Antibacterial resistance in the intensive care unit: mechanisms and management

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The incidence of multiple antimicrobial resistance of bacteria which cause infections in the intensive care unit is increasing. These include methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, penicillin-resistant Streptococcus pneumoniae and cephalosporin and quinolone resistant coliforms. More recently, pan antibiotic resistant coliforms, including carbapenems, have emerged. The rapidity of emergence of these multiple antibiotic-resistant organisms is not being reflected by the same rate of development of new antimicrobial agents. It is, therefore, conceivable that patients with serious infections will soon no longer be treatable with currently available antimicrobials. Strict management of antibiotic policies and surveillance programmes for multiple resistant organisms, together with infection control procedures, need to be implemented and continuously audited. As intensive care units provide a nidus of infection for other areas within hospitals, this is critically important for prevention of further spread and selection of these resistant bacteria.

Antibiotic resistance was first encountered clinically in the form of penicillin-resistant staphylococci in the early 1940s. Single- and multidrug resistance mediated by plasmids, which could be transferred between organisms in the gastrointestinal tract was subsequently reported in the late 1950s. By the mid-1970s, these resistance genes had become more widespread and included commensal organisms present in the respiratory and genito-urinary tracts of many hospitalised patients. Despite the significant improvements made in the performance of antibiotics and enhanced infection control measures, this spread of antibiotic resistance has continued throughout the 1980s and 1990s.

Two factors control the spread of resistance: the ability of organisms to transfer, acquire and rearrange resistance genes and the selective pressure generated by the use of broad spectrum antibiotics. The interaction of these two components of the 'drug resistance equation'
has resulted in the current position where there are only a limited number of antimicrobials available to treat some infections, with the prospect of untreatable organisms in the future\textsuperscript{1,2}. Indeed, a recent Select Committee of the House of Lords highlighted the potential problems associated with the emergence of antimicrobial resistant microorganisms in many areas of medicine\textsuperscript{3}. This report also outlined the difficulties in the management of patients with infections caused by these micro-organisms and the need to develop strategies for preventing further emergence and spread of multi-resistant strains. This current review summarises the threat of antimicrobial resistant bacteria in intensive care units (ICU), the organisms and mechanisms involved, and approaches which can be employed for prevention.

**Micro-organisms**

**Gram-positive bacteria**

Methicillin-resistant *Staphylococcus aureus* (MRSA)\textsuperscript{4,5} and vancomycin-resistant enterococci (VRE)\textsuperscript{6,7} have emerged as major nosocomial pathogens. Vancomycin is currently the most reliable treatment for infections caused by MRSA. However, the potential transfer of resistance genes from VRE to the MRSA may leave few therapeutic options in the future. Whilst the deliberate transfer of vancomycin resistance proved difficult to achieve in the laboratory, naturally-occurring vancomycin-intermediate *S. aureus* (VISA) have now been reported from a number of centres\textsuperscript{8,9}. VRE, as well as providing a reservoir of vancomycin resistance genes, can also cause infections which are difficult to treat, with some strains showing resistance to all major classes of antibiotic. Other Gram-positive cocci pose a less dramatic but significant threat. Coagulase-negative staphylococci (CNS) are an important cause of infections associated with prosthetic devices and catheters. Although they display lower virulence than *S. aureus*, they have intrinsic low-level resistance to many antibiotics (including β-lactams and glycopeptides). The additional ability of many of these bacteria to produce slime makes treatment of prosthetic associated infections difficult and often requires removal of the infected prosthesis or catheter. *Streptococcus pneumoniae*, regarded as fully sensitive to penicillin for many years, has now acquired the genes for resistance from oral streptococci. The prevalence of these resistant strains is increasing rapidly worldwide. This will limit the therapeutic options in serious pneumococcal infections, including meningitis and pneumonia, particularly when acquisition of resistance to other groups of antibiotics also occurs\textsuperscript{10}. 
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Gram-negative bacteria

Antibiotic resistant aerobic Gram-negative bacilli cause significant numbers of infections in ICU. Of these *Pseudomonas aeruginosa*, and the Enterobacteriaceae, including *Escherichia coli* and *Enterobacter* species, account for the majority of isolates where resistance has emerged. Resistance mechanisms in these organisms are partly intrinsic, with the low permeability of the Gram-negative cell envelope, but more importantly due to the presence of resistance genes. Genes encoding high level resistance to multiple antibiotics can assemble on plasmids which are transmissible between organisms. Smaller genetic elements termed transposons found within plasmids and in chromosomes contain resistance genes which, together with integrase genes, promote their own transfer both between plasmids and from plasmids to chromosomes. Other small mobile genetic elements related to transposons are termed gene cassettes and integrons. These are important determinants of the spread of resistance to β-lactams, aminoglycosides, trimethoprim and chloramphenicol among the Gram-negative aerobic bacilli.

Types of infections in intensive care units

Besides the patient's underlying disease, the main risk factors associated with the development of ICU-acquired infection include increased length of ICU stay, mechanical ventilation, trauma, intravascular and urinary catheterisation, and stress prophylaxis. Most of the infections in patients on an ICU result from the patient’s own endogenous flora. However, cross-infections may occur with outbreaks occasionally being recognised. Micro-organisms which may cause outbreaks include *S. aureus*, *Clostridium difficile*, *Acinetobacter* species and *E. coli*.

Pneumonia, septicemia and postoperative sepsis are the commonest types of infections which result in patients requiring intensive care treatment. In addition, up to 50% of patients being treated in ICU will also acquire nosocomial infection, which are associated with a relatively high degree of morbidity and mortality. Certain pathogens also more commonly cause a high mortality rate. For example, in a review of surgical ICU patients with *Xanthomonas* spp. infections, the associated mortality was significantly higher (P < 0.05) (26.9%) as compared to other patients without sepsis (10.3%). The types of infection in ICU patients were clearly identified in a recent large prevalence survey carried out on 40% of European units. Of all the patients studied, 44.8% were reported to be infected and 20.6% had an ICU-acquired infection. Infection of the lower respiratory tract (65%), urinary tract (18%) and bloodstream (12%) were
the most frequent sites of sepsis. Micro-organisms associated with these infections included Enterobacteriaceae (34%), *S. aureus* (30%), *P. aeruginosa* (29%), CNS (19%) and fungi (17%).

**Antimicrobial resistant organisms in intensive care units**

The identification of antimicrobial resistance patterns of organisms present in ICUs is important to prevent further spread. This type of surveillance will facilitate the choice of appropriate antimicrobial therapy and the implementation of infection control policies which may further restrict the development of resistance. The European Epic Study recorded antimicrobial resistance patterns for *S. aureus*, *P. aeruginosa* and CNS isolated from patients on ICU. Of the *S. aureus* isolated, 60% were methicillin resistant (MRSA). Of the *S. aureus* causing bacteraemias, 72% were MRSA. The resistance patterns of *P. aeruginosa* were multiple and included resistance to gentamicin (46%), imipenem (21%), ceftazidime (27%), ciprofloxacin (26%) and a ureido-penicillin (37%). Many of the CNS were also resistant to a wide range of antimicrobials. Of all the CNS isolated, 73% were resistant to one or more of the following antibiotics; methicillin (70%), cefotaxime (69%), gentamicin (66%), vancomycin (3.5%) and teicoplanin (9.3%).

More recently, multiple antimicrobial resistant organisms including acinetobacters and VRE which may also be resistant to teicoplanin have been reported in ICUs. Although acinetobacters have relatively low pathogenicity, their intrinsic resistance to many widely used antimicrobial agents, their ability to spread easily from patient-to-patient and to survive in the hospital environment have contributed to their increasing clinical importance especially in the ICU. In a recent review of ICUs in the UK, 45 out of 70 units reported the presence of acinetobacters, the majority being sporadic cases. Acinetobacters were most commonly associated with colonisation and infection of the lower respiratory tract.

In a further review of the antimicrobial susceptibility rates amongst aerobic Gram-negative bacilli isolated from patients in ICUs, resistance to third generation cephalosporins was further shown to be an emerging problem, particularly with *Klebsiella pneumoniae* and *Enterobacter* species. These bacteria were frequently also resistant to aminoglycosides and ciprofloxacin. In the US, as in Europe, new approaches for treating patients with serious infections in ICUs are being driven by similar increasing numbers of cephalosporin and other antimicrobial-resistant Gram-negative aerobic bacilli. In a survey of nearly 400 hospital ICUs in North America, resistance rates for *Klebsiella* species and *Enterobacter* species to third generation cephalosporins were shown to have increased during the 1990s, approaching 40% with some strains. The mechanism of resistance...
is related to production of extended spectrum β-lactamases which appears to have arisen through overuse of third generation cephalosporins.

Multi-drug resistant *P. aeruginosa* has also become endemic within some specialised ICUs, particularly those treating burns patients\(^2\). *P. aeruginosa*, which is resistant to antibiotics including piperacillin, ceftazidime, aztreonam, imipenem, ciprofloxacin and aminoglycosides, has been reported on a burns unit. The epidemic strain persisted for several months and resulted in various severe infections.

In a further study on the distribution of resistance patterns and serotypes of *P. aeruginosa*, multiple antibiotic-resistant strains have been shown to be more frequently present in the ICU than other areas within a hospital\(^3\). This reflects the level of antimicrobial selective pressure in the intensive care situation as compared to other clinical areas within the hospital.

The emergence of strains of Gram-negative aerobic bacilli, including acinetobacters, which produce broad spectrum β-lactamases or stable derepressed hyper producers of chromosomal *(ampC)* cephalosporinase are now making the carbapenems in many cases the only effective antibiotic treatment for this type of infection\(^4\). The more recent reports of carbapenem resistance in coliforms is, therefore, a cause for concern.

Besides Gram-negative organisms, multiple antibiotic resistant CNS and MRSA as identified in the Epic Study are commonly isolated from patients in the ICU. More recently, VREs have been isolated from patients in ICUs\(^5\). If the MRSA also becomes resistant to vancomycin, the emergence of a glycopeptide resistant MRSA on ICU will result in major difficulties in managing any associated infections.

### Mechanisms of antimicrobial resistance

**Methicillin-resistant *Staphylococcus aureus***

*S. aureus* illustrates the interaction between the genetic and selective pressure components of the drug resistance equation. Resistance originally arose through selection of strains which destroyed penicillin G by production of a β-lactamase. This enzyme probably originated by mutation of carboxypeptidase genes used in assembly of the vital peptidoglycan component of the organism's cell wall. Development and widespread use of β-lactamase-resistant penicillins, such as methicillin and later the isoxazolyl penicillins (cloxacillin, dicloxacillin and flucloxacillin), encouraged the emergence of MRSA strains\(^4\). These owe their resistance, not to production of β-lactamase, but to expression of an altered penicillin binding protein (PBP) target enzyme involved in cell wall synthesis (the *mecA* transpeptidase). This enzyme exhibits greatly reduced susceptibility towards the penicillins and can replace the function of the susceptible
enzymes. Separate selective pressure through the use of other antibiotics has led to the emergence of strains resistant to other major classes of antibiotics, including the aminoglycosides and tetracyclines, resulting in most MRSA strains being multi-drug-resistant. MRSA strains are not intrinsically more virulent than sensitive strains, most *S. aureus* isolates produce a wide range of virulence factors which are independent of their antibiotic resistance genes. The major threat posed by MRSA strains lies in the dependence for their control upon the glycopeptide antibiotics, vancomycin and teicoplanin. Hence the recent acquisition of vancomycin resistance genes from enterococci is of major significance.

**Vancomycin-resistant enterococci**

The enterococci (*Enterococcus faecalis* and *Enterococcus faecium*) are intrinsically resistant to a wide range of antibiotics, including the aminoglycosides and cephalosporins. Although they are not highly virulent, they have emerged as significant nosocomial pathogens in patients with compromised immunity. Glycopeptides are among the few antibiotics which are effective against the enterococci. They block bacterial cell wall synthesis by binding tightly to the D-alanyl-D-alanine region of the peptidoglycan precursor before it is incorporated into the cell wall. VRE were first reported in 1988 and are now encountered with increasing frequency, particularly in association with multiple antibiotic usage. A number of different resistance phenotypes are recognised: vanA, vanB and vanC. VanA is characterised as an inducible, high level resistance to both vancomycin and teicoplanin. The genes responsible for the vanA phenotype are carried on a transposon, a highly mobile genetic element found on many different plasmids in enterococci and able to transfer rapidly between strains. Of the nine genes carried on the transposon three (vanA, vanH and vanX) are responsible for producing an altered peptidoglycan precursor containing D-alanyl-D-lactate instead of the usual D-alanyl-D-alanine. The modification in the precursor results in much weaker binding and no effective inhibition of cell wall synthesis. The other genes carried by the transposon are involved in the induction of the vanA phenotype by vancomycin and teicoplanin. VanB resistance occurs by a similar overall mechanism involving a separate cluster of genes, resistance is induced by vancomycin but not by teicoplanin. The genes responsible for vanB resistance have been detected on plasmids in clinical isolates which transfer resistance between strains by conjugation.

The emergence and dissemination of glycopeptide resistance genes in enterococci over the last 10 years has resulted in clinical isolates which are resistant to all antibiotics of otherwise proven efficacy. The increasing incidence of VRE strains among clinical isolates of
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enterococci places them as important nosocomial pathogens. Of equal importance is their potential to act as reservoirs of resistance genes for transmission to MRSA.

**Streptococcus pneumoniae**

Until recently the pneumococcus, an encapsulated Gram-positive organism, had been exquisitely sensitive to penicillin G, with minimum inhibitory concentrations in the region of 0.001 µg/ml. Resistance first appeared in the 1960s in Papua New Guinea, Australia and the US. Since then, isolates with MICs between 1 and 16 µg/ml have been widely reported with incidences rising rapidly in some countries. Multi-drug-resistant strains were initially isolated in South Africa in the late 1970s and are now encountered worldwide, for example in Spain and South Africa 18% of penicillin-resistant strains are resistant to two or more classes of antibiotics. The genes for resistance to tetracycline, erythromycin and chloramphenicol appear to have been acquired on conjugative transposons. By contrast, penicillin resistance has resulted from a transformation process in which DNA encoding large regions of the penicillin binding protein targets from other organisms (especially oral streptococci) has been incorporated into the chromosome to form functional, resistant new ‘mosaic’ PBP genes. Unlike methicillin resistance in *S. aureus*, penicillin resistance in pneumococci results from alterations in several different PBPs and the mosaic genes may contain DNA from various donors (including *Streptococcus sanguis* and *Streptococcus oralis*).

**Gram-negative aerobic bacilli**

Resistance in Gram-negative bacteria to β-lactams is caused chiefly by the acquisition of plasmids encoding genes for enzymes which inactivate the antibiotics by hydrolysis. Many different β-lactamases have been identified. The emergence and spread of the plasmids has closely followed the development of the β-lactam antibiotics. Each improvement in β-lactamase stability of penicillins and cephalosporins has been followed within about 5 years by the appearance of strains producing enzymes for their destruction. The TEM-1 enzyme is produced by over 90% of ampicillin-resistant strains of *E. coli*. Plasmids carrying TEM-1 can transfer freely among the Enterobacteriaceae and *P. aeruginosa*. Following the introduction of cephalosporins such as cefuroxime, cefotaxime and ceftazidime, which are resistant to TEM-1, strains producing enzymes capable of their destruction appeared. Examples of these are TEM-12 and TEM-26, in which key amino acid residues in the original TEM enzyme
have been altered by mutation to produce an extended-spectrum of activity. Over 20 different extended spectrum enzymes have been reported and they are particularly prevalent in clinical isolates of *K. pneumoniae*.

Not all β-lactamases responsible for clinical resistance to β-lactams are plasmid-mediated. Many Gram-negative aerobic bacilli contain chromosomal genes for the expression of the *ampC* β-lactamase which is induced by the presence of the β-lactam antibiotics. Mutations in the genes which regulate the expression of *ampC* result in excess amounts of the enzyme to be produced. The enzyme only hydrolyses cephalosporins slowly, but a combination of a high level of expression and binding (trapping) of the antibiotics and the restricted permeability barrier of the outer membrane results in significant resistance. Clinical isolates exhibiting this form of resistance include strains of *Enterobacter cloacae*, *Citrobacter freundii*, *Acinetobacter* species and *P. aeruginosa*.

The introduction of the carbapenems, imipenem and meropenem, has encouraged the emergence of strains which produce carbapenemases. These are β-lactamases with a particular affinity for the carbapenems and have been reported in many isolates of *Bacteroides fragilis*, *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*, *E. cloacae*, *Serratia marcescens*, *Aeromonas* spp. and *P. aeruginosa*. Many of these β-lactams are metallo-enzymes, containing zinc atoms at their active site, but those produced by *S. marcescens* and *E. cloacae* contain a serine residue at this site. Most are chromosomally mediated, their transfer onto plasmids will undoubtedly speed up the spread to other organisms.

The aminoglycosides are another groups of antibiotics which are susceptible to inactivating enzymes. Instead of destroying these antibiotics by hydrolysis, the enzymes catalyse a chemical modification of hydroxyl and amino groups on the aminoglycosides introducing acetyl, phosphoryl and adenyl groups. The genes encoding the resistance are transferable. Resistance is widespread, in particular in the Enterobacteriaceae and *P. aeruginosa*. Individual strains can produce more than one modifying enzyme and the overall resistance phenotype can be enhanced by a reduced permeability to the aminoglycoside.

Another mechanism of resistance to antibiotics involves the removal (extrusion or efflux) of the drugs from organisms before inhibition of the targets can take place. It involves the function of a cytoplasmic membrane transport system that actively removes the drugs from the cells. This mechanism is currently most commonly encountered against the tetracyclines in clinical isolates of streptococci and staphylococci. Of increasing concern is the susceptibility of other groups of antimicrobial agents, including the macrolides and quinolones, to efflux mechanisms in Gram-positive and Gram-negative bacteria. Efflux may even occur across the outer membrane of Gram-negative bacteria and influence the susceptibility towards β-lactams, which do not cross the cytoplasmic membrane.
Prevention of infections associated with multiple antimicrobial resistant bacteria

Screening

Identification of the causative organism before therapy is commenced permits selection of specifically targeted antibiotics. It is also important that ICUs should have a surveillance programme for antibiotic resistant organisms so that empiric treatment can be selected based on known sensitivity patterns and can be altered immediately following the identification of a new resistance pattern of any organisms on a unit. Care must be taken in the use of appropriate sensitivity tests for detection of resistance. Although culture methods are widely used, new molecular techniques offer the prospect of rapid and sensitive detection of the presence of resistance genes\textsuperscript{30,31}.

Infection control in intensive care units

Microbial colonisation of critically ill patients is a prerequisite in many conditions for the development of subsequent sepsis. This process is facilitated by the use of invasive techniques including urinary and intravascular catheters, and ventilation equipment. The oropharynx and gastrointestinal tract are important sources of aerobic Gram-negative bacilli which may cause various infections including ventilatory associated pneumonia\textsuperscript{32}. The skin in comparison is a primary source of organisms, including the CNS, which are the main cause of intravascular catheter related infections\textsuperscript{33,34}, bacteraemia and septicaemia\textsuperscript{35}. Prevention strategies for catheter-related sepsis have been produced\textsuperscript{34} and include the use of catheters impregnated with antimicrobial agents.

Nosocomial outbreaks of multiple antibiotic resistant bacteria have been associated with failures in infection control. For example, contamination of ventilation equipment was shown to be related to an outbreak of acinetobacter\textsuperscript{36}. Following surveillance, the organism was detected in output ducts of a ventilator machine despite the use of bacterial filters. To overcome this particular outbreak ventilator equipment had to be sterilised internally.

The widespread use of antibiotics also selects out antibiotic resistant organisms which can become endemic within units. This is seen not only with the Gram-negative aerobic bacilli but also with MRSA and VRE. Outbreaks of these organisms can occur with spread being primarily from patient-to-patient via the hands of medical personnel. Fomites, including equipment and faulty air handling systems, can also enable organisms to spread around units\textsuperscript{37}. It is vitally important that appropriate and timely
cleaning schedules, including curtain changes and air handling plants as well as equipment, are in place. The development of alternatives to curtains, including cleanable glass panels which can be changed from opaque to transparent on demand, should be encouraged further.

Simple approaches for the prevention of spread of infection on the ICU have included attention to correct and timely handwashing. The appropriate use of antiseptic handwash preparations is also important. For example, the use of a triclosan handwash has been shown to eliminate MRSA from a neonatal ICU\(^38\). Similarly screening patients prior to admission to ICUs for carriage of specific resistant organisms can assist in control. The carriage of MRSA, for example, has been shown to identify those patients at increased risk of subsequent postoperative MRSA infection\(^39\). Eradication schedules and other infection control measures, including barrier nursing, can then be commenced earlier. Ideally, patients with multiple antibiotic resistant organisms in an ICU should be strictly isolated and cohort nursed. However, this is not commonly practised due to limitations of suitable facilities and financial support. Handwashing between patient contacts should, however, be mandatory to prevent transmission even when no multiple antibiotic resistant organisms are present on a unit. Staff health also needs to be considered. For example, the use of effective topical agents such as mupirocin and chlorhexidine for MRSA staff carriers can reduce the likelihood of spread\(^40\).

The highest percentage of micro-organisms which are resistant to antimicrobial agents in hospitals has been shown to be predominantly located in patients in the ICU. Indeed a significant sequential decrease in the percentage of resistant organisms has been shown in studies on patients located in ICUs, non-ICU patients and outpatients\(^41\). It is, therefore, evident that resources allocated to control antimicrobial resistance should continue to be focused in the hospital, particularly in the ICU situation. Indeed the emergence of antibiotic resistant pathogens suggests that to contain the problem of infections associated with these organisms, measures must primarily be focused towards careful surveillance of resistance, optimising antibiotic use and the prevention of transmission through effective infection control practices\(^42\).

**Selective decontamination of the digestive tract with non-absorbent antibiotics**

Many nosocomial infections in ICU are associated with carriage of Gram-negative aerobic bacilli in the gastrointestinal tract which may result in endogenous infections as described above. Selective decontamination of the digestive tract (SDD) is a method used for the prevention or eradication of carriage of these organisms in the gastrointestinal tract. Many trials of SDD have been published and several have shown a significant reduction
Antibacterial resistance in the incidence of nosocomial Gram-negative infections\textsuperscript{43}. The impact of SDD on morbidity and mortality however is less clear. Gastinne demonstrated in a randomised, double-blind, multi-centre study of patients receiving mechanical ventilation that SDD did not improve survival in these patient groups\textsuperscript{44}.

Where studies have tested the efficacy of SDD in ICU patients with morbidity related infection as a main end point, many of the results have demonstrated a reduction in infection rates but it is still unclear whether there is a decrease in mortality\textsuperscript{45}. In a recent meta-analysis of trials of SDD a reduction in respiratory tract infections and overall mortality in severely ill patients was demonstrated. However, concern with the emergence of antimicrobial resistance with the use of selective decontamination has been raised\textsuperscript{46}. Indeed, Lingnau demonstrated that bacterial resistance increased with the use of selective decontamination. It would, therefore, seem logical that the widespread use of SDD as a prophylactic approach for the prevention of Gram-negative aerobic bacilli infections should be limited to specific high risk patients and not used widely.

\textit{Antibiotic policies}

Antibiotic usage in ICU is relatively high due to the types of infections which patients have and also the predominant organisms found in such situations. The use of antibiotics, particularly broad spectrum agents, selects out multiple antibiotic resistant micro-organisms, ranging from \textit{Pseudomonas} species, \textit{Acinetobacter} species, \textit{Klebsiella} species and other Gram-negative aerobic bacilli to VRE and MRSA. Bacterial resistance to a number of antibiotics may develop in a unit and these may colonise or infect patients. It is, therefore, important to restrict the use of antibiotics and to be selective in the types of treatment schedules used. Before selecting an antibiotic, several factors need to be considered. Firstly, appropriate microbiological investigations must be carried out before the commencement of antimicrobial agents. This will enable directed antimicrobial agents to be given when the results of microbiology tests are available. The importance of obtaining cultures for microbiological investigation has been clearly demonstrated in the recent report\textsuperscript{47} in which the influence of repeated bronchiolar lavage cultures on patients with ventilator associated pneumonia was studied. Among 60 patients studied with microbiologically positive cultures, 44 were receiving inadequate antibiotic therapy with the causative micro-organism being resistant to the prescribed current treatment. Mortality rates of patients who required changes to their antimicrobial regimens was significantly higher as compared to those on appropriate treatment.

For the empiric use of antibiotics, factors such as the site of infection, the types of organisms prevalent in a particular unit and the patient's
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underlying disease, immune competence, liver and renal function also need to be taken into account. If, for example, a central venous catheter associated infection is thought to be the most likely source of sepsis then antimicrobial agents directed against CNS and \textit{S. aureus} need to be selected. Similarly, if a patient becomes septic following urinary catheterisation, this is likely to be associated with a coliform and cover for these should, therefore, be selected. If a patient has a respiratory tract infection which is community acquired the causative organisms are likely to include \textit{S. pneumoniae}, \textit{Mycoplasma pneumoniae}, \textit{Haemophilus influenzae} and, occasionally, \textit{Legionella pneumophila}. Antimicrobial agents to provide appropriate cover for this type of infection may include the use of cefotaxime and a macrolide. If, however, a patient has developed a hospital acquired pneumonia then coliforms are more likely to be the causative organisms and the antimicrobials need to be directed towards those which are prevalent in the ICU. If a patient has aspirated and subsequently developed pneumonia, metronidazole should be included in the treatment regimens as anaerobes may be associated with the infection.

The effects of restricting selected antimicrobials with appropriately controlled antimicrobial programmes have been studied\textsuperscript{48}. Not only was the total use of parenteral antimicrobials decreased by nearly one-third but susceptibility to all β-lactams and quinolone antibiotics subsequently increased in isolates recovered from patients on the ICU. This is obviously an important strategy for the prevention of development of antimicrobial resistance.

**New antimicrobials**

*Protection of existing agents against resistance mechanisms*

A notable success in combating resistance to β-lactam antibiotics through expression of β-lactamases has been the deployment of specific inhibitors to protect the vulnerable drugs\textsuperscript{49}. Clavulanic acid has been the most successful in this respect, used in combination with amoxyillin and ticarcillin. Sulbactam has also been used in combination with ampicillin and tazobactam with piperacillin. Unfortunately not all β-lactamases are susceptible to these inhibitors, for example the chromosomal \textit{ampC} enzyme is not inhibited by clavulanic acid and the metalloenzymes which destroy carbapenems are not sensitive to any available inhibitors. Inevitably, following prolonged used of clavulanic acid, resistant forms of enzymes previously sensitive have now emerged.

Some success in protecting aminoglycosides from inactivation by modifying enzymes has been achieved. The aminoglycoside amikacin is a modified form of kanamycin which contains a protective substituent at the
position most frequently vulnerable to attack. This deliberately introduced modification does not compromise the antimicrobial activity. Similar protection of chloramphenicol against acetylation has been investigated by the introduction of fluoro substituents but these chloramphenicol derivatives have not been developed further because of potential toxicity and poor pharmacokinetic properties.

With the recognition of efflux mechanisms of resistance, attention has been directed towards the design of agents which are not transported by the extrusion pumps

The glycylcyclines are modified tetracyclines which are not susceptible to efflux mechanisms. Another approach is to find compounds which inhibit the efflux pumps, thereby protecting susceptible agents from extrusion.

**Modification of existing compounds and the search for agents with novel mechanisms of action**

A number of cephalosporins and carbapenems have been reported to be active against MRSA, these compounds retain activity towards the mecA PBP. Similarly, some modified glycopeptides retain activity against vanA and vanB resistant enterococci

Derivatives of vancomycin are also being investigated for enhanced activity against the VRE

Compounds with mechanisms of action that are distinct from those of the β-lactams or glycopeptides have also been developed. The synergistic streptogramin combination of quinupristin and dalfopristin and the novel oxazolidinones are the most promising examples

These agents inhibit protein synthesis at sites which are separate from existing inhibitors. However, the potential for resistance development to these agents exists and has already been encountered. Other promising groups of antibiotics include the everninomycins and ketolides

Newer quinolones with activity against MRSA and VRE are also being developed

**Summary**

Antimicrobial resistance is increasing in many microbial pathogens, reflecting de novo selection due to antibiotic usage and pressure as well as the spread of resistant organisms both in the community and in hospitals. This situation is occurring worldwide and has been reflected by the emergence of both Gram-positive and Gram-negative bacteria with the ability to resist the action of many antimicrobial classes. The important organisms which are currently emerging include MRSA and VRE. The possibility of the emergence of pan-resistance in the MRSA, including vancomycin, is of major concern particularly as VISA have already been
reported in Japan, the US and France. Pan-resistance is more frequently seen in enterococci and some isolates of *E. faecium* are resistant to all β-lactams, aminoglycosides and glycopeptides, leaving only antimicrobial agents still in development to use. These include the streptogramins, quinupristin and dalfopristin (Synercid®), and the oxazolidonones, for example Linazolid®, as possible drugs of choice. Gene exchange can occur between enterococci and staphylococci and it is likely that high level glycopeptide resistance will spread to MRSA and possibly *S. pneumoniae*. Multiple antibiotic resistance is also increasing in Gram-negative aerobic bacilli including Enterobacteriaceae which are becoming resistant to all groups of antimicrobials. Even carbapenem resistance is being increasingly reported in *Acinetobacter* species worldwide. *P. aeruginosa* resistant to β-lactams, aminoglycosides and quinolones have evolved and some strains are now pan-resistant. Indeed plasmid-mediated carbapenems (carbapenem-destroying enzymes) have emerged in enterobacteria and *Pseudomonas* species in Japan which have resulted in resistance to all anti-pseudomonal β-lactams. Other organisms including *S. maltophilia* and *Burkholderia cepacia* also have inherent ability for broad spectrum resistance. The activity of the quinolones is also being challenged with many Gram-negative aerobic bacilli developing resistance by mutation of the gyrA subunit of the DNA gyrase target. More recently, an *E. coli* isolated with transferable quinolone resistance has been reported in Spain. This has important implications for further spread of resistance.

With the emergence of many antimicrobial resistant bacteria, particularly in ICUs, it is important that specific antimicrobial policies with strict infection control measures are implemented and units are continuously monitored for the emergence of antimicrobial resistance. If this action is not taken many patients will develop untreatable bacterial infections.

**Key points for clinical practice – antimicrobial resistance**

- Antimicrobial resistance is becoming a widespread major problem in the intensive care unit.
- Awareness needs to be improved.
- Strategies for prevention need to be developed.
- Multiple antimicrobial-resistant organisms include:
  - *Acinetobacter* species
  - Coagulase-negative staphylococci
  - *Enterobacter* species
  - *Escherichia coli*
Antibacterial resistance

*Pseudomonas aeruginosa*
*Stenotrophomonas maltophilia*
*Streptococcus pneumoniae*
Methicillin-resistant *Staphylococcus aureus*
Vancomycin-resistant enterococci

- Further antimicrobial-resistant organisms may develop and become widespread including:
  - Vancomycin-resistant *Staphylococcus aureus*
  - Pan-antibiotic resistant coliforms
- Development of new antimicrobials is not keeping pace with the rate of emergence of resistant organisms.
- Patients with untreatable infections are a clinical possibility.

**Key points for clinical practice – prevention of the emergence of antimicrobial resistant organisms**

- Develop care plans for treatment of infections including selection of empirical antimicrobials based on surveillance cultures and alter according to subsequent microbiology results.
- Monitor for endemic organisms within units including fomites and equipment.
- Restrict use of broad spectrum antibiotics and keep length of treatment to minimum.
- Consider antimicrobial rotation.
- Design and implement strict infection control procedures including handwashing, cohort nursing and cleaning schedules.
- Regularly review all procedures for possible transmission of infection.
- Consider infection control with any new procedures including equipment.

**Acknowledgements**

We wish to thank Mary McDermott for expert secretarial support, Carol House for carrying out the literature searches, and Derek Healing for useful comments.
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