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Mechanisms of Antimicrobial Resistance

Their Clinical Relevance in the New Millennium

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Abstract

Antimicrobials show selective toxicity. Suitable targets for antimicrobials to act at include the bacterial cell wall, bacterial protein and folic acid synthesis, nucleic acid metabolism in bacteria and the bacterial cell membrane. Acquired antimicrobial resistance generally can be ascribed to one of five mechanisms. These are production of drug-inactivating enzymes, modification of an existing target, acquisition of a target by-pass system, reduced cell permeability and drug removal from the cell.

Introduction of a new antimicrobial into clinical practice is usually followed by the rapid emergence of resistant strains of bacteria in some species that were initially susceptible. This has reduced the long-term therapeutic value of many antimicrobials. It used to be thought that antibacterial resistance was mainly a hospital problem but now it is also a major problem in the community. Organisms in which resistance is a particular problem in the community include members of the Enterobacteriaceae, including *Salmonella* spp. and *Shigella* spp., *Mycobacterium tuberculosis, Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria gonorrhoeae.* Multi-resistant Gram-negative rods, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci are major causes of concern in the hospital setting. Prevalence of antibacterial resistance depends both on acquisition and spread. Decreasing inappropriate usage of antimicrobials should lessen the rate of acquisition, and spread can be minimised by sensible infection control measures.

1. Sites of Action of Antimicrobial Agents

An antimicrobial agent is anything that inhibits microbial growth. Strictly speaking, an antibiotic is a naturally produced inhibitor of microbial growth, but mostly the terms antibiotic and antimicrobial agents are used synonymously. The ideal antimicrobial should exhibit maximal toxicity for the pathogen while causing the minimum damage to the host tissues. This is termed 'selective toxicity'. Selective toxicity is best achieved where an antimicrobial agent blocks a metabolic pathway that is absent in mammalian cells or is radically different to that in bacteria. Suitable targets for antimicrobials to act at and the reasons they show selective toxicity at these sites are listed in table I.

Antibiotics that act on the cell wall by inhibiting peptidoglycan synthesis include β-lactams and glycopeptides. β-Lactams include penicillins, cephalosporins, monobactams and carbapenems. β-Lactams show excellent selective toxicity as humans do not have cell walls like bacteria and are generally the antimicrobials of choice in pregnancy. Many of them have a broad spectrum of activity including

Table I. Reasons why bacteria show selective toxicity at various sites

Site of action	Reasons for selective toxicity	Examples of antimicrobials active at this site
Bacterial cell wall synthesis	The bacterial cell is bounded by a wall composed of peptidoglycan, whereas mammalian cells lack this	β-Lactam agents: penicillins, cephalosporins and carbapenems
		Glycopeptides: vancomycin and teicoplanin
Bacterial protein synthesis	Protein synthesis in bacteria is by the 70s ribosome: that in mammalian (or other eukaryotic) cells is by the 80s ribosome	Macrolides
		Tetracycline
		Chloramphenicol
		Aminoglycosides
Folic acid synthesis	Folic acid synthesis in bacteria and in higher organisms differs radically.	Sulphonamides
		Trimethroprim
Nucleic acid metabolism	Nucleotide synthesis and polymerisation is similar in bacteria and mammals, and drugs that affect these processes often have toxicity for mammals	Quinolones
		Rifampicin
		Metronidazole
Membrane disorganising agents	Some are used but the selective toxicity is poor because of the similarity between bacterial and mammalian membrane	Amphotericin B (an antifungal)
		Polymyxin

activity against streptococci, staphylococci and Gram-negative rods. The glycopeptides in current clinical use in most parts of the world are vancomycin and teicoplanin. They are only active against Gram-positive organisms and have no activity against Gram-negative rods.

Agents that inhibit protein synthesis, include aminoglycosides, tetracyclines, chloramphenicol, macrolides, lincosamides and fusidic acid. Of these, aminoglycosides and tetracyclines act on the 30s ribosomal subunit, and chloramphenicol, macrolides, lincosamides and fusidic acid act on the 50s ribosomal subunit. Among the agents inhibiting protein synthesis, the aminoglycosides are the only bactericidal drugs; the remainder are bacteriostatic.

Antifolates include sulphonamides and trimethoprim. The numerous sulphonamides available commercially differ in their pharmacokinetics but share a common mode of action. They are structural analogues of p-aminobenzoate and act as inhibitors of dihydropteroate synthase, an enzyme which catalyses the condensation of p-aminobenzoate and pteridine pyrophosphate to form dihydropteroic acid, which itself is a precursor of folic acid. Initially sulphonamides were thought to be simple competitive inhibitors of dihydropteroate synthase; it is now thought that the enzyme manages to catalase some linkage of the antimicrobial to pteridine pyrophosphate, yielding a product that cannot be converted to folic acid. Trimethoprim is an inhibitor of dihydrofolate reductase, which catalyses the final stage in bacterial folate synthesis. It does not significantly inhibit human dihydrofolate reductase. Trimethoprim and sulphamethoxazole when used together in the combination cotrimoxazole show synergistic activity against many microbes.

Drugs affecting nucleic acid metabolism include some cytotoxic drugs and many agents affecting nucleic acid synthesis show poor selective toxicity. However, there are exceptions to this. Antimicrobial agents affecting nucleic acid metabolism and which show good selective toxicity include the quinolones (nalidixic acid and newer derivatives such as ciprofloxacin), rifampicin and the nitroimidazoles. Quinolones act by inhibiting the enzyme DNA gyrase that is responsible for supercoiling DNA such that it will fit into the cell. Rifampicin is the most important of the rifamycins and is very active against Gram-positive bacteria and bactericidal to mycobacteria. It specifically inhibits the synthesis and function of DNA-dependent RNA polymerase in bacteria; the corresponding mammalian enzyme is much less sensitive. The drug does not inhibit transcription once it has be-

gun but prevents the initiation of transcription. The nitroimidazoles have a wide spectrum of activity encompassing both Gram-positive and Gram-negative anaerobic bacteria, protozoa and some helminths. Metronidazole has been the most studied. It is selectively toxic for anaerobic bacteria and has no action against aerobes. To achieve this it must inhibit a biochemical process unique to anaerobes. Metronidazole interacts with the pyruvate phosphoroclastic reaction and it is now generally accepted that the reduction products of the nitroimidazoles are responsible for the killing effects. Their main site of action is DNA and extensive strand breakage occurs. There is no effect on RNA.

There are a number of agents that act as membrane disorganising agents. In addition some antibacterials that inhibit other cell functions also affect the cell membrane when present in high concentration. They generally show relatively poor selective toxicity. They interact specifically with the cell membrane, and the agents of clinical importance are the polymyxins and the polyenes. Only two polymyxins have been developed commercially, polymyxin B and E (colistin). Their activity is restricted to Gram-negative rods, where they bind to the membrane phospholipids. The result of binding is a disruption of the cell membrane. Polyenes are a large group of structurally related agents, most of which are too toxic for clinical use. The important ones are the antifungal agents, amphotericin B and nystatin. They act by making sterol-containing membranes (found in fungi but not in bacteria) leaky, leading to loss of internal contents and subsequently cell death. Greenwood[1] provides a more comprehensive review of sites of action of antimicrobials.

2. Resistance to Antimicrobials

Resistance can be intrinsic or acquired. Intrinsic resistance is a naturally occurring phenomenon, which occurs in the absence of antimicrobial selection pressure, and the term implies that not all species are intrinsically susceptible to all antimicrobials. This article mainly deals with acquired resistance. Acquired resistance to antimicrobials can be considered either on a genetic or biochemical basis. On a genetic basis resistance may be permanent or temporary. Temporary resistance is often termed 'adaptive' and is dependent on the growth conditions e.g. *Pseudomonas aeruginosa* is resistant to polymyxins and aminoglycosides when starved of magnesium ions and *Escherichia coli* is resistant to aminoglycosides when grown under anaerobic conditions.[2]

Permanent resistance arises either from mutation or from acquisition of extrinsic DNA (i.e. additional DNA from an outside source). It is vital to appreciate that antimicrobials do not cause mutations (they wouldn't get product licenses if they did!). However, their use tends to select pre-existing spontaneous mutants that are resistant; this is simply an example of the Darwinian 'survival of the fittest' theory.

Sources of extrinsic DNA can occur via transformation, transduction or conjugation. Conjugation, which is the transfer of DNA from living cell to living cell, is far the most important of these. Spread of plasmids by this method has accounted for much of the development of drug resistance in bacteria. The resistance genes (determinants) commonly are on transposons, defined as 'sticky ended' sections of DNA that can jump from one plasmid to another. This process evidently facilitates the spread of resistance. Transposons can sometimes also be inserted into the chromosome, reducing transmissibility but increasing their stability.[3]

The genetic bases of many antimicrobial resistance mechanisms are known. Some examples include the *mecA* gene which determines methicillin resistance in *Staphylococcus aureus*,[4] *vanA*, *vanB*, *vanC-2* and *vanC-2/3* genes in enterococci which determine resistance to glycopeptides,[5] and genes in enterococci controlling enzymes that modify aminoglycosides conferring high level aminoglycoside resistance.[6] Other important examples are rifampicin resistance in *Mycobacterium tuberculosis* where mutation in a region of the *rpoB* gene that encodes the β-subunit of RNA polymerase leads to an alteration of the rifampicin-binding site[7] and

quinolone resistance due to mutations in *gyrA*/*gyrB*/*parC*/*parE*.[8]

From a biochemical point of view resistance generally can be ascribed to one of the five mechanisms shown in table II. However, these resistance mechanisms can overlap i.e. an organism can become resistant to an antimicrobial by more than one mechanism.

Table II. Biochemical bases of bacterial resistance to antimicrobials

Resistance mechanism	Examples
Production of drug-inactivating enzymes	β-Lactamases
Modification of an existing target	Ribosomal resistance to streptomycin via modification of S12 protein
Acquisition of a target by-pass system	Additional penicillin binding protein PB2′ in methicillin- resistant *Staphylococcus aureus*
Reduced cell permeability	Impenem-resistance in *Pseudomonas aeruginosa*
Drug removal from the cell	Tetracycline resistance

2.1 Modifying Enzymes

Modifying enzymes may be plasmid mediated or chromosomal. Many species naturally have chromosomally-mediated β-lactamases, but plasmidic types also occur, these being biochemically distinct from the chromosomal enzymes. β-Lactamase production is a major cause of resistance in enteric Gram-negative rods as well as in infections caused by *S. aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria gonorrhoeae*. Some β-lactam drugs are stable to certain β-lactamases, e.g. flucloxacillin is stable against the β-lactamases produced by S. *aureus* and some of the newer cephalosporins tend to be stable against many of the β-lactamases produced by Gram-negative rods apart from the extended spectrum β-lactamases. In other instances β-lactamase production can be overcome by combining a β-lactam antibiotic with a β-lactamase inhibitor such as clavulanic acid, sulbactam or tazobactam; however, this often leads both to increased treatment adverse effects and costs. Aminoglycoside modifying enzymes conferring resistance to aminoglycosides and chloramphenicol actelytransferases are other examples of modifying enzymes.[3,9]

2.2 Modification of an Existing Target

Ribosomal resistance to streptomycin, via modification of the S12 protein is an example of modification of an existing target. A single amino acid change at either of two sites gives resistance. DNA gyrase-determined resistance to quinolones is another example - several mutations of *gyrA*, *gyrC* or *gyrD* can cause such resistance. Further examples include penicillin resistance in gonococci due to modified penicillin-binding proteins, and sulphonamide and trimethoprim resistances arising from modified dihydropteroate synthase and dihydrofolate reductase, respectively. These mechanisms all depend on mutation.[3,9]

2.3 Acquisition of a Target By-pass System

Examples of acquisition of a target by-pass system include acquisition of plasmid-mediated dihydropteroate synthase and tetrahydrofolate reductases resistant to sulphonamides and trimethoprim, respectively, which confers resistance to these agents by a method other that modification of an existing target. The presence of an additional penicillin binding protein PB2′ in methicillin-resistant *S. aureus* (MRSA), which does not bind to β-lactams and hence renders the organism resistant to flucloxacillin, is another example of this. These mechanisms all arise from the acquisition of extrinsic DNA and may be more or less readily transferable.

Reduced cell permeability: this can occur as a result of porin loss, which may reduce uptake of many hydrophilic drugs across the outer membrane of Gram-negative bacteria and hence cause multidrug resistance. Narrow spectrum imipenem resistance, which can arise in *P. aeruginosa*, is another example of reduced cell permeability. This occurs as a result of loss of a specific uptake pathway due to mutation.[3,10]

2.4 Drug Removal from the Cell

Drug removal from the cell is usually 'lumped' with impermeability but is an active mechanism,

whereas impermeability is passive. The classic example is tetracycline resistance. Resistant cells take up the drug as rapidly as do sensitive ones but differ in being able to pump it out again. This is usually plasmid-mediated. Efflux may be an important mechanism of ciprofloxacin resistance in several species of bacteria.[3,8]

3. Cross-Resistance and Multiple Resistance

The term cross-resistance refers to resistance occurring in several different members of a group of chemically related compounds, which are affected by the same resistance mechanism. For example, i) extended spectrum β-lactamases in Gram-negative rods may confer resistance to several different penicllins and cephalosporins, and ii) MLS_B resistance in streptococci and staphylococci caused by methylation of adenine in the 23S fraction of ribosomal RNA, which confers resistance to macrolides, lincosamides and $streptogramin_B$ antimicrobials.[11] Occasionally cross-resistance occurs between unrelated antibacterials e.g. a change in the outer membrane of a Gram-negative rod may prevent several unrelated compounds gaining access to their target site. The term multiple resistance refers to a bacterium becoming resistant to several unrelated antibacterials by different resistance mechanisms. This can be a major problem in patients with Gram-negative bacteraemia in many intensive care units (ICUs).

4. Detection of Antimicrobial Resistance

The susceptibility of bacteria to antimicrobials can be assessed in several ways. Traditional methods include agar diffusion tests, broth dilution tests and agar incorporation tests. However, in the 21st century there is an ever-increasing interest in developing molecular techniques for the rapid detection of antimicrobial resistance genes. For instance, single tube assays using hybridisation capture techniques are already commercially available for the detection of some resistance genes.[12] In addition, real time polymerase chain reaction (PCR) is now finding many applications in the bacteriology laboratory and is likely to prove useful in the rapid detection of antimicrobial resistance as well as for strain identification, epidemiological typing and detection of virulence markers.[12] Molecular techniques are of increasing importance in outbreak investigation and in monitoring shifts of epidemic and endemic clones.[13] However, although molecular biology techniques are widely used in routine clinical virology laboratories both for the initial diagnosis of infections and the monitoring of therapy,[14] as yet the majority of routine clinical microbiology departments use traditional agar diffusion, agar incorporation or broth dilution tests as their mainstay for obtaining susceptibility data on bacteria. Exceptions to this are testing for the *mecA* gene which determines methicillin resistance and is used in some laboratories for the diagnosis of MRSA infections [4] and the rapid detection of rifampicin resistance in *M. tuberculosis* by looking for mutations in the region of the *rpoB* gene.[7]

5. Relevance of Resistance in the New Millennium

Introduction of a new antimicrobial into clinical practice is usually followed by the rapid emergence of resistant strains of bacteria in some species that were initially susceptible. This acquisition of resistance has reduced the long-term therapeutic value of many antimicrobials. It has also been a major contributing factor in the pharmaceutical industry's continual search for new anti-infectives.

Acquisition of resistance is not a new phenomenon. For instance, when penicillin was introduced into clinical practice in the early 1940s less than 1% of *S. aureus* were resistant to it but by 1946, as a result of selective pressure, the proportion of penicillin-resistant strains found in the hospital setting had risen to 14%.[15] Currently, over 90% of *S. aureus* are resistant to penicillin as a result of β-lactamase production. Interestingly, acquisition of resistance to an antimicrobial does not always occur with all organisms following its widespread use - it depends on the antimicrobial/organism combination. For instance, even after over 50 years of penicillin use there have been no reports of

penicillin-resistant *Streptococcus pyogenes* or *Treponema pallidum.* Similarly, although temporary partial or complete withdrawal of an antimicrobial from clinical use may result in a decline in resistance occurring because of lack of selective pressure,[16] this does not always occur.[17,18]

It has been suggested by some that the 21st Century may resemble the pre-antimicrobial era in that we may run out of all effective antimicrobials. Most people feel that this view is unduly pessimistic but concerns about antimicrobial resistance are undoubtedly increasing globally.[19] It is an international public health issue which was addressed in the UK in recent years by reports both from the House of Lords[20]and the Standing Medical Advisory Committee.[21] From a financial point of view increasing antimicrobial resistance is a major cause of concern because although, in most cases, we still have agents available to treat most infections caused by resistant bacteria, these agent are often new and expensive compounds. Even in developed countries there is not an unlimited health budget and choices continually have to be made regarding the best use of available resources, and in developing countries use of the more expensive antimicrobials may be severely restricted for economic reasons.

It used to be thought that resistant organisms mainly occurred in hospitals but they are becoming an increasing problem in the community setting as well. Major resistance problems in the community are summarised in table III and those in hospitals in table IV. Organisms in which resistance is a particular problem include members of the Enterobacteriaceae, and staphylococci, enterococci, *S. pneumoniae*, *H. influenzae, M. tuberculosis* and *N. gonorrhoeae*.

Table III. Antimicrobial resistance problems in the community

Clinical problem	Bacteriological causes
Urinary tract infections	β-Lactamase producing coliforms
Respiratory tract infections	Resistant pneumococci and β-lactamase producing *Haemophilus influenzae*
Tuberculosis	Multi-drug resistant *Mycobacterium tuberculosis*
Gonorrhoea	Penicillin resistant *Neisseria gonorrhoeae*
Diarrhoea	Multi-drug resistant *Salmonella* spp., *Shigella* spp. and *Campylobacter* spp.

Table IV. Antimicrobial resistance problems in hospitals

Methicillin resistant *Staphylococcus aureus* and coagulase negative staphylococci
Staphylococci with decreased susceptibility to vancomycin
Vancomycin resistant enterococci
Multi-resistant *Pseudomonas* spp. *Klebsiella* spp. *Enterobacter* spp. and *Acinetobacter* spp.

6. Antimicrobial Resistance Problems in the Community

Urinary tract infections are extremely common. In the United States, a study performed by Hooton et al.[22]in women aged 18 to 40 years in a university health setting and a large health maintenance organisation in Seattle showed that these women had approximately one episode of uncomplicated cystitis per two person years. Hence, treatment of urinary tract infections is a major cause of antimicrobial prescribing. *E. coli* is the cause of about 75% of community-acquired urinary tract infections. Unfortunately β-lactamase production in *E. coli* now occurs in over 50% of isolates in many parts of the world making amoxicillin inappropriate first line empirical therapy of these infections in many places. Although they usually cause localised infection, is important to remember that urinary tract infections, partially because of the huge number that occur each year, are a common cause of Gram-negative septicaemia. Livermore et al.[23] found β-lactamase production to be a major cause of concern in isolates of *E. coli* obtained from the bloodstream or cerebrospinal fluid (CSF). In a UK survey of over 4000 isolates obtained either from the blood or CSF in 1997 they found over 55% to be resistant to amoxicillin.

The Alexander Project was established in 1992 to examine antimicrobial susceptibilities of community-acquired infections from the lower respiratory tract. From 1996 onwards the study included European countries, various states in the USA, Mex-

ico, Brazil, Saudi Arabia, South Africa and Hong Kong. It found that in 1997, overall, 14.1% of all *S. pneumoniae* showed decreased susceptibility to penicillin and 21.9% were resistant to macrolides, although in some countries over 50% of isolates showed decreased susceptibility to penicillin.[24] Resistance to *H. influenzae*, chiefly by β-lactamase production, was also found to be common. For instance, in the USA in 1997 23.3% of all isolates were found to be β-lactamase producers.[24] Overall, at the same time, over 90% of *M. catarrhalis* isolates were found to be amoxicillin-resistant as a result of β-lactamase production.

A global survey estimated that 9.9% of *M. tuberculosis* isolates from previously untreated patients were resistant to rifampicin, isoniazid, streptomycin or ethambutol, and that worldwide 0.2% of all isolates demonstrated multiple resistance and were resistant to all four of these drugs. The highest prevalence of resistance was found in the former Soviet Union.[25] Multi-drug resistant *M. tuberculosis* is more common in people where compliance in taking therapy is a problem and in those with HIV infection.[25]

There has also been a trend for increasing resistance, including multiple resistance, in bacteria causing infections of the gastrointestinal tract. For instance, Prats et al.[26]evaluated 3797 enteropathogenic bacteria including *Campylobacter* spp., *Salmonella* spp., *Shigella* spp. and *Yersinia* spp. between 1985 to 1987 and 1995 to 1998. They found that quinolone resistance in *Campylobacter jejuni* rose from 1% in the earlier survey to 82% in the second survey, and tetracycline resistance rose from 23% to 72%. They also found that, whereas in the 1985 to 1987 survey ampicillin resistance in gastroenteric *Salmonella* spp. was 8% and chloramphenicol resistance was 1.7%, in 1995 to 1998 it was 44% and 26%, respectively. In the same two time periods co-trimoxazole resistance went from 0.5% to 11% and tetracycline resistance from 1 to 42% in gastroenteric salmonella infections. In the 1995 to 1998 survey, 67% of *Shigella* spp. were found to be resistant to cotrimoxazole.

Sexually transmitted infections are extremely common. It was recently estimated that among adults between 15 and 49 years of age there were 332 million cases worldwide of which *N. gonorrhoeae* accounted for 18.7%.[27] Penicillin or amoxicillin used to be the mainstay of treatment for these infections but in many part of the world penicillin resistance is becoming a problem; it can occur either as a result of changes in the penicillin binding proteins of the organism or β-lactamase production. If it is due to alteration of penicillin binding proteins, the resistance is usually low level and hence penicillin may still be effective, but if it is due to β-lactamase production, alternative therapy is required. In recent years there have also been an increasing number of isolates with decreased susceptibility to the fluoroquinolones.[28]

7. Antimicrobial Resistance Problems in Hospitals

In the hospital setting, especially in ICUs, Gram-negative rods such as *Klebsiella* spp., *Pseudomonas* spp. and *Acinetobacte*r spp. are a major cause of sepsis and may be multi-resistant. The SENTRY Antimicrobial Surveillance Programme looked at nosocomial pneumonia in ten Latin American centres and found that the four most frequently isolated pathogens were *P. aeruginosa* (26%), *S. aureus* (12%), *Klebsiella* spp. (12%) and *Acinetobacter* spp. (10%).[29] *P. aeruginosa* and *Acinetobacter* spp. exhibited high levels of resistance to most of the antimicrobials tested i.e. they showed multiple resistance. In addition, only 77% of the *P. aeruginosa* and 50% of the *Klebsiella* spp. were found to be sensitive to the aminoglycoside, amikacin. Over 22% of the *Klebsiella* spp. were found to produce extended-spectrum β-lactamases (ESBLs). A survey carried out from May 1997 to October1998 in 24 ICUs in Western and Southern Europe found similar results; 25% of the *Klebsiell*a spp. submitted were ESBL producers.[30]

Resistance to *S. aureus* and *Enterococcus* spp. varies greatly from country to country; in some it is a major therapeutic problem. For instance, the SENTRY Antimicrobial Surveillance Programme

in the US and Canada found that in 1997 whereas 26.2% of *S. aureus* isolates obtained from the USA were oxacillin resistant, the proportion in Canada was only 2.7%.[31] Vancomycin-resistant enterococci (VRE) accounted for 17.7% of the US enterococcal isolates but none of the Canadian isolates.

8. Prevalence of Resistance

Prevalence of bacterial resistance depends on both acquisition and spread. Early, appropriate antimicrobial therapy can help limit spread of multi-resistant infections. Knowledge of local, national and international resistance patterns is required in order to prescribe rational empirical therapy, if this is indicated, and for the development of antimicrobial policies. Unfortunately the validity of susceptibility data obtained from routine clinical isolates sent to the diagnostic laboratory to ascertain local prevalence of resistant strains is sub-optimal. This is because many community physicians treat most patients with, for instance, urinary or respiratory tract infections empirically and only send samples to the laboratory from patients who have failed initial therapy. In the hospital setting, more doctors send samples before starting therapy but resistance patterns, even within the same hospital may vary widely. For instance, a urinary tract infection in a long-term ICU patient is much more likely to be due to a multi-resistant Gram-negative rod than one in a patient on a general medical or surgical ward. Ideally, data obtained from different areas within a hospital should be analysed separately but unfortunately this rarely happens. Having taken cultures from individual patients, treatment may require modification depending on results of antimicrobial susceptibility tests.

Spread, particularly within the hospital setting, is also minimised by enforcing sensible infection control measures. For example, isolating patients with multi-resistant organisms in a side-room (or cohort nursing patients with the same multi-resistant organism together) if at all possible, and washing and drying hands thoroughly between patients with soap and water or using antiseptic lotions/wipes. However, even within Europe different countries seem to put a very different emphasis on the importance of infection control. In Scandinavia, for instance, great emphasis is put on its importance and cross-infection is low. In contrast, in parts of Southern Europe scanty heed is paid to it and the cross-infection rate is high.[32,33]

Lack of sufficient good infection control is generally attributed to one or more of three causes – lack of resources (both people and money), apathy and ignorance. However, hospital-acquired infections have major financial implications because of the likelihood of increased hospital stay, the possible need for expensive agents to treat multi-resistant infections and the potential cost if litigation ensues. For instance, a recent study by Martinez et al.[34] found that if a patient developed Gram-negative bacteraemia post-surgery the cost of their hospital stay was 1 108 252 pesetas more expensive than for a similar control group of patients who did not develop Gram-negative bacteraemia.

Some staff, especially medical ones, feel that practising infection control is a waste of time which could more profitably be spent treating patients. They thus require educating that prevention of hospital-acquired infections by simple measures such as hand-washing etc. is far more time- and cost-effective than treating infections when they occur. Both medical staff and hospital managers, as well as the general public, need to be made aware of the importance of following sensible infection control procedures, and investing time and money into providing decent isolation facilities for infected/potentially patients in order to minimise the risk of cross-infection

9. Conclusion

The advent of effective antimicrobials last century brought major benefits to us by decreasing both morbidity and deaths due to infective causes. However, they have at times been used indiscriminately and it is widely believed that unnecessary and/or inappropriate use of antimicrobials is a major cause of the widespread emergence of resistant organisms, which is beginning to threaten the continued effectiveness of antimicrobial therapy.

Spread of these resistant organisms is a further threat to the continued effectiveness of many antimicrobials.

Being able to obtain a wide range of antimicrobials over-the-counter without prescription, especially if no advice is given about their appropriate use, is a major potential cause of antimicrobial abuse but this practice occurs widely in many parts of the world. Other unnecessary uses of antimicrobials include prescribing them for presumed viral, self-limiting infections, and using clinically useful antimicrobials as growth promoters in animal feeds or on crops. Pharmaceutical companies may also have a role in promoting indiscriminate use of antimicrobials if they advertise their compounds as 'wonder drugs'- this is a particular problem in places where over-the-counter antimicrobials are freely available. Yet another factor predisposing to the development of antimicrobial resistance is the illicit manufacture of 'street antibiotics' containing sub-optimal amounts of active compound resulting in the patient being exposed to sub-therapeutic doses of the active antimicrobial; these are sometimes difficult to distinguish from the original product. Thus consumers, medical personnel, dispensers, manufacturers and governments all need to understand the importance of minimising spread of resistant organisms and playing a part in the prudent use of antimicrobials to help ensure that these compounds remain effective therapeutic agents throughout the 21st century.

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