonly associated with nosocomial isolates of *Klebsiella pneumoniae* (51–54) inactivates a wider spectrum of antibiotics, including broad-spectrum cephalosporins and monobactams.

As yet, these isolates remain susceptible to the cefamycins, cefoxitin and cefotetan. However, given the frequency with which similar mutant enzymes have been selected by exposure to broad-spectrum cephalosporins under laboratory conditions (55–57), the clinical introduction of new cephalosporins and other beta-lactam antibiotics seems destined inevitably to favour selection of beta-lactamases with ever wider spectra of activity (58). It is portentous that one well-characterized enzyme not only extends the spectrum of activity to embrace the cefamycins; it is also resistant to the lactamase inhibitors, clavulanic acid and sulbactam (59).

Consequential efforts have been made to develop antibiotics with specific activity against beta-lactamase-producing organisms. These have

resulted in the introduction of imipenem and other carbapenems, a class of broad-spectrum beta-lactam antibiotics resistant to known clinically-relevant beta-lactamases. However, this success has been tempered by the discovery of an enzyme capable of hydrolysing these antibiotics which is expressed by chromosomal genes in strains of several Enterobacteriaceae species — including *E. cloacae*, *Bacteroides fragilis*, *Serratia marcescens*, and virtually all isolates of *Xanthomonas maltophilia* (60–62).

Some organisms, notably *Pseudomonas aeruginosa*, have developed resistance to beta-lactams through other genetically-determined mechanisms. These have resulted in expression of binding proteins with reduced affinity for penicillin (63–64) and in loss of an outer membrane protein which provides a channel for the entry of beta-lactam antibiotics into the periplasmic space (65). Some strains of *P. aeruginosa* and *P. cepacia* are now additionally resistant to the carbapenems. Not only do these strains produce substantial amounts of beta-lactamase, they are also essentially impermeable to beta-lactam antibiotics.

Analogous depletion of specific binding sites has resulted in many strains of *P. aeruginosa* and *P. cepacia* becoming comparably resistant to fluoroquinolone antimicrobials (66, 67) and to aminoglycosides (68, 69). This resistance even extends to amikacin, a semi-synthetic derivative of kanamycin designed to provide a poor substrate for the various enzymes that mediate resistance to aminoglycosides in staphylococci (70) and enterococci (71).

Increasingly, untreatable *Pseudomonas* infections are causing deaths within intensive care units (16) and in patients with cystic fibrosis or other conditions that render them vulnerable to infection (72). A closely related organism, *Xanthomonas maltophilia* — formerly known as *Pseudomonas maltophilia* — has similarly been implicated in such outbreaks in units where imipenem has been extensively used. Such deaths have also been attributed to *Acinetobacter*, a common skin commensal, only recently identified as an important cause of nosocomial disease (73). (See p. 25).

Anaerobic bacteria

Bacteroides species and other anaerobic bacteria that reside in the mouth are a frequent cause of aspiration pneumonia in vulnerable patients. Initially, these infections were consistently respon-

sive to penicillins, but beta-lactamase-producing strains are now reported to be widespread (16). Potent beta-lactamase activity is also evident in strains of *B. fragilis*, the major anaerobe in the large bowel, while strains of a closely-related species, *B. thetaiotaomicron* hydrolyse highly beta-lactamase stable compounds, including cefoxitin and even imipenem and other carbapenems (60). The disturbing possibility exists that the responsible gene may eventually be transferred to *E. coli* and other potentially pathogenic enterobacteria (16).

The outlook

For as long as present trends prevail — and there are no means immediately in prospect of creating radical change — strains of pathogenic bacteria resistant to all available therapy are at risk of emerging within the hospital environment under the pressure of antibiotic use. The very real possibility of vancomycin resistance emerging in a meticillin-resistant strain of *S. aureus*, or of resistance to carbapenems spreading more widely among the aerobic, Gram-negative enterobacteria would have particularly serious implications for the safety of patients in hospitals.

But precisely which patients are at risk? In the Nordic countries, it seems, “mainly immune-compromised people are involved, especially those who have a long history of treatment with antibacterials” (74). This implies that multidrug-resistant hospital bacteria are essentially opportunistic pathogens dangerous only to the most vulnerable of patients. However, to return to the example of staphylococci, this has not been the experience in the United States (27, 75, 76), or even in the United Kingdom (78–80). In these countries meticillin resistance is not considered to be a correlate for either virulence or spread in staphylococci: some, but by no means all such strains of staphylococci, possess each of the acknowledged virulence factors, have epidemic potential, and may cause severe infections (36).

Within the United Kingdom, the cost of treating infections caused by these strains and of containing endemic outbreaks in the worst affected hospitals is already recognized to be an onerous charge on the public health budget (36). Similarly, within the United States, it has been estimated that in some intensive-care units, patients now have a 25–70% risk of acquiring a nosocomial infection, and that most of these are caused by multidrug-resistant organisms (11, 29, 32).

To what extent drug-resistant organisms are prevalent within hospitals in developing countries is unclear. It is commonly assumed that "infections caused by multiple resistant strains are rife throughout the developing world" (13, 80). It is evident that emergence of resistance is favoured wherever chronic shortage of antibiotics results in under-dosing, where lack of microbiological laboratories results in blind prescribing, and where lack of reserve agents augments the risk of therapeutic failure. It would be illogical to contend, however — within the context of hospital-acquired infections — that less-developed countries serve as a reservoir of multidrug-resistant hospital pathogens. These strains are likely to emerge only in institutions where expensive reserve antibiotics are used on such a scale as to generate the necessary selection pressure.

Developing countries desperately need hospital microbiological laboratories, reliable supplies of first-line and reserve antibiotics, and effective clinical and laboratory surveillance systems. This need, however, is generated by their concern to serve their own populations and to overcome high levels of resistance to first-generation antibiotics, and not because they pose an illusory threat as a source of newly-emerging resistant strains to other countries.

The containment of hospital-acquired infections is based everywhere upon the application of a well-validated set of general principles which, in some countries, has long been codified (3). These stress two complementary needs (81):

- the importance of developing, within every hospital, a simple and flexible antibiotic-prescribing policy on a disease-specific basis, relying whenever possible on knowledge of prevailing antibiotic sensitivity patterns and controlled use of reserve antibiotics; and
- the institution of rigorous standards of hygiene, barrier nursing and, whenever appropriate, bed isolation.

In the longer term, such measures are manifestly no more than palliative. Meanwhile, fears are being realized of a crisis in the management of acute infections. Innovative approaches need to be explored. Experience with the beta-lactam antibiotics and the aminoglycosides indicates that much more is needed than the introduction of variants of antibiotics already compromised by the emergence of resistant strains. New insights are

needed that can be obtained only through increased investment in basic research (11, 58). Yet economic circumstances are eroding such investment, both in the public and the private sectors (11).

There is a case also to be made for a basic re-orientation of antibiotic prescribing strategy within hospitals. The emphasis over the past decade — during which the current crisis has developed — has been to favour the use of products with a broad antibacterial spectrum. These provide a certain margin of security for patients seriously ill with an undiagnosed infection. By the same token, when they are extensively used, they also exert significant selection pressure on an increasing number and variety of potential pathogens. This, it is argued, points to a need for new types of antimicrobials, each with a narrow spectrum of activity, which are intended to be held in reserve as strategic tools to contain specific drug-resistant organisms (10, 11). Breakthroughs, it has been suggested, might be possible not only with new antibiotic substances but also with synthetic agents, conceptually similar to the beta-lactamase inhibitors, clavulanic acid and sulbactam, designed to block specific receptor mechanisms (82).

The challenge is formidable. If technological progress is to be made within a time frame that reflects the urgency of the situation, a political climate must be fostered immediately that will encourage an alliance among the major interest groups, including governments, academia and research-based pharmaceutical companies (83). An environment must be created in which valid concerns about the need for cost containment in the provision of medical services are balanced by the recognition that continued investment in innovative research is required simply to conserve the hard-won gains of the past.

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