Multidrug-resistant bacteria

Antimicrobials are crucial in the management of significant infections in animals and humans. Although some bacteria display intrinsic resistance to specific antimicrobial agents, with repeated antimicrobial exposure, bacteria can develop resistance mechanisms which can spread widely between bacteria thereby limiting treatment options for common infections. The direct implications of infections with resistant organisms include a longer duration of illness and increased mortality. Other aspects such as the safe delivery of chemotherapy or high-risk surgery are also threatened if effective prophylaxis becomes unavailable (World Health Organization, 2015).

Beyond health care, the impact of resistance can lead to reduced productivity which in turn adversely affects the global economy, especially within low to middle income countries. It has been estimated that by 2050, if solutions to antimicrobial resistance are not found, up to 10 million deaths each year and a cumulative US$100 trillion global output will be directly attributed to this issue (O'Neill, 2016).

In order to address this, the World Health Organization set out a global action plan on antimicrobial resistance which includes:

- Improving awareness and education
- Strengthening knowledge through surveillance and research
- Reduction of infection through effective sanitation, hygiene and infection prevention measures
- Optimizing use of antimicrobial medicines in human and animal health
- Promoting investment in new medicines, diagnostic tools, vaccines and other interventions (World Health Organization, 2015).

Many of the objectives set out by the World Health Organization can be supported on an individual level by the clinician.

Although drug resistance is a widespread issue affecting the management of many infections such as malaria and tuberculosis, this article will focus on common multidrug-resistant bacterial organisms encountered in clinical practice, the principles of reducing antimicrobial resistance in a local setting, and approaches in management. This article does not replace the expertise provided by an infection specialist (microbiologist or infectious diseases physician), which is often essential in the management of complex infections caused by multidrug-resistant organisms.

Core practice

Adhering to good infection control practices and hand hygiene are key to reducing transmission of multidrug-resistant organisms between patients. Physical contact is the main method of spread (World Health Organization, 2009, 2014), and otherwise difficult-to-treat organisms are removed through hand washing or use of alcohol gels. Hand hygiene should therefore be practiced before patient contact, before an aseptic task, after body fluid exposure, and after patient contact and contact with patient surroundings, as summarized in the five moments for hand hygiene (Sax et al, 2007).

In real-life clinical practice, the balance between the need to treat severe infections such as sepsis and judicious use of antimicrobials can be difficult to achieve. Adopting the principles of antimicrobial stewardship such as the 'Start Smart and then Focus' campaign can help – see *Figure 1* (Public Health England, 2015).

The following sections will address how to approach management of the common multidrug-resistant organisms encountered in clinical practice. *Table 1* outlines these organisms, and their common mechanisms of drug resistance, potential sites of infection and treatment options.

Meticillin-resistant *Staphylococcus aureus*

Meticillin-resistant *Staphylococcus aureus* (MRSA) initially emerged in the UK health-care setting in the 1960s and is a major cause of health-care-associated infections from indwelling venous catheters or devices. It can spread endogenously when the organism from a colonized patient spreads from one part of his/her body to another, and exogenously when the organism is transferred through direct skin contact or through contaminated environments or equipment. MRSA infections are associated with high mortality and can cause severe skin and soft tissue infections, bone and joint infections, abscesses and endocarditis. Although more resistant, it is not thought to be more virulent than the susceptible strain of *S. aureus*.

MRSA is intrinsically resistant to conventional β-lactam antibiotics including penicillins, cephalosporins and carbapenems. Primary therapy for severe and life-threatening MRSA infections therefore tends to be with vancomycin or teicoplanin. Drugs such as linezolid, daptomycin and tigecycline also have activity against MRSA and serve as alternatives. MRSA has variable susceptibility to other antimicrobial agents such as trimethoprim, sulphonamides, rifampicin, sodium fusidate, tetracyclines and lincosamides (Lowy, 2003), allowing the possibility of oral therapy. Novel antimicrobials recently licensed include tedizolid, oritavancin, dalbavancin and other novel cephalosporins (ceftaroline

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and ceftobiprole) (David et al, 2017), but these agents can be costly and should only be used after consultation with an infection specialist.

For over a decade there has been a notable decline in MRSA rates, which is likely to have multifactorial causes including intensification of infection control measures. Patients found to be MRSA colonized are isolated during hospital admissions and undergo MRSA decolonization from nostrils and skin. Health-care staff are required to adhere to isolation protocols and practice good hand hygiene when in contact with patients or their surroundings.

Vancomycin-resistant Enterococcus

Enterococci are Gram-positive organisms which normally live in the gut of humans and animals. They can cause a variety of infections, including urinary tract infections, endocarditis and rarely meningitis occurring in patients with head trauma or those post-neurosurgery (Bayer et al, 1976; Stevenson et al, 1994).

The two most significant human pathogens in this group are *E. faecalis* and *E. faecium*, with the former considered to be more virulent. Following isolation from a clinical specimen, the decision to treat should be made based on the clinical context, as they do not always require targeted therapy (for example, as colonisers in long-term urinary catheters). *E. faecalis* usually retains susceptibility to amoxicillin, whereas *E. faecium* is usually resistant. An additional way of distinguishing between the two subspecies is susceptibility to Synercid (quinupristin-dalfopristin), with *E. faecalis* inherently resistant and *E. faecium* usually susceptible. In the setting of an invasive infection, however, vancomycin is usually first-line therapy as a result of its bactericidal activity, until susceptibility data are available.

Although there are certain Enterococcal species, e.g. *E. gallinarium* and *E. casseliflavus*, which are intrinsically vancomycin resistant, there has been an emergence and spread of vancomycin resistance within *E. faecalis* and *E. faecium* in hospital settings, with *E. faecium* more commonly affected. Among vancomycin-resistance phenotypes in Enterococci, VanA and VanB genotypes possess the highest clinical importance, with VanB strains retaining susceptibility to teicoplanin. Once identified, agents with vancomycin-resistant Enterococcus activity

Figure 1. Antimicrobial stewardship treatment algorithm. Adapted from Public Health England (2015).

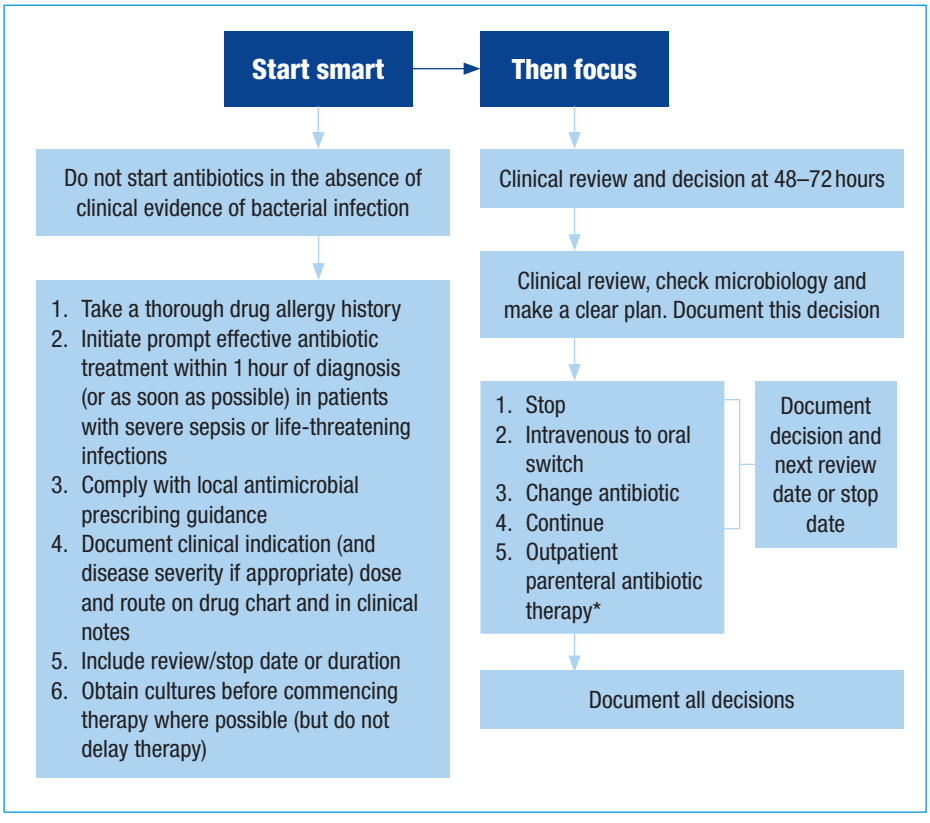

Table 1. Multidrug-resistant bacterial organisms encountered routinely in clinical practice, common drug resistance, potential sites of infection and treatment options

Resistant bacteria	Common drug resistance	Potential infections	Treatment options
Meticillin-resistant *Staphylococcus aureus*	β-lactams, e.g. penicillins, cephalosporins and carbapenems	Skin and soft tissue, bone and joint, abscesses and endocarditis	Vancomycin, teicoplanin, linezolid (tetracycline, clindamycin, rifampicin, sodium fusidate and trimethoprim, depending on susceptibility testing)
Vancomycin-resistant enterococcus	Vancomycin and/or teicoplanin	Urinary tract infections, intra-abdominal infections, endocarditis and rarely meningitis	Linezolid, tigecycline, daptomycin, Synercid
Chromosomally-mediated β-lactamases or extended spectrum β-lactamases	β-lactams, e.g. penicillins, cephalosporins	Urinary tract infections, intra-abdominal infections, hospital-acquired or ventilator-associated pneumonia	Aminoglycosides, fluoroquinolones, pivmecillinam, temocillin, fosfomycin, carbapenems
Carbapenem-resistant enterobacteriacae	β-lactams, e.g. penicillins, cephalosporins and carbapenems	Urinary tract infections, ventilator-associated pneumonia, central venous catheter infections, intra-abdominal infections	Colistin, high dose meropenem (depending on minimum inhibitory concentration level), tigecycline, aminoglycosides, fosfomycin, ceftazidime-avibactam (depending on sensitivities)

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include linezolid, daptomycin, tigecycline and Synercid (not readily available in the UK). Newer agents with potential activity against vancomycin-resistant Enterococcus but which are not yet widely used include oritavancin and telavancin.

It is challenging to have a standard infection control protocol for patients colonized with vancomycin-resistant Enterococcus. The need for patient isolation will often depend on the site of vancomycin-resistant Enterococcus isolation, as well as the presence of other factors such as diarrhoea, which represents a major risk for transmission. For this reason, cases should be discussed with the infection control team or on-call microbiologist.

AmpC-producing Enterobacteriacae

Chromosomally determined AmpC β-lactamases should be suspected in the following groups of coliforms: *Citrobacter freundii*, *Enterobacter cloacae*, *Serratia marcescens*, *Providencia stuartii* and *Morganella morganii*. Commonly these organisms are associated with urine or gut infections, often after exposure to β-lactam antibiotics. It is also possible for other groups of bacteria to acquire genes for AmpC enzymes via transmissible plasmids, which can only be detected on extended antibiotic susceptibility testing.

Strains with AmpC genes are inherently resistant to cefoxitin, but the potential for AmpC induction and selection of high enzyme level mutants can confer resistance to multiple antimicrobial agents, including β-lactam–β-lactamase inhibitor combinations, e.g. co-amoxiclav, cephalosporins and penicillins (Jacoby, 2009) (with the exception of temocillin and pivmecillinam which can retain activity). Treatment with any of the above agents is associated with poor clinical outcome, making the selection of an effective antibiotic difficult.

Depending on the suspected source of infection, empirical antibiotic agents with potential activity against AmpC-producing Enterobacteriacae include fluoroquinolones, pivmecillinam, aminoglycosides, temocillin and carbapenems; however, it is always best to tailor treatment as soon as culture sensitivity results become available.

Extended spectrum β-lactamases (in Gram-negative bacteria)

β-lactam antibiotics such as penicillins, cephalosporins and carbapenems act on the cell wall of bacteria, leading to cell lysis. Extended spectrum β-lactamases are a group of plasmid-mediated, rapidly evolving enzymes with the ability to break down cephalosporins, as well as most penicillins. However, they are inhibited by clavulanic acid, which distinguishes extended spectrum β-lactamases from AmpC-type-β-lactamases (Rawat and Nair, 2010). Despite the fact that β-lactam–β-lactamase inhibitor combinations, e.g. co-amoxiclav and piperacillin-tazobactam, are often active against extended spectrum β-lactamases in vitro, in clinical practice they are more often than not associated with treatment failure, so should be used with extreme caution with a low threshold to change antibiotics.

Carbapenems are the treatment of choice for serious infections caused by extended spectrum β-lactamase-producing organisms, but should be used judiciously in order to limit potential resistance. Examples of carbapenem-sparing agents include fluoroquinolones, aminoglycosides, temocillin, fosfomycin and pivmecillinam. One advantage of fluoroquinolones and the latter two agents are that they are also available in oral formulations, particularly for the treatment of urinary tract infections. There can be wide variation in susceptibility patterns for carbapenem-sparing agents, so empirical prescribing should be led by local guidelines and with reference to individual isolate susceptibilities.

Infection control measures for extended spectrum β-lactamases differ across trusts, but in recent years most hospitals in the UK have shifted from routinely isolating patients colonized with extended spectrum β-lactamase-producing organisms to prioritizing those with carbapenem-resistant Enterobacteriacae for isolation. It is important to consult your local infection control policy.

Carbapenem-resistant Enterobacteriacae

Carbapenem antibiotics such as meropenem have been extremely useful in clinical practice because of their broad activity against Gram-positive, Gram-negative and anaerobic bacteria, as well as those possessing chromosomal cephalosporinases and extended spectrum β-lactamases. There are two main mechanisms for development of resistance:

1. High levels of production of β-lactamases (extended spectrum β-lactamases or AmpC) combined with structural mutations (e.g. porin loss or efflux)
2. Production of carbapenemase enzymes which break down carbapenems (Logan and Weinstein, 2017).

Carbapenemases are encoded on plasmids and can be easily transferred between bacteria, causing outbreaks, especially in the setting of poor hand hygiene and infection control practices. The plasmids often carry other β-lactam genes and genes conferring resistance to multiple different antibiotics (Logan and Weinstein, 2017).

Carbapenem-resistant Enterobacteriacae can either be carried asymptomatically in the gut or cause clinical infections, including bloodstream infections, ventilator-associated pneumonia, urinary tract infection and central venous catheter infections. These infections are associated with a poor prognosis and high mortality (Satlin et al, 2017; Tamma et al, 2017), so an infection specialist should always be included in patient management. Depending on the severity of the infection, a polymyxin-based regimen such as colistin can be used with or without a second agent such as an aminoglycoside, tigecycline, fosfomycin, aztreonam or fluoroquinolone, depending on susceptibilities. The addition of high dose carbapenem to the treatment regimen for clinical infections has also been shown to improve clinical outcomes, particularly when the expression of the carbapenemase appears to be low on laboratory susceptibility testing (Bassetti et al, 2016).

Although some recently launched β-lactamase inhibitor compounds show stability against some of the carbapenem-resistant Enterobacteriacae (e.g. ceftazidime/avibactam against *Klebsiella pneumoniae* carbapenemase and some OXA48 producing strains and ceftolozane/tazobactam against

non-carbapenamase-producing drug resistant Enterobacteriacae), given the state of play with so few novel antimicrobials in the pipeline effective against carbapenem-resistant Enterobacteriacae, the mainstay of management remains prevention and limiting spread. Acquisition of carbapenem-resistant Enterobacteriacae in a health-care setting can occur from transmission between patients or emergence of resistance de novo, in which genetic mutations and selection pressures render the organism resistant. Enforcing antimicrobial stewardship, especially limiting the use of carbapenems, will in some part address the issue of emerging resistance (Bogan and Marchaim, 2013).

With regards to reducing transmission, strict hand hygiene practice, contact isolation precautions, environmental cleaning, and risk assessment and surveillance programmes (to identify asymptomatic carriage) can be effective (Barnes et al, 2014; Richter and Marchaim, 2017). Suspected cases of carbapenem-resistant Enterobacteriacae carriage should include anyone in the last 12 months admitted to any hospital abroad or to a UK hospital with a known high prevalence of carbapenem-resistant Enterobacteriacae (Public Health England, 2013). If suspected or found to be colonized with a carbapenem-resistant Enterobacteriacae, isolation is mandatory for the duration of the hospital stay, and for all subsequent hospital visits with enhanced infection control measures enforced.

Conclusions

Multidrug-resistant organisms threaten progress across all medical and surgical disciplines. This is especially worrying in the context of limited therapeutic options, and insufficient investment in novel agents and diagnostics. This article discusses the evidence-based principles which aim to protect the efficacy of existing antimicrobials and significantly reduce spread of multidrug-resistant organisms, and emphasizes that this can be achieved on an individual level through simple, good stewardship practices. In reality these practices can be difficult to adhere to, in part because of the lack of an immediate effect on the individual patient or tangible feedback for the clinician. It is important that future research promotes awareness to, and beyond the medical field in order to tackle this growing problem. **BJHM**

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KEY POINTS

- The emergence and spread of multidrug-resistant organisms is a global problem, and all health-care professionals have a responsibility to tackle the issue.
- Antimicrobial stewardship is a key strategy, although this should not delay therapy in patients with severe infections. 'Start Smart and then Focus' is a useful principle to adopt.
- Simple infection control practices such as hand hygiene can limit the spread of multidrug-resistant organisms and protect patients.
- Screening of high risk patients is key to detecting and limiting spread of patients with asymptomatic Carbapenem resistant enterobacteriacae carriage.
- Invasive *Staphylococcus aureus* and meticillin-resistant *S. aureus* infections carry a high mortality and can be a common health-care-associated infection associated with indwelling venous devices.
- Carbapenems are the treatment of choice for severe chromosomally mediated β-lactamases or extended spectrum β-lactamase-producing Gram-negative infections, although alternatives including oral antibiotics are appropriate in certain cases.

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