Antibiotic resistance mechanisms in the intensive care unit 1A02 2C03 3A13

JC Hatcher, R Dhillon, B Azadian

Antibiotic resistance is increasingly recognised as a major threat to global health, with few new antimicrobial agents in development. The intensive care unit provides a unique environment for the growth and spread of drug-resistant organisms. Knowledge of the pathogenesis and mechanisms of resistance of drug-resistant organisms provides a conceptual framework which underpins the clinical manifestation of infections caused by these organisms, and is crucial for the intensivist to understand. Particular importance lies in the prevention of infection and the control of drug-resistant pathogens. The major resistance mechanisms of these organisms will be highlighted, focusing on specific gram-positive (meticillin-resistant *Staphylococcus aureus* and glycopeptide-resistant *Enterococci*), gram-negative (*Pseudomonas aeruginosa, Acinetobacter baumannii* and multi-drug resistant *Enterobacteriaceae*) organisms, and then placed in historical and clinical context.

Keywords: *antibiotic resistance; intensive care*

Introduction

Antibiotic resistance has been recognised ever since antibiotics were first discovered. Penicillin was first used to treat a patient in 1941 and in the following year, strains of *Staphylococcus aureus* were shown to be resistant to penicillin.[1] Although perceived as a modern phenomenon caused by overuse of antibiotics, resistance is likely to be ancient and natural. Meta-genomic analysis of 30,000-year-old permafrost samples, using rigorously authenticated ancient DNA from radiocarbon-dated tephra (permafrost) samples identified genes encoding resistance to beta-lactam, tetracycline and glycopeptide antibiotics.[2] This natural resistance influences the efficacy of all antimicrobial products made from natural substances.

Antibiotic resistance has long been known within the medical profession; however there has been a recent push to increase awareness in the wider community to highlight this major threat to global health. World Health Day 2011 had the theme 'antimicrobial resistance: no action today and no cure tomorrow.' The Infectious Diseases Society of America announced their initiative 'Bad Bugs, No Drugs – 10 by 20' in 2009, supporting development of 10 new antibiotics by 2020.[3] Antibiotic development has decreased in the past few decades. This is primarily because of lack of pharmaceutical company research, with high costs of production of new antibiotics and relatively low profits. Increasing resistance to our most potent antimicrobials and a lack of new therapeutic options is of serious concern.

Generation of antibiotic resistance and subsequent nosocomial transmission make intensive care units (ICUs) uniquely placed in the hospital setting to target intervention strategies. Factors promoting antibiotic resistance in ICU include the use of broad-spectrum antimicrobial agents, ease of cross-transmission and impairment of host defences.[4] The aim of this review is to highlight important mechanisms of bacterial resistance, focusing on pathogens commonly encountered in ICU, and to introduce strategies to reduce the burden caused by such infections.

Principles of resistance and mechanisms

Antibiotic resistance is a concept that many clinicians take as an absolute phenomenon; pathogens are either 'resistant' or 'susceptible,' but the reality is quite different. Laboratory resistance is significantly different to clinical resistance. Often pathogens termed 'resistant' can be killed or inhibited by sufficient concentrations of antibiotics, which would not be tolerated by the patient. Laboratory testing has to take into account clinically tolerated doses of antibiotics. The method of determining *in vitro* resistance is beyond the scope of this review. Clinical resistance is complex, taking into account pharmacodynamic and pharmacokinetic properties of the antibiotic, the infecting bacterium, the immune status of the patient and the location in the body of the infection.[5]

Regardless of the complexity of these issues, there are basic biological mechanisms employed by bacteria to confer phenotypic resistance to antibiotics. Many resistant strains of bacteria have more than one mechanism of resistance. These are shown in **Figure 1**.

Altered target site

An antibiotic may be able to enter the bacterial cell, but by changing its target site, the bacteria are able to render the antibiotic inactive. This can occur to a wide variety of antibiotics and may only require a single mutational event. Rifampicin is a classic example, with rifampicin-resistant Staphylococci easily produced by antibiotic pressure; thus,

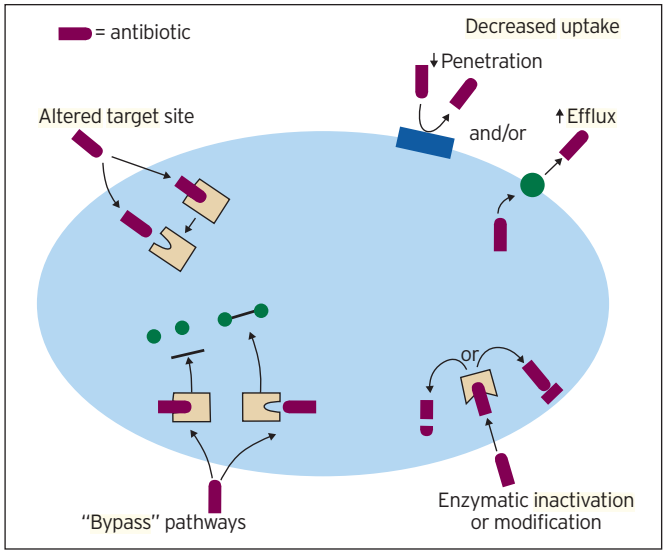

Figure 1 Four main biochemical mechanisms of antibiotic resistance. Hawkey P. *BMJ* 1998 (with permission).

clinicians use rifampicin usually in combination with another antibiotic for treatment of deep-seated bone and joint infections or *Mycobacterium tuberculosis*. Modification of penicillin-binding proteins is the primary cause of penicillin resistance in *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Enterococcus faecium*.[6]

Fluoroquinolone (ciprofloxacin) resistance is caused by amino acid substitution in a region of the subunit termed the 'quinolone-resistance-determining region' located on the DNA-binding surface of the enzyme topoisomerase IV.[7] Multiple genes are involved in encoding this region and therefore phenotypic resistance occurs in a stepwise process as a result of accumulation of mutations, for example, single step parC mutation in *Staphylococcus aureus* is associated with low-level resistance, with highly resistant isolates possessing several mutations.[8]

Decreased antimicrobial uptake

Decreased intracellular concentrations of antimicrobial drugs can result from decreased permeability, preventing drugs entering the cell, or active efflux pumps removing the drug faster than it enters the cell. Porins are proteins forming small holes within the cellular membrane that allow entry of substances including antibiotics into the intracellular space. Reduction in the amount of membrane-bound porins reduces the amount of antibiotic within the cell; for example, lack of the D2 porin confers resistance to imipenem by *Pseudomonas aeruginosa*.[5]

Efflux mechanisms can be drug-specific or can act on multiple drug combinations. Multi-drug mechanisms are almost invariably chromosome-encoded intrinsic mutations in regulatory genes, whereas single drug efflux pumps are often encoded on mobile genetic elements. These can be passed to other bacteria.[9]

'Bypass' pathways

Bacteria can produce alternative target sites to resist inhibition by the antibiotic, usually by an enzyme. The bacteria can selectively survive by bypassing the effect of the antibiotic.[5] This mechanism is exploited by gram-positive bacteria leading to meticillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococci.

Enzymatic inactivation or modification

Bacteria can produce enzymes that modify or render an antibiotic inactive. Penicillin's structure has a β-lactam ring, which can be changed to produce penicillin derivatives such as amoxicillin, but also cephalosporins (eg cefotaxime, ceftriaxone) and carbapenems (eg meropenem, imipenem). Bacteria have developed enzymes known as β-lactamases that inactivate these antibiotics, thus stopping them reaching their target site. Over 200 types of β-lactamases have been described.[5] Genetic material encoding these enzymes may be mediated chromosomally or via plasmids, the latter having important infection control implications. Other important examples include aminoglycoside-modifying enzymes (resistance to gentamicin and amikacin) and chloramphenicol acetyltransferase.[10]

Why are ICUs vulnerable?

Intensive care units provide an ideal environment for the generation of multi-drug-resistant organisms. Multiple risk factors associated with both the patient and with the environment allow the development and spread of such pathogens. This enables close monitoring of interventional strategies and new therapies to broaden our knowledge of pathogenesis and treatment of such infections.

Critically ill patients are increasingly vulnerable to nosocomial infections, not just because of their impaired immune responses but also from the use of invasive medical devices which provide conduits for infection. ICU patients often have significant underlying medical conditions, are malnourished and have frequent hospital admissions, increasing the risk of colonisation by multi-drug-resistant pathogens.[4] An international study of the prevalence and outcomes of infection in ICUs concluded that the acquisition of nosocomial infections significantly increased with the duration of ICU stay.[11] Pneumonia, urinary tract infections and bacteraemia account for 60% of nosocomial infections, all of which are associated with medical devices such as intra-vascular devices, urinary catheters and endotracheal intubation.[12]

The intensive care environment provides a haven for resistant bacteria to flourish and facilitates their cross-transmission. Immediate life-threatening circumstances needing urgent medical intervention often do not allow for aseptic technique or adequate infection control measures. Overcrowding, understaffing and transfer of patients between ICU facilities have all been shown to increase hospital-associated infection rates.[13-15] Certain pathogens, such as *Acinetobacter sp*, are particularly hardy once introduced into the environment, increasing the risk of transmission and complicating the process of decontamination.[16] *Enterococcus faecium* are becoming increasingly prevalent. They are often glycopeptide-resistant and show enhanced capacity to disseminate in the nosocomial setting.[17]

It is clear that antimicrobial use is linked to antimicrobial resistance.[18,19] Due to the complexity and severity of their

illnesses, patients often receive multiple courses of broad-spectrum antibiotics. Empirical broad-spectrum antibiotic therapy is recommended commonly in severe sepsis, as the focus of infection is often not immediately identifiable. Introduction of antimicrobial stewardship has been shown to decrease the number of antibiotic prescriptions and antimicrobial resistance without adversely affecting outcomes.[20]

Specific pathogens relevant to ICU

Pathogenic organisms can be thought of in two broad categories – those that cause primary disease resulting in admission to ICU and those acquired during admission. Community-acquired highly virulent organisms that often result in severe sepsis include *Streptococcus pneumoniae*, β-haemolytic Group A *Streptococcus* and *Neisseria meningitidis*. These organisms are rarely acquired nosocomially, remain largely sensitive to multiple antibiotics and rarely recur. Organisms that are becoming increasingly problematic in ICU are discussed below; these are less common in the community, spread within hospitals and, by their nature, are multidrug resistant.

Gram-positive bacteria

Meticillin-resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus is an aerobic gram-positive coccus that colonises the skin and nasal passages. Approximately 20% of normal healthy adults persistently carry *S.aureus* within the nasal passages and up to 60% harbour *S.aureus* intermittently.[21] Carriage on human skin allows contamination of the surrounding environment and transmission by direct or indirect contact, resulting in cross contamination. Infections caused by *S.aureus* range from minor skin and soft tissue infections to life-threatening septicaemia and endocarditis. Infections associated with invasive intravascular devices are of particular importance in ICU.

Meticillin, introduced in 1960, is a semi-synthetic penicillin not hydrolysed by Staphylococcal β-lactamase. In 1961 the first strains of meticillin-resistant staphylococci were identified.[22] Meticillin is no longer in clinical use and has been superseded by flucloxacillin. Mechanism of resistance involves a 'bypass' pathway via expression of a novel protein (PBP2a). Penicillin-binding proteins (PBPs) are enzymes involved in cell wall synthesis; these are inhibited by penicillin, causing cell death. *S.aureus* has four PBPs, but when it produces a novel protein called PBP2a, it is able to perform the same function as the other enzymes and therefore meticillin does not need to be degraded, bypassing the antibiotic. PBP2a is encoded by the mecA gene that is not found in meticillin-susceptible *S.aureus* (MSSA), suggesting this 'foreign' DNA was transferred by mobile genetic elements. This leads to resistance to all β-lactam antibiotics, making cephalosporins and carbapenems ineffective as well.

The ease of resistant gene transfer and bacterial selection pressure by antibiotic use, combined with an increase in community-acquired MRSA, has increased the prevalence of MRSA in ICUs dramatically.[23] The National Nosocomial Infections Surveillance (NNIS) in the United States reported an increase in MRSA from 3% in the 1980's to 53% at the beginning of the 21st century.[24] Point prevalence data from the EPIC II study showed 50% of *S.aureus* isolates were meticillin-resistant in ICUs across Europe.[11]

Glycopeptides, particularly vancomycin, have been the mainstay of treatment for serious infections caused by MRSA. Glycopeptide intermediate-susceptible *S.aureus* (GISA) has been reported worldwide, including MRSA isolates.[25] Glycopeptides inhibit cell wall synthesis. *S.aureus* exposed to glycopeptides can produce increased extracellular material associated with the cell wall effectively 'soaking up' glycopeptides, leading to reduced susceptibility.[26]

Staphylococcal resistance to glycopeptides was first described in 2002 from a clinical isolate from the United States,[27] although this had been demonstrated *in vitro* 10 years previously.[28] It appears that the resistance gene has been transferred from enterococcal spp. Eleven cases have been reported to date (all in the United States) with prior MRSA and enterococcal colonisation, underlying medical co-morbidities and vancomycin exposure demonstrated in these patients.[29]

Glycopeptides remain the 'workhorse' of anti-MRSA treatment in hospitals but linezolid, quinupristin/dalfopristin, tigecycline and daptomycin are widely marketed and new agents telavancin and ceftaroline are in advanced development.[36]

Glycopeptide-resistant enterococci (GRE)

Enterococci are aerobic gram-positive cocci that are common commensals of the human gastro-intestinal tract. Enterococci were historically part of the Streptococci genus, however in 1984, via DNA hybridisation and 16sRNA analysis, a new genus was designated: Enterococci. Although there are 28 species of Enterococci, *E.faecalis* and *E.faecium* are most relevant to human disease.[30] Although low-level pathogens, due to intrinsic and acquired resistance to multiple antibiotics and the ability to survive in the environment, *Enterococci* have become important nosocomial pathogens.[31]

Enterococci are intrinsically resistant to cephalosporins, clindamycin and low-level gentamicin. Cephalosporin resistance is due to poor affinity for enterococcal PBPs, and gentamicin at low levels is unable to penetrate the cell wall.[10] Penicillin resistance is rare in *E.faecalis*, but *E.faecium* is characteristically resistant which is chromosomally mediated.[32]

Glycopeptides work by binding to a crucial component of the cell wall, preventing cell wall extension and crosslinking, causing eventual lysis. Glycopeptides are large molecules that are unable to cross the outer membrane of gram-negative bacteria, therefore only exhibiting gram-positive activity. Vancomycin was introduced in 1956 and for 30 years no resistance was recognised, with many scientists feeling resistance would not occur due to the critical component glycopeptides target. In 1988 the first reports of vancomycin-resistant enterococci (VRE) appeared.[33] Enterococci have acquired a complex gene cluster that encodes for an alternative cell wall component that does not allow glycopeptides to bind, thus altering the target site. These genes can be acquired via mobile genetic elements allowing clonal spread, but also between species as shown with Staphylococci.[5]

Surveillance data from the UK between 2001-2006 has shown an increase in prevalence of VRE among enterococcal

bacteraemia.[34] Vancomycin-resistant *Enterococcus faecalis* would remain susceptible to β-lactam antibiotics, however *E.faecium* constitute the majority of VRE infections limiting antibiotic choice. Linezolid, daptomycin and quinuprostin-dalfopristin (Synercid) are therapeutic options, but are not without significant toxic side effects.

Gram-negative bacteria

The public press has demonised meticillin-resistant *Staphylococcus aureus* as the quintessential 'superbug.' Although a significant healthcare burden and problem in ICU, development of numerous anti-gram positive agents has given the clinician more treatment options.[35] Many in the microbiology community fear multidrug resistant gram-negative organisms to a greater degree.[36]

Pseudomonas aeruginosa

The Pseudomonad family contains over 100 species of bacteria, of which *Pseudomonas aeruginosa* is one. It is a gram-negative aerobe that is highly motile and able to produce diffusible fluorescent pigments. The Pseudomonads (and *Acinetobacter baumannii* – see later) are often referred to as non-fermenting organisms, due to their incapacity to utilise carbohydrate as a source of energy. This helps distinguish these organisms from the *Enterobacteriaceae* and other lactose-fermenting coliforms.

Pseudomonas aeruginosa is a ubiquitous environmental organism that adapts and survives highly efficiently in damp, moist environments. In the hospital setting, this has been shown to be a distinct problem in sinks and taps, as well as medical devices including ventilators. This has clear implications for infection control. It is primarily an opportunistic pathogen, causing infection in the susceptible host. In the critical care setting, it is the commonest cause of ventilator-associated pneumonia (VAP), but it may also cause other infections such as bacteraemias, osteomyeltis, endocarditis, urosepsis, meningitis, and skin and soft tissue infections.

Pseudomonas aeruginosa is armed with a plethora of defences contributing to its pathogenicity and its ability to survive. These include a variety of virulence factors such as capsule formation, toxin production, the ability to form biofilms and an innate resistance to antibiotics.

The intrinsic resistance to antimicrobials is mediated mainly via the low permeability of its outer membrane, expression of several efflux pumps and the production of antibiotic-inactivating enzymes, such as cephalosporinases.[37] It also has the capacity to acquire new resistance mechanisms, such as acquiring resistance genes (including expression of beta-lactamases) and target modification particularly in response to fluroquinolone pressure. This is thought to be due, in the main, to its large genome and its persistence in aquatic environments, where it acts as a reservoir for other resistant organisms.[38]

The emergence of such resistance organisms is of grave concern, as they are associated with a three-fold higher rate of mortality, doubling in length of stay and significant increase in hospital costs.[39] As with all infections, source control is of primary importance and, due to its innate resistance mechanisms, antimicrobial options are limited.

Effective agents include:

- Anti-pseudomonal beta-lactams – tazobactam-piperacillin, ceftazidime
- Aminoglycosides – gentamicin, amikacin, tobramycin
- Fluoroquinolones – ciprofloxacin
- Carbapenems – meropenem, imipenem, doripenem
- Polymyxins – colistin

Antibiotic treatment of these infections remains challenging, especially regarding optimal length of treatment and whether or not to use combination therapy. Meta-analytical investigations have failed to demonstrate a benefit in using dual agents in treating non-resistant isolates, either for ventilator-associated pneumonia or sepsis.[40,41]

Duration of treatment is controversial but recent trends are for shorter courses. A seven-day course to treat a sensitive isolate causing VAP reduces adverse effects, saves cost and has no discernible adverse effect on clinical outcome.[42] Sadly, there is a lack of new anti-pseudomonal agents, with the recent focus on targeting gram-positive organisms. Doripenem has been mooted as an addition but a lack of clinical data to show superiority over meropenem and its cost inhibits its use, certainly in the UK. The development of CXA-101 (an anti-pseudomonal cephalosporin) is promising but clinical data is lacking.[43]

Acinetobacter baumannii

A. baumannii is a gram-negative, non-fermenting, aerobic organism with an ability to survive for days on dry surfaces. It is a ubiquitous organism and can be found on animate and inanimate objects. It is a major nosocomial pathogen, usually causing serious infection in immunocompromised patients, particularly the critically ill.[44]

During the recent times of conflict in the Middle East, *A. baumanii*, especially multidrug resistant (MDR) strains, has been isolated in servicemen and women returning from overseas.[45] There is a worldwide surge in the number of infections caused by MDR (ie resistant to three or more classes of antibiotics) strains of *A.baumannii*, and such infections are associated with a significantly increased morbidity and mortality.[46-48] Such strains have the capacity to cause outbreaks of infection that are not just confined to one ICU, but can spread throughout hospitals, cross cities, countries and even continents.[49]

A.baumannii demonstrates a broad spectrum of resistance to antimicrobial agents. It has a powerful intrinsic resistance, mediated mainly by a low membrane permeability, basal expression of efflux pumps and chromosomally-encoded cephalosporinase.[50] This species is also easily able to acquire genetic elements that encode for additional resistance mechanisms, for example, beta-lactamases (including the Oxa-23 strain, a major enzyme responsible for carbapenem resistance), and aminoglycoside-modifying enzymes. The ability to become resistant to so many antibiotics twinned with the capacity to persist in the hospital environment is thought to be the main driver behind the epidemics of *A.baumannii*.[51]

Although *A.baumannii* is primarily an opportunistic pathogen infecting susceptible patients in the hospital setting, case reports of serious community infections have been described.[52] In the ICU setting, it is most frequently implicated

in ventilator-associated pneumonia, bacteraemia and urinary tract infections. It may also cause skin and soft tissue, gastrointestinal and central nervous system infections.[53]

Risk factors for acquiring these strains include exposure to a high incidence area, previous antibiotic usage, prolonged hospitalisation, intubation, aspiration and neurosurgery.[54] Antibiotic treatment should be tailored to the sensitivity of the organism, but penicillins and macrolides are usually ineffective.

As with resistant pseudomonas, there is a dearth of effective antimicrobials in targeting MDR strains of *A.baumannii*. Carbapenems are increasingly ineffective and no longer represent salvage therapy. Current options for severe infection include:

- Fully sensitive isolate: aminoglycosides, third generation cephalosporins, combination beta-lactam and beta-lactamase inhibitors (piperacillin-tazobactam)
- More resistant: carbapenems, amikacin, colistin
- Multidrug-resistant: colistin, tigecycline

The most widely used agent for MDR *A.baumannii* is colistin, which has been shown to be effective in the treatment of VAP.[55] Colistin represents our best current option and can be used as monotherapy. Combination of colistin with other agents, particularly rifampicin and meropenem, has demonstrated clinical benefit.[56] The main concern with colistin has been the perceived nephrotoxic effect of the agent by IV administration, based on studies conducted in the 1960s and early 1970s.[57,58] Recent evidence suggests that this agent is not as toxic as once thought and it is generally well tolerated in critically ill patients. The renal damage is believed to be due to total cumulative dose, so careful monitoring is required with prolonged therapy.

Other potential antibiotic agents against MDR *A.baumannii* include tigecycline (but note lack of anti-pseudomonal activity and recent cautions regarding safety profile), rifampicin (never use alone, as high rates of resistance occur) and older agents such as minocycline and fosfomycin. However, in the ICU setting these latter agents are of limited value due to oral only preparations. Newer therapeutic modalities, such as cationic peptides are being evolved, but clinical applications are a long way off.

Source control and stringent infection control procedures are of paramount importance in limiting the spread of such organisms. An outbreak of MDR *A.baumannii* is a hugely worrying problem and even with intense safeguards (focussing on environmental decontamination, medical devices and healthcare worker hygiene practices), ward closure and even structural change may be required.[59]

Extended spectrum beta-lactamases (ESBL)

Beta-lactamase enzymes are one of the most important weapons in the armamentarium of gram-negative organisms. They are predominantly produced by members of the *Enterobacteriaceae* family (especially *Escherichia* and *Klebsiella spp*), but also non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

These enzymes are able to hydrolyse the beta-lactam ring of one or more of penicillins, cephalosporins, monobactams and carbapenems, rendering these agents ineffective.[60] There are

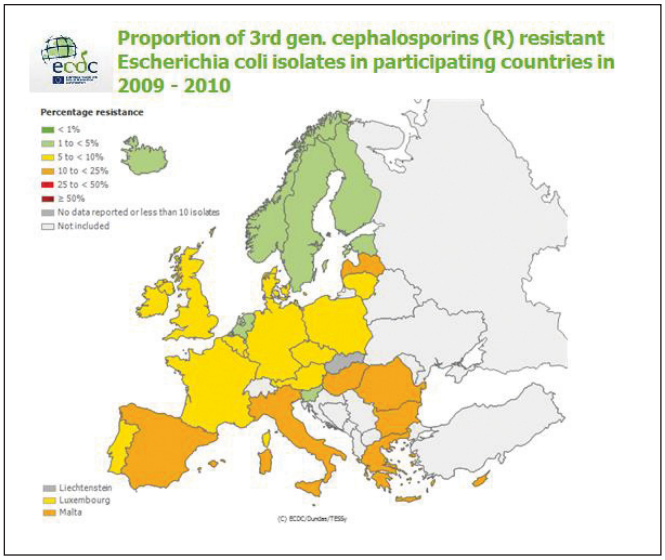

Figure 2 From the EARSS network (www.earss.rivm.nl)

different methods of classifying beta-lactamases. The original Ambler method categorised them into fours groups (A, B, C and D) based on molecular structure, whereas the Bush-Jacoby system utilised their functional properties and substrate profile.[61,62] ESBLs are usually defined using the Ambler method as plasmid-mediated Class A beta-lactamases that hydrolyse penicillins, cephalosporins and monobactams, but not carbapenems.[63]

In vitro they are inhibited by clavulanate, so for less invasive infections caused by these organisms, co-amoxiclav or piperacillin/tazobactam may be effective. In the ICU setting, however, this is rarely appropriate.

There are numerous genotypes of ESBLs but the main ones are TEM, SHV and CTX-M. TEM followed by SHV were the first to be described, but currently the CTX-M genotype is dominant globally, with CTX-M-14 and-15 endemic in many areas, including Europe and Asia.[64] Prevalence rates of ESBL-producing organisms vary geographically but there is no doubt that there is a general upward trend. Recent data from the European Centre for Disease Prevention and Control is shown in **Figure 2**.

The threat ESBL-producing organisms pose to clinical practice cannot be underestimated. They inactivate broad-spectrum antibiotics that are commonly used as empirical treatment for severe infection; as such, a higher morbidity and mortality is seen with such infections.[65] ESBLs are associated with infections affecting all major systems, including the respiratory tract, gastro-intestinal tract, urinary tract, bone and joint and the central nervous system.

These enzymes are plasmid mediated; these plasmids are able to jump between species and therefore represent a significant infection control problem. In addition they often carry genes that confer resistance to other antimicrobials; it is therefore not unusual for such organisms to be multidrug resistant, with simultaneous resistance to fluoroquinolones, aminoglycosides, tetracyclines and trimethoprim-sulfamethoxazole. These organisms may also possess more than one type of ESBL.[66]

Risk factors for acquiring ESBLs include prolonged hospital stay, ICU admission, mechanical ventilation, indwelling medical devices, invasive procedures and previous antibiotic exposure.[67] Treatment options can be limited and should be based upon the sensitivity of the organism and site of infection. Currently carbapenems remain the mainstay of treating ESBL-producers causing serious infections,[68] with monotherapy shown to be effective and superior compared to fluoroquinolones.[69]

Concerns are growing regarding over-reliance on carbapenems as resistance is starting to spread. This is propagated mainly via porin loss during therapy (especially seen with ertapenem) and the proliferation of carbapenemases, a subset of beta-lactamases that may belong to Ambler class A, class B (includes the NDM and VIM enzymes) and class D (includes OXA enzyme, found in *Acinetobacter species*).[70]

If sensitive, aminoglycosides can be a useful adjunct. Other current alternative therapies include fluoroquinolones, tigecycline, temocillin and colistin. Older agents such as fosfomycin and nitrofurantoin can also be effective. Newer agents being developed include cephalosporin and beta-lactamase inhibitors combinations (eg CXA-101+clavulanate or NXL104+cephalosporin). These agents target beta-lactamase resistance and are undergoing clinical trials.

ESBLs represent a significant infection control challenge. They can cause outbreaks of infection within specific units and throughout hospitals. Transient carriage on the hands of healthcare workers is commonly implicated in the dissemination of infection.[71] Ensuring good hand hygiene, preventing unnecessary antibiotic usage, active surveillance and contact isolation precautions are key strategies in controlling and preventing these infections.[72]

Conclusion

Antibiotic resistance is inevitable. No current antibiotic available in clinical practice has been shown to be effective against all pathogens, and all have associated resistance. Multi-drug resistance is not surprising given the abuse of antibiotics, facilitation of colonisation in hospital settings and the extraordinary ability bacteria have to adapt to their environment. Understanding the mechanisms whereby organisms acquire resistance allows physicians to make educated antibiotic selection and manipulate the intensive care environment to decrease colonisation of patients with resistant bacteria. Antimicrobial stewardship, adherence to infection prevention strategies, and pressure for pharmaceutical companies to develop new antibiotics may help to delay the inevitable, but the continued rise of resistant bacteria looks ominous for the future treatment of infections in the ICU.

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James Hatcher Specialty Registrar in Infectious Diseases and Medical Microbiology, Chelsea and Westminister NHS Foundation Trust
james.hatcher@imperial.nhs.uk

Rishi Dhillon Specialist Registrar in Microbiology, Imperial College NHS Foundation Trust

Berge S Azadian Consultant Microbiologist, Chelsea and Westminister NHS Foundation Trust