Antimicrobial Therapeutics in Critical Care

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The purpose of this manuscript is to summarise current issues in antimicrobial therapeutics, specifically relating to antibacterial drugs, in the critical care setting. Antimicrobial taxonomy, mode of action, pharmacokinetics and pharmacodynamics are important considerations in choosing the most appropriate agent for treatment of infections. Adverse effects of antibiotics can range from mild gastrointestinal disturbance to anaphylactic shock. Prompt escalation and appropriate de-escalation of antimicrobials are central to effective treatment of sepsis associated with important infections in critical care including ventilator-associated pneumonia (VAP) and catheter-related blood stream infection (CRBSI). Improved diagnostic techniques for earlier detection of pathogens may aid such stewardship of antibiotics. The emergence, and continued rise, of antibiotic-resistant bacteria in recent years has highlighted the importance of antimicrobial stewardship.

Keywords: Sepsis; Healthcare-associated infection; Antimicrobial resistance; Antibiotic stewardship

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Antimicrobial pharmacology

The aim of antimicrobial therapy is to achieve selective toxicity by inhibition of the microorganism without damage to the host. This is achieved by exploiting the differences between metabolism or structure of the microorganism and the corresponding features of human cells [1]. Antimicrobials can be divided into different categories according to their mode of action. These include cell wall inhibition, nucleic acid synthesis inhibition, protein synthesis inhibition and cell membrane damage. Major drug classes, sites of action, antimicrobial spectra, and adverse effects are summarised in Table 1 and Figure 1.

Agents acting on the cell wall

Beta-lactams

All beta-lactam agents feature a beta-lactam ring and act on the bacterial cell wall by binding to proteins involved in cell wall construction [2].

Benzylpenicillin, or penicillin G, has excellent activity against streptococci. However, it is easily degraded by gastric acid and has a short half-life; therefore, it must be given intravenously and at frequent intervals [1].

Flucloxacillin is a narrow spectrum antimicrobial used to treat staphylococcal infections; it also has short half-life and is poorly absorbed following oral administration. It is not active against methicillin-resistant *Staphylococcus aureus* (MRSA), because of alteration to its cell target (penicillin-binding protein).

Amoxicillin is a further development of the penicillin family and has activity against non-beta-lactamase-producing Gram-positive and Gram-negative organisms. Several bacteria produce a beta-lactamase enzyme which hydrolyses the beta-lactam ring causing it to be ineffective. Clavulanic acid, added to amoxicillin in co-amoxiclav, inhibits this enzyme and hence breakdown of the beta-lactam. Piperacillin/tazobactam acts in a similar manner, with beta-lactamase inhibition provided by tazobactam, and has a broader spectrum of coverage, including activity against *Pseudomonas* species [1](Figure 2).

The first generation cephalosporins (e.g. cefazolin) primarily have activity against Gram-positive organisms with a limited Gram-negative spectrum. The second (e.g. cefuroxime) and third generation (e.g. ceftriaxone) cephalosporins have improved Gram-negative cover and cannot be hydrolysed by all beta-lactamases, with a notable exception being the extended-spectrum beta-lactamases (ESBL). The fourth (e.g. cefepime) and fifth (e.g. ceftaroline) generations have activity against an extended Gram-negative spectrum, and MRSA, respectively [2].

Carbapenems are structurally different from penicillins and cephalosporins. They are more stable as they are not affected by most beta lactamases. This class of beta-lactams are extremely broad spectrum with activity against Gram-negative bacilli

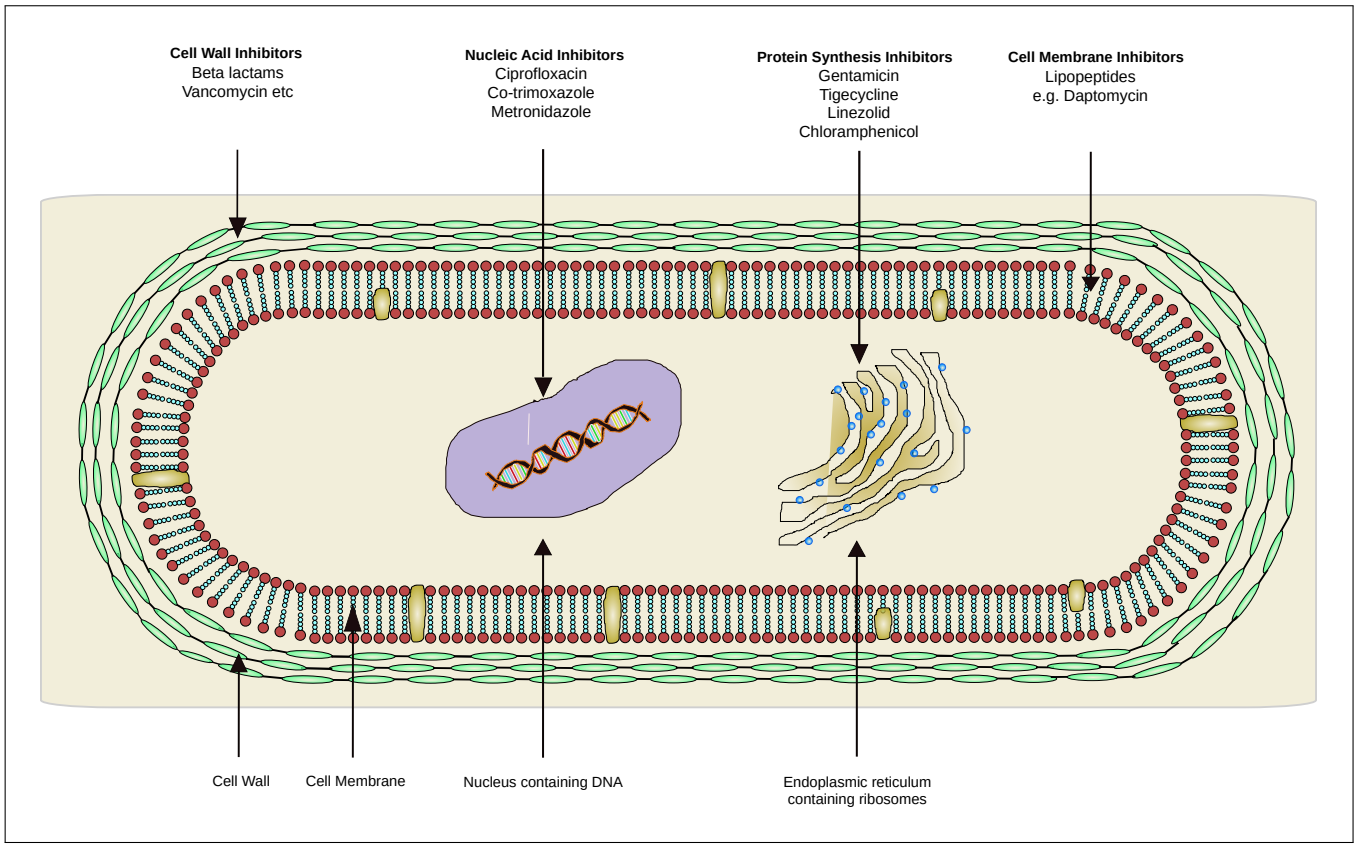

Figure 1. Antibacterial sites of action

which produce ESBL enzymes as well as *Pseudomonas aeroginosa*. However, carbapenem resistance is now emerging with a recent rise in carbapenemase-producing enterobacteriaceae.

Glycopeptides

Glycopeptides, like beta-lactams, act on the cell wall; however, they inhibit the last stages of cell wall assembly by preventing cross linking reactions between constituent peptidoglycans. Their antimicrobial spectrum is exclusively Gram-positive organisms. Intravenous teicoplanin and vancomycin are widely used for treatment of staphylococcal infections, including MRSA [2].

Protein synthesis inhibitors

The protein synthesis inhibitors are constituted by a large number of antibiotics; perhaps the most commonly prescribed examples are macrolides and tetracyclines.

A relatively new member of this group, tigecycline, has a very broad spectrum of activity which includes glycopeptide-resistant enterococci (GRE). Its main use is for skin/soft tissue and intra-abdominal infections [1]. It is important to note that, because of its pharmacokinetics, tigecycline is not indicated in the treatment of septic shock, primary bacteraemia, and urinary tract infections [3].

Aminoglycosides also act by inhibiting protein synthesis and are bactericidal drugs that are especially active against Gram-negative bacilli. They exhibit synergy when used with beta-lactams to target both Gram-positive and -negative organisms; hence, they are useful in treatment of severe infections with bacteraemia.

Chloramphenicol acts against a broad range of organisms, however, it is indicated for treatment of only a limited number of infections because of toxicity concerns; these include meningitis in patients for whom beta-lactams are contraindicated e.g. severe allergy.

Linezolid and tedizolid are oxazolidinones with very broad Gram-positive activity. These antimicrobials also target protein synthesis and can be used to treat skin/soft tissue infections, especially when involving MRSA. Linezolid is effective in treating lower respiratory chest infections, particularly MRSA pneumonia [4].

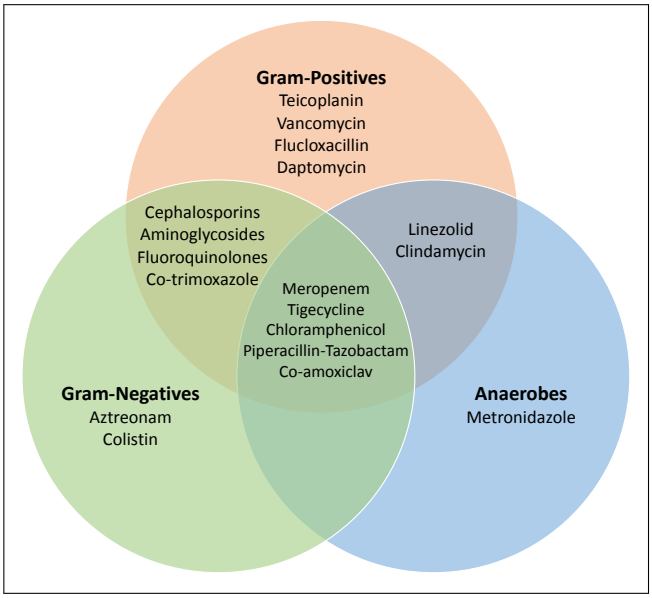

Figure 2. Summary of antibacterial spectra

Agents acting on the cell membrane

Daptomycin (a lipopeptide) is a bactericidal antibiotic acting on the cell membrane and, like the oxazolidinones, has a very broad Gram-positive spectrum of activity including MRSA and GRE. It is effective in treating bacteraemia due to *Staphylococcus aureus* and *Enterococcus* species.

Nucleic acid inhibitors

Fluoroquinolones act by inhibiting bacterial nucleic acid synthesis, providing broad Gram-negative cover, with some members having good Gram-positive activity. Ciprofloxacin is the most widely prescribed member of this group in critical care and has excellent oral bioavailability. It is the only oral antimicrobial with action against *Pseudomonas* species and also has activity against some ESBL-producing organisms. Levofloxacin has better Gram-positive cover because of its anti-streptococcal activity [1].

Cotrimoxazole contains sulphamethoxazole and trimethoprim (in a 5:1 ratio), both of which inhibit DNA synthesis by acting on the folate pathway. It is used to treat a variety of bacterial, fungal and protozoal infections and is particularly useful in treatment of *Pneumocystis jirovecii* pneumonia and *Stenotrophomonas maltophilia* infections (such as catheter-related bacteraemia) [1].

Metronidazole has cytotoxic effects on anaerobes, though its mode of action is not fully understood. It is well absorbed when administered orally and is a first-line treatment for non-severe *Clostridium difficile* infections [5].

Adverse effects

Several antimicrobials have non-specific adverse effects (e.g. headache and gastro-intestinal disturbances) as well as specific side effects relating to certain antibiotics.

Antimicrobial allergy may occur in the form of immediate or non-immediate (delayed) hypersensitivity reactions. Immediate reactions are Ig-E mediated whereas delayed reactions are non-IgE, or T-cell, mediated [6].

Beta-lactams

The penicillin family of drugs are generally well tolerated, but they have been associated with a wide range of hypersensitivity reactions [7]. True penicillin allergy occurs in 7-23% of patients who give a history of penicillin allergy [8]. IgE-mediated hypersensitivity reactions are the most feared adverse event and are a well-recognised effect attributed to beta-lactam agents, especially the penicillin family. These reactions manifest with urticaria, pruritus, hypotension, bronchospasm, and laryngeal oedema [9].

Non-immediate reactions may be immune-mediated or direct-toxicity-mediated, usually occurring more than one hour after drug administration. The main non-immediate reaction is maculopapular exanthem, particularly during treatment with a penicillin [10]. High intravenous doses can cause direct central nervous system toxicity, with myoclonic jerks, seizures or coma; this is a particular problem in patients with renal impairment [11].

Platelet-mediated bleeding caused by ticarcillin and piperacillin is often duration-related and, while not particularly common, can be substantial [12]. Incidence of delayed adverse reactions to beta-lactams increases sharply when parenteral treatment is extended beyond 2 weeks. Beta-Lactam-induced neutropenia occurs on average after 3 weeks of treatment, and may be due to either immunologic or toxic effects of treatment [13]. Patients with a late adverse reaction to penicillin can safely be re-treated with penicillin subsequently, with close surveillance [13].

Cephalosporins are considered safe for the patient who experiences a penicillin-induced maculopapular rash - but not an urticarial skin eruption, or other immediate reaction, indicating IgE-mediated allergy [14]. Cross-reactivity between penicillins and second/third generation cephalosporins is low and may be even lower than the cross reactivity between penicillins and some unrelated antibiotics: anaphylaxis with cephalosporins is uncommon [8]. In life threatening infections such as bacterial meningitis, septicaemia, and severe respiratory tract infections, consideration should be given to using second and third generation cephalosporins, even in patients with a history of penicillin allergy, when the risk of different options is being weighed-up [8].

Cephalosporin, clindamycin and fluoroquinolone use has been associated with diarrhoea and pseudo-membranous colitis [15–17]. Uncommon, but important, adverse effects of fluoroquinolones include seizures, elevation of liver enzymes, and tendinopathy [18].

Meropenem demonstrates cross-reactivity with penicillin and is contraindicated for the patient with a history of immediate or accelerated hypersensitivity reactions to penicillin. A retrospective analysis demonstrated the incidence of patients with a reported or documented penicillin allergy experiencing an allergic-type reaction to a carbapenem was 11%, which is over five times greater than the risk in patients who were reportedly not allergic to penicillin [19].

Aztreonam, a monocyclic beta-lactam, does not appear to cross-react with penicillin, and has been safely administered to penicillin-allergic patients [20].

Vancomycin

The most dramatic adverse effect of intravenous vancomycin is the red man syndrome: a non-immunologically mediated reaction consisting of pruritus and erythema involving the upper body, with or without hypotension. It appears to be dependent on dose, frequency of administration, and rate of infusion, and is thought to be mediated by histamine release [21].

Aminoglycosides

Concerns regarding administration of aminoglycosides include nephrotoxicity, ototoxicity (both the auditory and vestibular components) and neuromuscular blockade (particularly in patients with myasthenia gravis). Factors contributing to these adverse effects include duration of therapy, age, liver disease, shock and the co-administration of drugs that have the potential to cause ototoxicity or nephrotoxicity [22].

Linezolid

Linezolid is a weak inhibitor of monoamine oxidase (MAO) and may potentially cause 'serotonin syndrome' in patients taking selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, MAO inhibitors, cocaine and other recreational drugs such as 3,4-methylenedioxymethamphetamine (MDMA) [23].

Linezolid has been notably associated with reversible myelosuppression which manifests in three ways: thrombocytopaenia, anaemia, and neutropenia. Patients should be monitored appropriately, especially those with pre-existing bone marrow suppression or diminished bone marrow reserves. For those being treated for longer than 14 days, the clinical benefit of linezolid in serious Gram-positive infections should be

Drug and mode of action	Spectrum	Adverse Effects
Beta-lactams (cell wall)		
Benzylpenicillin	Gram-positive, mainly streptococcal	Hypersensitivity (rashes, fever, eosinophilia, angio-oedema, serum sickness, anaphylaxis), vomiting, diarrhoea, convulsions, nephrotoxicity, cholestatic jaundice, Stevens-Johnson syndrome
Flucloxacillin	Gram-positive, mainly staphylococcal	
Amoxicillin	Gram-positive, Non beta-lactamase gram negative	
Co-amoxiclav	Gram-positive, Gram-negative, Anaerobes	
Piperacillin/tazobactam	Gram-positive, Gram-negative, Anaerobes	
Cephalosporins	Gram-positive, Gram-negative, Anaerobes	
Carbapenems	Gram-positive, Gram-negative + *Pseudomonas* species, Anaerobes	
Glycopeptides (cell wall)		
Vancomycin	Gram-positive + MRSA	Renal toxicity, red man syndrome, oto-toxicity, thrombocytopaenia, rash
Aminoglycosides (protein synthesis)		
Gentamicin	Gram-negative + *Pseudomonas* species, some Gram-positive	Renal toxicity, ototoxicity
Amphenicols (protein synthesis)		
Chloramphenicol	Gram-positive, Gram-negative, Anaerobes	Marrow suppression, aplastic anaemia, hypersensitivity
Oxazolidinones (protein synthesis)		
Linezolid	Gram-positive + MRSA, Anaerobes	Haemopoietic disorders, optic neuropathy
Glycylcyclines (protein synthesis)		
Tigecycline	Gram-positive + MRSA, Gram-negative, Anaerobes	Nausea and vomiting, hepatotoxicity
Lipopeptides (cell membrane)		
Daptomycin	Gram-positive + MRSA	Myalgia, nausea and vomiting
Fluoroquinolones (nucleic acid synthesis)		
Ciprofloxacin	Gram-negative including *Pseudomonas* species	Diarrhoea, nausea and vomiting, tendon damage, seizures
Anti-folates (nucleic acid synthesis)		
Co-trimoxazole	Gram-positive, Gram-negative + *Stenotrophomonas* species, *Pneumocystis jiroveci*	Haemopoietic disorders, Stevens-Johnson syndrome, nausea
Nitroimidazoles (nucleic acid synthesis)		
Metronidazole	Anaerobes	Nausea, disulfiram-like reaction with alcohol, peripheral neuropathy

Table 1. Synopsis of drug classes, sites of action, antimicrobial spectra, and adverse effects.

weighed against potential, but reversible, haematological effects [24].Linezolid-associated toxic optic neuropathy is recognised complication of prolonged treatment [25]. These adverse reactions have led to the recommendation to limit treatment courses to a maximum of 28 days [26].

Dosing strategies and monitoring

Many antibiotic-related adverse events are precipitated by an extension of the drug's normal pharmacology and are predictable complications of high serum levels; hence, many adverse reactions may be avoided by appropriate dosage

adjustment.

The major determinants of bacterial killing include the maximum serum concentration reached (Cmax), and the time the antibiotic concentration remains over an efficacy threshold such as the minimum inhibitory concentration (MIC), T>MIC. The area under the serum concentration-time curve (AUC) after a dose of antibiotic is a measure of total drug exposure and is reflected by both Cmax and T>MIC. Therefore, the AUC accounts for both how high, and for how long, the antibiotic levels remain above the MIC of the target organism during any one dosing interval [2](Figure 3).

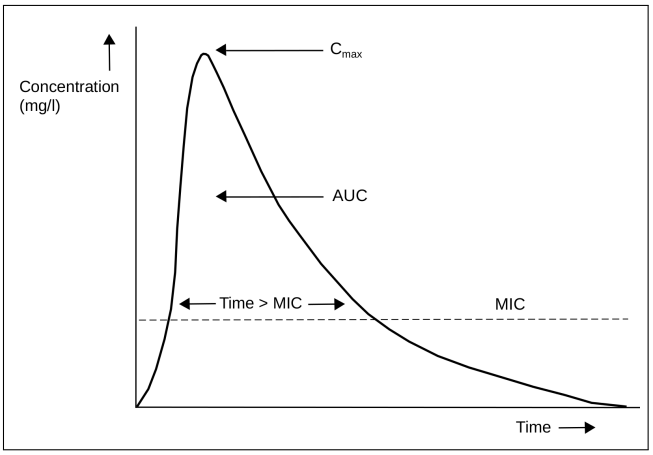

Figure 3. Pharmacodynamic parameters relevant to antimicrobial therapy

For *time-dependent antibiotics*, such as beta-lactams and glycopeptides, optimal bacterial kill is achieved by maximizing the duration of time drug concentration is greater than the MIC of the target organism for that particular antibiotic (T >minimum inhibitory concentration). For this reason, frequent dosing with penicillins is more effective than administering higher unit doses less frequently.

With *concentration-dependent antibiotics*, such as aminoglycosides, a high initial concentration is required to ensure maximum bacterial kill. The efficacy of these agents is related to the achievement of a high Cmax/MIC ratio, hence, gentamicin is usually best given in a large dose, once daily. This high initial concentration may also aid tissue penetration [27]. For most antibiotics, however, the ratio of the AUC (over 24-h) to MIC of the target organism is most important in determining the extent of antibacterial effect [28]. Therefore, for many antibiotics, adjusting either the unit dose or dosing interval increases the antibacterial effect.

The target vancomycin therapeutic trough concentration for treatment of infections is usually between 10-15mg/litre [26]. A higher vancomycin concentration at 15-20mg/litre is recommended for severe infections such as bacteraemia, endocarditis, osteomyelitis, meningitis and hospital-acquired pneumonia caused by *Staphylococcus aureus* [29]. However, a systematic review suggested a strong relationship exists between higher vancomycin trough concentrations and nephrotoxicity. Patients with vancomycin troughs in excess of 15 mg/litre were found to have a greater risk of nephrotoxicity than those with concentrations of <15 mg/litre [30]. Hence, there is a trade-off between efficacy and risk of toxicity, guided by the severity of infection.

Knowledge of antibiotic pharmacodynamic properties and the potential altered antibiotic pharmacokinetics in critically ill patients can allow clinicians to develop tailored dosing regimens. Measured creatinine clearance can be used to drive many dose adjustments for renally cleared drugs [31]. Antibiotics can be broadly categorized according to their solubility characteristics which can help describe possible altered pharmacokinetics that can be caused by the pathophysiological changes common to critical illness. Hydrophilic antibiotics (e.g. beta-lactams, glycopeptides) are mostly affected with the pathophysiological changes observed in critically ill patients with increased volumes of distribution and altered drug clearance (related to changes in creatinine clearance). Lipophilic antibiotics (e.g. fluoroquinolone, tigecycline) have lesser volume of distribution alterations, but may develop altered drug clearances. Using antibiotic pharmacodynamic bacterial kill characteristics, dosing regimens can be altered to optimize treatment [31].

Treatment of patients with sepsis

Mortality figures for severe sepsis and septic shock have commonly been quoted as ranging from 20% to 50% [32]. A retrospective analysis of 17,990 patients with septic shock noted that the time to initiation of appropriate antimicrobial therapy was the strongest predictor of mortality [33].

Intravenous antibiotic therapy should be initiated as a matter of urgency, ideally after obtaining appropriate cultures. The choice of antibiotics can be complex and should reflect the patient's history (e.g. recent antibiotics received, comorbidities), the clinical context (such as community or hospital acquired infection), Gram stain result, previously cultured organisms, and local resistance patterns [32]. When the potential pathogen or infection source is not immediately obvious, broad-spectrum antimicrobial coverage directed against both Gram-positive and Gram-negative bacteria are favoured [34].

Combination therapy can be used to broaden the spectrum of antimicrobial coverage when used empirically to increase the chance of adequately targeting the causative organism. Secondly, some combinations may possess an enhanced potential for synergism, when compared with the additive effect of each of the antibiotics assessed separately. Synergy between beta-lactam antibiotics and aminoglycoside antibiotics has been shown in vitro for Gram-negative bacteria and specifically for *Pseudomonas aeruginosa* [35]. A meta-analysis suggested combination antimicrobial therapy improves survival and clinical response of high-risk, life-threatening infections, particularly those associated with septic shock, but may be detrimental to low-risk patients [36].

In observational studies of almost 10,000 critically-ill patients with community-acquired pneumonia, macrolide use was associated with a significant relative reduction in mortality (18%) compared with non-macrolide therapies [37]. These results suggest macrolides be considered first-line combination treatment in critically ill patients with community-acquired pneumonia and support current guidelines. Furthermore, it may be inferred this benefit is not limited to patients with atypical pathogens and a speculative mechanism for this effect is immunological.

Optimal management of patients with sepsis includes early goal-directed therapy, lung-protective ventilation, and adequate antimicrobials [38]. Later in the course of sepsis, appropriate management may necessitate organ support and prevention of nosocomial infection. Studies focused on novel targets, mechanisms of action, and combination therapy may improve current treatment [39].

The Surviving Sepsis Campaign guideline clearly endorses

de-escalation to the most appropriate single therapy as soon as the susceptibility profile is available [32]. A prospective observational study published recently concluded de-escalation therapy for severe sepsis and septic shock is a safe strategy associated with lower mortality; efforts to increase the practice of early de-escalation are, therefore, justified [40].

Treatment of community-acquired pneumonia (CAP)

Approximately 10% of hospitalized patients with CAP require ICU admission [41]. The most common aetiologies of community-acquired pneumonia are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Legionella* species, Gram-negative bacilli and *Haemophilus influenzae* [42].

The Infectious Diseases Society of America (IDSA) recommends [43] using a beta-lactam plus a fluoroquinolone for critically ill patients. Aztreonam and a respiratory fluoroquinolone is the recommended alternative regimen for penicillin allergic patients. Once the aetiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen.

For all critically ill patients, coverage for *S. pneumoniae* and *Legionella* species should be ensured by using a potent anti-pneumococcal beta-lactam and either a macrolide or a fluoroquinolone [43, 44]. Macrolide use has been associated with decreased mortality in patients with severe sepsis due to pneumonia even with macrolide-resistant pathogens [45]. A recent trial demonstrated non-inferiority of a beta-lactam alone compared with a beta-lactam and macrolide combination in moderately severe community-acquired pneumonia [46].

Reduction in patient exposure to antibiotics may limit the increasing rates of antimicrobial drug resistance, decrease cost, and improve patient adherence and tolerability [47]. It has been suggested adults with mild to moderate community-acquired pneumonia can be safely and effectively treated with an antibiotic regimen of 7 days or less [47]. IDSA recommends patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should be clinically stable before discontinuation of therapy [43].

Treatment of hospital and ventilator-associated pneumonias (HAP/VAP)

Ventilator-associated pneumonia (VAP) contributes up to half of all cases of hospital-acquired pneumonia, is estimated to occur in up to 27% all mechanically ventilated patients and is the most common nosocomial infection in this group [48–50]. Risk of VAP is greatest during the first 5 days of ventilation, with the mean time period between intubation and development of VAP being 3.3 days [51]. Over the years, the attributable risk of death from VAP has decreased and was recently estimated at 9-13% [52]. Despite surveillance data from recent years suggesting a much lower incidence of confirmed VAP, suspected VAP remains challenging and also drives use of empirical antimicrobials in intensive care units.

The type of organism that causes VAP usually depends on the duration of mechanical ventilation. In general, early VAP is caused by pathogens sensitive to antibiotics, whereas late onset VAP is caused by multi-drug resistant and more difficult to treat bacteria. These include MRSA, *Acinetobacter baumanii*, *Pseudomonas aeroginosa* and ESBL-producing organisms. However, this is by no means a hard and fast rule and is merely a guide to initial antibiotic therapy until further clinical information is available [53].

Not all organisms isolated from respiratory specimens should be regarded as pathogens that necessarily require therapy; they should be interpreted and treated in the light of the full clinical picture. The choice of empirical antibiotic therapy of patients with HAP in an individual unit should, ideally, be based on the nature and susceptibility patterns of the pathogens prevalent on that unit and should also take account of such variables as duration of hospital stay (i.e. early- or late-onset infection), recent administration of antimicrobial therapy and co-morbidities. Similarly, definitive therapy should be determined by culture and susceptibility test results. For patients with early-onset infections who have not previously received antimicrobial, and in the absence of other risk factors, the use of co-amoxiclav would be appropriate. For patients who have recently received antibiotics and/or who have other risk factors, a third-generation cephalosporin, a fluoroquinolone or piperacillin/tazobactam may be appropriate [54].

Nebulised antimicrobial therapy may have an adjunctive role in treatment of VAP, although its incremental efficacy is uncertain. Direct pulmonary administration might be effective by achieving high local concentrations by nebulisation. Nebulised colistimethate sodium (CMS), used as adjunctive therapy for Gram-negative VAP, seems to be safe although in one study no beneficial effect on clinical outcomes was seen with adjunctive nebulised CMS for treatment of Gram-negative VAP. [55].

Aminoglycosides have a suitable antimicrobial spectrum for the treatment of serious Gram-negative infections. However, their use in pneumonia is limited by the risks of toxicity and by poor penetration into infected lung tissues when administered intravenously. A recent study concluded that nebulised amikacin, for the treatment of Gram-negative pneumonia in mechanically ventilated patients, warrants further clinical evaluation [56]. It is worth noting traditional breakpoints used to determine whether pathogens are susceptible or resistant are not readily interpretable in the nebulised setting.

Treatment of complicated intra-abdominal infections

The empiric use of antimicrobial regimens with broad spectrum activity against gram-negative organisms such as meropenem or piperacillin/tazobactam is recommended for patients with high-severity community-acquired intra-abdominal infection [57]. Ciprofloxacin or aztreonam plus metronidazole is an alternative in the context of beta-lactam allergy, but addition of an agent effective against gram-positive cocci is recommended [57]. In these high-risk patients, antimicrobial regimens should be adjusted according to culture and susceptibility.

Antifungal therapy for patients with severe community acquired or healthcare-associated infection is recommended if Candida is grown from intra-abdominal cultures [57]. For the critically ill patient, initial therapy with an echinocandin (caspofungin, micafungin, or anidulafungin) instead of a triazole has recommended when invasive infection has been proven [58, 59].

Empiric therapy directed against glycopeptide-resistant *Enterococcus faecium* (GRE) is usually not recommended except when the patient is at very high risk for an infection due to this organism, such as a liver transplant recipient with an intra-abdominal infection originating in the hepatobiliary tree or a patient known to be colonized with GRE [57].

An appropriate source control procedure to drain infected foci, control ongoing peritoneal contamination by diversion or resection, and restoration of anatomic and physiological function is recommended for nearly all patients with intra-abdominal infection [57].

Antimicrobial therapy for established infection should be limited to 4–7 days, unless it is difficult to achieve adequate

source control [60, 61]. Longer durations of therapy have not been associated with improved outcome [57]. Appropriate diagnostic investigation should be undertaken In patients who have persistent or recurrent clinical evidence of intra-abdominal infection after 4–7 days of therapy. Antimicrobial therapy effective against the organisms initially identified should be continued. Extra-abdominal sources of infection and non-infectious inflammatory conditions should also be investigated if the patient is not experiencing a satisfactory clinical response to a microbiologically adequate initial empiric antimicrobial regimen.

Treatment of catheter-related bloodstream infection (CRBSI)

Catheter-related bloodstream infection (CRBSI) accounts for 10-20% of hospital-acquired infections in the UK and is associated with both increased ICU stay and mortality [62]. Coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic Gram-negative bacilli, and *Candida albicans* most commonly cause CRBSI [62].

After appropriate cultures are taken, empirical IV antimicrobial therapy should be initiated on the basis of clinical suspicion, the severity of the patient's acute illness, underlying disease, and the potential pathogens involved. The central venous catheter (CVC) should be removed in most cases of non-tunnelled CVC-related bacteraemia [62].

Coagulase-negative staphylococci, such as *Staphylococcus epidermidis*, are the most common cause of catheter-related infections. Five to seven days antimicrobial duration is recommended for uncomplicated CRBSI if the catheter is removed. If the catheter is retained, 10–14 days duration, in combination with intraluminal antibiotic therapy, is recommended [62]. Glycopeptide antibiotics are the usual choice for these infections [1].

Patients with *S. aureus* CRBSI should have the infected catheter removed, and receive 2–6 weeks of antimicrobial therapy. Patients can be considered for the shorter duration of antimicrobial therapy (a minimum of 14 days) when [62]:

- the patient is not diabetic or immunosuppressed
- the infected catheter is removed
- the patient has no prosthetic intravascular device
- there is no evidence of endocarditis
- fever and bacteraemia resolve within 72 hours after initiation of appropriate antimicrobial therapy
- there is no evidence of metastatic infection

Resistant organisms

Antimicrobial resistance is a problem that is becoming increasingly challenging and is a predictable consequence of antibiotic use.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to almost all beta-lactam antimicrobials (with the exception of fifth generation cephalosporins). Therefore options are limited and glycopeptides are the mainstay of treatment for serious infections [1]. A trial in 2012 demonstrated improved clinical and microbiological outcomes of linezolid for MRSA nosocomial pneumonia compared with vancomycin [63]. However a meta-analysis demonstrated linezolid and vancomycin have similar efficacy and safety profiles and concluded neither drug is superior for the treatment of hospital-acquired pneumonia [64]. A randomised trial in 2006 showed that high dose daptomycin is non-inferior to standard therapy (beta lactam or glycopeptide) for treatment of *Staphylococcus aureus* bacteraemia [65]. Similarly, daptomycin has not displaced beta-lactams and glycopeptides as first-line therapy; the relatively wide non-inferiority margin reported in this trial in conjunction with the principle of antibiotic conservation may have contributed to this.

In the UK, Glycopeptide resistant enterococci (GRE) were first detected in 1986. The most frequent site of colonisation is the bowel, hence, GRE may cause infections in patients with severe, and often complicated, intra-abdominal pathology in critical care [66]. Treatment options are limited and include daptomycin or linezolid for patients who have bacteraemia, with tigecycline an option for patients with intra-abdominal infections who are not bacteraemic.

Extended spectrum beta-lactamases (ESBL) are enzymes carried by Gram-negative bacteria that mediate resistance to extended-spectrum cephalosporins. Carbapenems are the mainstay of therapy for these infections in critical care [67]. Alternatives are needed because of the emergence of carbapenemase-producing enterobacteriaceae (CPE). Such alternatives may comprise aminoglycosides, colistin, and in some circumstances, tigecycline [68].

There has been a marked increase in the incidence of CPE in the UK in recent years. Over the last decade, CPE have spread throughout the world and are now endemic in healthcare facilities in many countries. Infections can be extremely difficult to treat, as these isolates are highly resistant [69]. CPE are typically resistant to carbapenems, as well as many other classes of antimicrobials, leaving few choices for treatment of infections with combination therapy being usual.

Mortality from infections due to *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*, an exemplar CPE, has been reported to be at least 50% [70]. The optimal antimicrobial therapy for infections with KPC-producing organisms has not been well established. In recent studies patients who received monotherapy with either colistin or tigecycline had poorer outcomes compared to those who had combination therapy [71, 72]. The most commonly used combination therapy was either colistin or tigecycline with a carbapenem in isolates that are not fully resistant [73]. Other combinations which have been used are colistin with tigecycline or colistin with an aminoglycoside [71]. Mortality was reported to be up to 50% for patients receiving tigecycline-gentamicin combination and up to 64% for tigecycline-colistin; in patients treated with tigecycline monotherapy, mortality was up to 80% [74]. In vitro studies provide experimental evidence for the use of ceftazidime combined with avibactam (a novel synthetic beta-lactamase inhibitor) to treat infections due to certain types of CPE e.g. *Klebsiella pneumoniae* with OXA-48 enzyme [75].

Multiple drug-resistant *Acinetobacter baumanii* (MDRAB) may cause serious infections in critically ill patients for which colistin often remains the only therapeutic option. Addition of rifampicin to colistin is synergistic in vitro and has been widely reported to confer a clinical outcome benefit in cohort studies. However, a randomised trial concluded that 30-day mortality is not reduced by addition of rifampicin to colistin in serious MDRAB infections [76]. Nonetheless, the increased rate of *A. baumannii* eradication with combination treatment could still bring clinical benefit by limiting transmission. The optimal dosing of colistin has not been established. A loading dose of 9 MU and a 9 MU twice-daily maintenance dose have been suggested to be beneficial without causing significant toxicity [77].

Antimicrobial stewardship

Current evidence demonstrates that the widespread use of broad-spectrum antibiotics is associated with antimicrobial resistance (e.g. ESBL-producers, MRSA, CPE) and the induction of *Clostridium difficile* infection (CDI). Antimicrobial stewardship aims to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity, reduce the costs of health care, and limit the selection for antimicrobial resistant strains [78].

Early detection of the pathogen is essential for optimal antimicrobial treatment. A diagnostic test that could reduce time to adjustment of antibiotic treatment, in comparison with conventional blood cultures, would be favourable in critically ill patients with sepsis. SeptiFast®is a CE-marked multi-pathogen real-time PCR system capable of detecting DNA sequences of bacteria and fungi present in blood samples within a few hours; such a test has potential to impact stewardship processes. However, a recent systematic review and meta-analysis of diagnostic accuracy studies of SeptiFast®, in the context of suspected sepsis, concluded that firm recommendations about the clinical utility of SeptiFast®within this setting could not be made [79].

Early identification of pathogens from blood cultures using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry may optimize the choice of empirical antibiotic therapy in the setting of bloodstream infections. A prospective observational study in 2010 demonstrated MALDI-TOF had an impact on clinical management in 35.1% of all Gram-negative bacteraemia cases, showing a greater utility than Gram's stain reporting. Thus, MALDI-TOF could become a useful second step beside Gram stain in guiding the empirical treatment of patients with bloodstream infection [80] .

Measurement of procalcitonin levels to guide antibiotic decisions in patients with respiratory tract infections and sepsis appears to reduce antibiotic exposure without worsening clinical outcomes [81]. Procalcitonin (PCT)-based algorithms have been used to guide antibiotic therapy in several clinical settings. In a trial of a PCT-based algorithm to reduce antibiotic exposure in secondary peritonitis, antibiotics were discontinued if PCT was <1.0 ng/mL or decreased by 80%, with resolution of clinical signs. The PCT-based algorithm safely reduced antibiotic exposure in this study [82]. A more recent study demonstrated that, in critically ill adults with undifferentiated infections, a PCT algorithm including 0.1 ng/ml cut-off did not achieve the expected 25% reduction in duration of antibiotic treatment [83]. However, it is worth noting that a target of 25% reduction in antibiotic exposure is ambitious, especially in the critical care setting.

Rapid biomarker-based exclusion of infection may improve antibiotic stewardship in VAP; however, successful validation of the usefulness of potential markers in this setting is rare. A prospective, multicentre study validated the ability of specific host inflammatory mediators to exclude pneumonia in patients with suspected VAP [84]. The study concluded low bronchoalveolar lavage fluid levels of Interleukin-1-beta, in combination with interleukin-8, confidently excludes VAP and could form a rapid biomarker-based rule-out test, with potential to improve antibiotic stewardship.

The optimal duration of antimicrobial treatment for VAP has not been firmly established. A randomised trial published in 2003 compared 8 and 15 days of antibiotic treatment in microbiologically-proven VAP and reported comparable clinical effectiveness [85]. Therefore, both excluding VAP when suspected and shortening duration of treatment in confirmed infection may be useful strategies to support stewardship.

With current pressures to find alternatives to carbapenems, a study in 2013 reported that extended-infusion of cefepime provides increased clinical and economic benefits in the treatment of invasive *Pseudomonas aeruginosa* infections [86]. This type of research is needed to allow confident diversification of antimicrobials in common use, to reduce selection pressure in key drug classes.

Conclusion

There are well-rehearsed points regarding antimicrobial use that every clinician should consider. As a general rule, there should be a clear indication for starting antibiotic treatment. Withholding antimicrobials should always be considered when they are not clearly necessary, though this is particularly difficult in severely ill patients. Improved diagnostic techniques may aid clinical decisions on the initiation, and early cessation, of antimicrobials. Furthermore, appropriate initial selection of antimicrobials is crucial for adequate treatment of time-critical infections, as is ensuring the appropriate dosage, taking into account the pharmacokinetics and pharmacodynamics of different drug classes. Lastly, prompt initiation of broad spectrum antimicrobials should be complemented by early de-escalation strategies to control the antimicrobial resistance burden driven by antibiotic exposure.

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