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CLINICAL PRACTICE REVIEW

Antibiotic use in critical illness

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Abstract

Objective: To provide a review on the current use of antimicrobials with a discussion on the pharmacokinetic and pharmacodynamic profiles of antimicrobials in critically ill patients, the challenges of drug resistance, the use of diagnostic testing to direct therapy, and the selection of the most likely efficacious antimicrobial protocol.

Etiology: Patients in the intensive care unit often possess profound pathophysiologic changes that can complicate antimicrobial therapy. Although many antimicrobials have known pharmacodynamic profiles, critical illness can cause wide variations in their pharmacokinetics. The two principal factors affecting pharmacokinetics are volume of distribution and drug clearance. Understanding the interplay between critical illness, drug pharmacokinetics, and antimicrobial characteristics (ie, time-dependent vs concentration-dependent) may improve antimicrobial efficacy and patient outcome.

Diagnosis: Utilizing bacterial culture and susceptibility can aid in identifying drug resistant infections, selecting the most appropriate antimicrobials, and hindering the future development of drug resistance.

Therapy: Having a basic knowledge of antimicrobial function and how to use diagnostics to direct therapeutic treatment is paramount in managing this patient population. Diagnostic testing is not always available at the time of initiation of antimicrobial therapy, so empiric selections are often necessary. These empiric choices should be made based on the location of the infection and the most likely infecting bacteria.

Prognosis: Studies have demonstrated the importance of moving away from a "one dose fits all" approach to antimicrobial therapy. Instead there has been a move toward an individualized approach that takes into consideration the pharmacokinetic and pharmacodynamic variabilities that can occur in critically ill patients.

KEYWORDS
antibiotics, cats, dogs, pharmacodynamics, pharmacokinetics

1 | INTRODUCTION

Human and veterinary patients in intensive care units (ICUs) have higher levels of illness severity and increased mortality rates compared to patients in general ward environments.[1–3] These patients often possess profound pathophysiological changes that require aggressive medical interventions.[2,3] There are increasing numbers of critically ill human and veterinary patients requiring antimicrobial treatment; however, the clinical outcomes for many subgroups of these patients are not improving substantially.[1,4] A retrospective study looking at two groups of dogs with septic peritonitis treated in a university hospital, the first group presenting from 1988 to 1993 and the second group from 1999 to 2003, showed no significant difference in survival rate over time (64 vs 57% respectively).[1] More recent studies for septic peritonitis in dogs have reported survival rates ranging from 44 to 70%.[5,6]

ICU patients are particularly likely to have or develop infection, in part because infection is the reason for admission and in part because

Abbreviations: ARC, augmented renal clearance; CLSI, Clinical and Laboratory Standards Institute; GFR, glomerular filtration rate; ICU, intensive care unit; MDR, multiple drug resistance; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; PAE, post-antibiotic effect; T>MIC, time above minimum inhibitory concentration; TDM, therapeutic drug monitoring; Vd, volume of distribution.

of immunosuppression associated with critical illness and the number of invasive devices used to support and monitor these patients. Appropriate and adequate antimicrobial coverage is essential in patients with infections, but can be difficult to achieve due to delayed identification of micro-organisms, the impact of critical illness on the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobials, and the high prevalence of antimicrobial-resistant strains of bacteria.[7]

The diagnosis of infection in critically ill patients and identification of the causative micro-organisms and their antimicrobial susceptibilities can be a challenge.[8] In studies of people with sepsis and septic shock, interventions that optimized antimicrobial therapy, such as early initiation of antimicrobials and appropriate drug choices, improved clinical outcomes the most.[9,10]

After many years of dosing antimicrobials in critically ill patients with a "one dose fits all" approach, there is now strong rationale in human medicine to move to a customized approach to dosing. The necessity for this change is further supported by the added problems of reduced antimicrobial development, the increasing occurrence of antimicrobial resistance, and therefore the need to make better use of the antimicrobials that are currently available.[11] Low et al stated: "The antibiotic era led to the widespread use and abuse of antimicrobials and to the global antimicrobial-resistance crisis that exists today. Although there is little we can do to prevent the evolution of resistance or to reverse it once it is established, we can reduce selection intensity (drug consumption): this may help impede the spread of antibiotic resistant organisms in humans and animals."[12]

In this review we will describe the means with which we determine the efficacy of a given antimicrobial against a certain bacterial pathogen and how this directs the selection of the antimicrobial agents that we use in practice. We will also discuss the alterations in PK and PD that can affect their function and how variations in standard antimicrobial therapy can ameliorate for these alterations.

2 | ANTIMICROBIAL MECHANISM OF ACTION

The means with which antimicrobials agents induce cell death (if bactericidal) or arrest bacterial growth (if bacteriostatic) is centered on the essential cellular function that is inhibited by the primary drug-target interaction. Bactericidal antimicrobials kill bacteria through the inhibition of cell wall synthesis (as with β-lactams) or through the inhibition of bacterial enzymes or protein translation (as with fluoroquinolones). Bacteriostatic antimicrobials function by interfering with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism (as with tetracyclines and chloramphenicol). Once bacterial growth is inhibited, the antimicrobial then relies on the immune system to remove the pathogen. Antimicrobial action generally falls within 1 of 4 mechanisms: via the inhibition of cell wall synthesis, protein synthesis, DNA synthesis, or RNA synthesis (Table 1).[13]

3 | PK/PD

Pharmacokinetics describes the time course of drug concentrations in the body (ie, how the body metabolizes a given drug). PK can explain why a drug may display a concentration-time profile in one patient group that is different than that of another group. For antimicrobial agents, PD is the discipline that links drug exposure (drug concentration) with bacterial killing or the inhibition of bacterial growth. In essence, PK is the effect the body has on a drug and the PD is the effect the drug has on the body (and on an infecting pathogen when discussing antimicrobials). Clinically relevant PD endpoints for antimicrobials include the effect of that antimicrobial on the infecting pathogen, the emergence of drug resistance, and the development of drug toxicity.[7]

Extreme PK variability of antimicrobial agents can be encountered in critically ill patients due to alterations in cardiac output, tissue perfusion, organ dysfunction, capillary leakage, and hypoalbuminemia.[14] The two principal factors that affect PK include the volume of distribution (Vd) and drug clearance.

4 | VOLUME OF DISTRIBUTION

The Vd is a proportionality constant that correlates the amount of drug in the body to the measured concentration in serum. Essentially Vd refers to the degree of dispersion of antimicrobial from the circulation to the surrounding tissues, specifically the interstitial space. Antimicrobials need to reach effective concentrations in the interstitial fluid of tissues, as this is the site of most infections.[15] An increase in Vd results in a reduction in peak drug concentration, whilst the area under the concentration curve remains unchanged.[16] Therefore, as the degree of dissemination of a drug around the body increases, this will cause the end concentration of that drug at its desired target to be lower. There are two exceptions to this concept. The first would be that an increased Vd may result in a greater loss of antimicrobial from the intravascular space, therefore actually increasing the concentration in the interstitial space.[17] The second would be the treatment of a urinary tract infection using a renally cleared antimicrobial in a patient with increased renal clearance. This concept, known as augmented renal clearance (ARC), will be discussed further in the next section. Conversely, patients that develop severe dehydration can actually have a decreased Vd resulting in reduced tissue perfusion.[18]

Increasing levels of sickness severity have been associated with increasing Vd. The increased Vd associated with critical illness is a result of critical illness-related pathophysiology (eg, vascular dysfunction, microvascular failure, fluid extravasation) and medical interventions, including fluid resuscitation.[16] Due to the possibility of critically ill patients having an increased Vd, they may therefore have reduced antimicrobial exposure at their site of infection when using standard dosing protocols.[17] Subtherapeutic concentrations of antimicrobials in tissues have been shown to be common in human patients in the early phases of treatment, particularly in patients with septic shock.[19]

The effect on changes to Vd is predominantly restricted to hydrophilic drugs (Table 1).[2] For this reason it has been recommended to administer loading doses of hydrophilic antimicrobials in critically ill human patients to ensure that therapeutic concentrations are achieved.[20] It has also been recommended to administer hydrophilic antimicrobials as extended infusions. The Vd for lipophilic drugs is usually high and often unchanged in critically ill patients compared to

TABLE 1 Antimicrobial characteristics

Mechanism of action	Antimicrobial class	Hydrophilic/ Lipophilic	Primary route of clearance	Side effects
Cell wall synthesis inhibitors (blocks crosslinking of peptidoglycan causing cell lysis)	Penicillins Cephalosporins Vancomycin Monobactams Carbapenems Bacitracin	Hydrophilic	Renal	Gastrointestinal upset Hypersensitivity Neurotoxicity
Protein synthesis inhibitors (inhibits 30S and 50S ribosomal subunits, preventing mRNA translation)	30S subunit inhibitors: Aminoglycosides Tetracyclines	 Hydrophilic Lipophilic	 Renal Renal/hepatic	Nephrotoxicity Hypersensitivity Gastrointestinal upset Delayed bone growth Esophageal stricture
	50S subunit inhibitors: Macrolides Chloramphenicol Clindamycin	Lipophilic	Hepatic	Gastrointestinal upset Hypersensitivity
DNA synthesis inhibitors (inhibits DNA gyrase and topoisomerase IV)	Fluoroquinolones Metronidazole	Lipophilic	Renal/hepatic	Gastrointestinal upset Neurotoxicity Cartilage damage Hepatotoxicity Hypersensitivity
RNA synthesis inhibitors (inhibits RNA polymerase)	Rifampin	Lipophilic	Hepatic	Discolored urine Gastrointestinal upset Hepatotoxicity Hypersensitivity

healthy volunteers.[2] A loading dose has not been recommended for lipophilic drugs in septic patients.[20]

For all antimicrobial classes, including concentration-dependent antimicrobials, an increased Vd can prolong the time needed to reach therapeutic concentrations.[11] With recovery from infection (and correction of the changes associated with critical illness), the Vd will return to normal resulting in the need for dose modifications throughout treatment during longer courses of antimicrobials.

5 | DRUG CLEARANCE

The clearance of a drug is defined as the volume of plasma completely cleared of drug per unit time.[16] The clearance of hydrophilic agents is predominantly via renal mechanisms while hepatic clearance is more common for lipophilic agents (Table 1).[20] The rate of drug clearance is greatly dependent on glomerular filtration rate (GFR), the presence of pre-existing renal or hepatic damage, hemodynamic alterations, and changes in the Vd.

Renal excretion of antimicrobials is particularly affected during critical illness. A reduction in GFR, as occurs in acute kidney injury, reduces the clearance of renally-excreted antimicrobials.[21] In contrast, due to a phenomenon known as ARC, the GFR in critically ill patients increases as a result of increased renal perfusion due to high cardiac output and low systemic vascular resistance, therefore increasing antimicrobial clearance. In some human cases of ARC antimicrobial clearance has been as much as tripled[22] and is a potential reason for underdosing.[11] It is believed that some critically ill patients with renal impairment might actually need more intensive regimens of antimicrobials. ARC is frequently seen in critically ill patients with normal serum creatinine concentrations and is most common in patients with trauma, sepsis, burns, hematological malignant disease, or pancreatitis.[23] Udy et al showed that up to 82% of human patients with documented ARC did not achieve therapeutic antimicrobial concentrations using standard doses.[24] Another study in people showed that patients that experienced ARC had a greater rate of therapeutic failure than patients that did not experience ARC (27.3 vs 12.9%, respectively).[25]

To a large extent, clinical and biochemical assessment of renal function in the ICU focuses on identifying acute kidney injury, with a goal of correcting potential causes, avoiding complications, and monitoring the need for renal replacement therapy. When renal dysfunction is suspected there is generally a prompt anecdotal dose reduction in renally eliminated drugs; however, escalating drug doses in response to ARC is infrequently considered in clinical practice. There has been growing evidence in human medicine demonstrating the importance of recognition and management of ARC in critical illness, particularly with antimicrobial drug dosing as accurate and timely drug exposure is essential for clinical success.[22] This concept needs to be further investigated in veterinary populations.

6 | BACTERIAL CULTURE AND DETERMINATION OF SUSCEPTIBILITY

The principal goal of antimicrobial therapy is eradicating the underlying infection and resolution of its clinical impact while trying to avoid adverse effects and the development of drug resistance. To achieve this, a culture should be taken from the suspected site of

infection in attempt to identify the infecting pathogen and to determine its antimicrobial susceptibilities. This culture would then allow for the determination of a minimum inhibitory concentration (MIC) for the bacteria grown. MIC is defined as the lowest concentration of an antimicrobial agent that will inhibit the visible growth of a micro-organism after overnight incubation.[26]

Most laboratories report bacterial susceptibility to antimicrobials as susceptible, intermediate-susceptible, or resistant. These classifications are made based on MIC breakpoints (ie, the concentration at which a bacterium is deemed either susceptible or resistant to the antimicrobial being investigated). It is important to note that some labs do not report the actual MIC value and only provide the diagnostic interpretation (ie, susceptible vs resistant). In the face of critical illness, however, it is important to be aware of the measured MIC value as it will be a guide in formulating the most appropriate dosing regimen for the antimicrobials chosen.

MIC breakpoints are reported by groups, such as the Clinical and Laboratory Standards Institute (CLSI), which often determines these values derived from non-critically ill people. There is a subcommittee of CLSI that then disseminates the interpretive criteria that applies to animal approved drugs and makes recommendations regarding the applicability of the human drug guidelines.[11,27] Although the majority of the microbes investigated by CLSI are similar between people and animals, extrapolation of antimicrobial PK/PD data among the species is questionable, particularly for drugs that are orally administered or are lipophilic.[27] As an example, the oral bioavailability of ciprofloxacin, a lipophilic antimicrobial, in dogs and cats has been reported to be 40 and <20% respectively, while in people its bioavailability is 80–100%.[28,29] This difference in bioavailability can result in lower antimicrobial concentrations reaching the target site and possibly reduce its efficacy.

7 | CHALLENGES WITH BACTERIAL SUSCEPTIBILITY: EFFECT OF BACTERIAL MIC ON THERAPY

Knowledge of the MIC for an antimicrobial against a pathogen is essential in order to calculate the dose needed. The MIC is a critical factor in the PK/PD relationship and defines how much antimicrobial exposure is necessary to achieve predefined PK/PD targets that would be associated with maximal effectiveness.[11]

Infections in human ICU patients are often caused by pathogens with higher MICs than those encountered in other clinical settings.[30] A study comparing critically ill people to other patients showed that the MIC needed to kill 90% of gram-negative isolates was 4–8 times higher in those that were critically ill.[31] This decrease in susceptibility is likely multifactorial and is influenced by the severity of disease, the presence of MDR pathogens within the ICU, and the increased use of antimicrobials.[30] For time-dependent antimicrobials it has been shown that the exposure needed to achieve PK/PD targets rises proportionally with increasing MIC,[11] and when serum concentration falls below the MIC, bacterial multiplication occurs immediately.[32]

8 | EFFECT OF BACTERIAL RESISTANCE ON THERAPY

Another difficulty in the treatment of infections in critically ill patients is reduced bacterial susceptibility to routinely used antimicrobials.[33,34] Antimicrobial drug resistance is primarily a genetic process that occurs through either spontaneous mutation within a microbe or by horizontal gene transfer between microbes. Horizontal gene transfer is of considerable concern as this mode of resistance often occurs to multiple drugs and can spread from one bacterium to another rapidly during times when the serum antimicrobial concentration is low.[35] The standard method of reporting MIC values are as either susceptible, intermediate, or resistant. This approach might not be suitable for critically ill patients as a patient's MIC may be determined to be susceptible to a particular antimicrobial, but the PK/PD targets may still not be able to be achieved due to the profound PK changes associated with critical illness. Furthermore, standard, fixed antimicrobial regimens for infections with pathogens that have MICs close to the resistance breakpoint may result in the possibility of underdosing.[11,36]

A study of 74 dogs who were admitted to a tertiary referral veterinary teaching hospital with bacterial cultures submitted within the first 48 hours of admission were found to have a multiple drug resistant (MDR) isolation rate of 27%.[34] Repeat cultures that were then performed after 48 hours of hospitalization showed that the isolation of MDR infections had increased to 59% ($P < 0.001$).[34] This finding highlights the high prevalence of MDR development in critically ill patient populations, even after antimicrobial therapy has been initiated. This increased rate of MDR isolation is likely due to altered selection pressure from the antimicrobials being used (caused by killing of susceptible bacteria while allowing antimicrobial resistant bacteria to survive and multiply) and emphasizes the need to focus antimicrobial treatment regimens on preventing this from occurring.

9 | TIME-DEPENDENT VERSUS CONCENTRATION-DEPENDENT ANTIMICROBIALS

The bacterial killing characteristics of antimicrobials are mostly characterized in terms of time-dependent and concentration-dependent killing (Table 2). With time-dependent antimicrobials bacterial killing occurs when the drug concentration exceeds the MIC of the infecting pathogen.[37] This is often expressed as time above minimum inhibitory concentration (T>MIC), or the amount of time that the serum concentration of an antimicrobial agent is greater than the MIC of the infecting organism. Ideally this concentration would exceed the MIC for as much time as possible (ie, a T>MIC as close to 100% as possible). It has been demonstrated that maximal bacterial killing is achieved when antimicrobial concentrations are maintained at 4–5 times the MIC of the infecting pathogen.[38] Maintaining a T>MIC of 100% is more important in critically ill patients that have altered or diminished immune function, as healthier patients will still possess adequate

TABLE 2 Time-dependent versus concentration-dependent antimicrobials

Time-dependent (with minimal or no PAE)	Concentration-dependent (with PAE)	Time-dependent, concentration enhanced (with PAE)
Penicillins	Aminoglycosides	Clindamycin
Cephalosporins	Fluoroquinolones	Erythromycin
Vancomycin	Metronidazole	Linezolid
Monobactams	Azithromycin	Tetracyclines
Carbapenems		

PAE, post-antibiotic effect

immune function to combat an infection in the event of a serum antimicrobial concentration that is below the MIC.

In concentration-dependent antimicrobials the maximum antibacterial effect occurs when the peak drug concentration exceeds the MIC several times (>8–10 times).[37] These antimicrobials generally work through the inhibition of DNA synthesis and therefore inhibit bacterial growth. Following their administration, there is sustained suppression of bacterial growth due to the need for the bacteria to synthesize new proteins before their growth can continue. This is a theory known as the post-antibiotic effect (PAE). The duration of this suppression is what dictates the frequency with which the antimicrobial will need to be given (i.e., once a day administration for aminoglycosides). The PAE may be absent for some organisms or some patients, especially those that are immunocompromised. The duration of PAE varies with each antimicrobial, each pathogen, and each patient.[27]

There is a third PD category of antimicrobials that have prolonged PAEs, but have been classified as time-dependent. These have been termed time-dependent, concentration enhanced antimicrobials. This group primarily consists of bacteriostatic agents (see Table 2).

10 | THERAPY

When a serious infection is suspected the early administration of antimicrobials, the appropriateness of the initial empirical antimicrobials selected, and the early achievement of therapeutic levels (ideally after the first dose) are the 3 pillars of effective antimicrobial therapy. Applying these principles will reduce the microbial burden, therefore reducing the risk of irreversible shock and death.[9]

11 | EARLY INITIATION OF ANTI-MICROBIAL THERAPY

Delay in the initiation of appropriate antimicrobial therapy is associated with a higher microbial load, which is then associated with increased morbidity and mortality.[9] The optimal goal of antimicrobial therapy is to rapidly reduce the microbial load and to minimize the time that systemic inflammatory stress is able to develop.[39] The early initiation of appropriate antimicrobial therapy with optimized speed of bacterial clearance should reduce the risk of reaching individually indeterminate pathophysiologic points at which recovery is no longer possible and can be associated with improved morbidity and mortality.[40,41]

A retrospective analysis of septic shock in people suggested that delaying the initial administration of an effective antimicrobial is the single strongest predictor of non-survival. This study showed that every hour of delay in appropriate antimicrobial administration in the first 6 hours after hypotension is documented led to a decrease in survival by 7.6%.[9] These results have not always been repeatable in other studies investigating the timeliness of antimicrobial administration in septic shock,[42] however similar findings have been documented in studies looking at sepsis without concurrent shock.[43,44] In view of this data, intravenous administration of broad-spectrum antimicrobials should be initiated as rapidly as possible in response to the clinical suspicion of infection in the presence of hypotension.[41]

In a busy emergency room or ICU, it can often be challenging to implement antimicrobial therapy in the time frame outlined by these studies. It has been recommended for hospitals to have a sepsis protocol that can be used to assist clinicians in earlier diagnosis of sepsis and therefore reduce the amount of time to antimicrobial administration. Such a protocol was studied for aiding in the diagnosis of abdominal sepsis in dogs presenting to a university teaching hospital.[5] In this study, the median time to antimicrobial administration following sepsis diagnosis prior to the protocol implementation was 6 hours. After implementing the protocol, this was reduced to 1 hour. Furthermore, dogs that met the guidelines for antimicrobial administration as recommended by the Surviving Sepsis Campaign only received antimicrobials 10% of the time prior to protocol use compared to 87.5% following utilization of the protocol.[5]

12 | CHOOSING APPROPRIATE EMPIRIC ANTIMICROBIAL THERAPY

Empiric antimicrobial therapy must cover every reasonably likely pathogen, as failure to initiate antimicrobial therapy to which the infecting pathogen is susceptible is associated with marked increases in mortality, especially in cases of septic shock. Inadequate antimicrobial therapy is started frequently, with an occurrence in human medicine of 15–35%. Recent data suggests that inappropriate empiric antimicrobial treatment reduces survival 5-fold in serious infections with septic shock.[45]

Black et al showed that dogs in an intensive care population, on average, received 3 antimicrobials per patient throughout their hospitalization, with ampicillin and enrofloxacin being the most commonly used.[34] When these antimicrobial therapies were chosen empirically they were determined to have been appropriate in 75% of cases once susceptibility reporting was available.[34] A similar study showed empiric antimicrobial choices in dogs with septic peritonitis to be appropriate in only 52.6% of cases.[46] In this study there was no significant difference in survival to hospital discharge between dogs treated with appropriate antimicrobial choices (58.5%) compared to those that received inappropriate antimicrobial choices (52.6%), which is in

contradiction to similar human studies.[45] This dichotomy is suspected to be due to a small sample size (78 dogs) and only including patients with septic peritonitis and not other forms of sepsis. This study also did not account for the timing of antimicrobial administration following the diagnosis of sepsis.[46]

Another study looking at dogs with bacterial pneumonia in a university teaching hospital showed that 26.1% of the dogs had at least one bacterial isolate that was resistant to the empirically selected antimicrobials and that these dogs also had longer median hospital stays (5 vs 3 days), however this did not reach statistical significance ($P = 0.0729$). In the same group of dogs, those that had been started on antimicrobials before presentation to the hospital were found to have 57.4% of bacterial isolates that were resistant to the initial antimicrobial therapy.[47] It was discussed that the antimicrobial empirically chosen were very similar to the ones used in previous studies of dogs with pneumonia and were adherent to current antimicrobial recommendations. [48–52] For this reason, in tandem with current human recommendations, it may be prudent to avoid recently administered antimicrobials as part of the initial empiric therapy.[53] Boothe suggests that a 3-month antimicrobial-free period should elapse before a patient can be considered antimicrobially naïve, however this has not been scientifically validated.[27]

13 | SELECTION OF ANTIMICROBIAL SPECTRUM

When selecting antimicrobials to use in serious infections it is recommended to have a culture and susceptibility to aid in the selection process. Due to the amount of time needed to perform a culture and susceptibility empiric antimicrobial treatment often needs to be implemented before these results are obtained. The empiric antimicrobial choice(s) should be made based on the location of the infection and the suspicion of the most likely infecting bacterial organisms (ie, facultative and obligate anaerobes from gastrointestinal sources). Geographical location, time of year, and common bacterial isolates from within a hospital should also be taken into consideration. It is also important to consider the susceptibilities of previously documented infections in a patient, especially if those microbial agents had known drug resistance. New antimicrobial selections in these patients should be based around the possibility of continued drug resistance for the reported agents. As discussed previously it is also suggested to avoid antimicrobial classes that had been administered in the previous 3 months.

For severe infections broad spectrum coverage is ideal. To achieve this spectrum of coverage the 4 quadrant technique (Figure 1) is often used in which the antimicrobial(s) chosen are effective against both Gram-positive and Gram-negative organisms and have aerobic and anaerobic coverage.[54] Cytologic analysis from the site of infection (ie, aspiration, impression smear) is a quick and easy diagnostic that can be used to help narrow empiric antimicrobial choices based on the microbial morphology (cocci vs bacilli) and staining properties (Gram-positive vs Gram-negative).

14 | COMBINATION VERSUS MONOTHERAPY FOR EMPIRIC ANTIMICROBIAL THERAPY

There has been, and still is, considerable debate regarding the potential benefits of combination versus monotherapy in the empiric management of infection in critically ill patients. Advantages of combination therapy are that they provide a greater overall spectrum of activity and can prevent the emergence of resistance.[7] It also has the possible advantage of synergism between the two drugs, resulting in improved bacterial killing.[41,55] Nevertheless, clinical studies have been unable to demonstrate an effect of synergy on outcome.[56,57] Disadvantages of combination therapy include an increased risk for toxicity/adverse effects,[58] increased risk for the development of resistance,[59] increased cost, and possible antagonism between the drugs.[7]

The increased risk of MDR development can occur when susceptible organisms are killed by the selected antimicrobial regimen, but the growth of resistant subpopulations of bacteria occurs.[27,34,47] Healthy patients that are immunocompetent can successfully suppress an emergent infection, explaining why lower doses of antimicrobials are often successful at resolving their infections despite the potential for emergent resistance. Critically ill patients may lack these means of dealing with emergent bacterial populations, making new and concurrent infections more likely.[27] Resistant organisms that develop can then be shed into the environment, increasing the risk for spread through an ICU population.[35] For this reason empiric combination therapy is recommended to be initiated for the first few days of treatment, however it must be adjusted to a narrower regimen in the first 72 hours, if possible, to minimize selection pressure toward resistant organisms.[41]

In a study of human patients with septic shock, combination therapy of a beta-lactam with other antimicrobials was associated with a decrease in 28-day mortality compared with beta-lactam monotherapy.[60] Additional studies have been unable to demonstrate an advantage of combination therapy over monotherapy, however these studies have compared different antimicrobial regimens in varying patient populations, making it difficult to generalize the results.[61–64] Kumar et al stratified 50 studies according to baseline mortality risk and was able to show that combination therapy was consistently associated with a benefit in the more severely ill patients.[65] Kumar et al also conducted a study evaluating the therapeutic benefit of early combination therapy with at least two antimicrobials with confirmed activity against the isolated pathogen versus monotherapy. The results showed an improved 28-day survival (36.6 vs 29%) and a reduction in ICU mortality (28.8 vs 35.7%) and hospital mortality (37.4 vs 47.8%). The antimicrobials used in this study were limited to the β-lactams family in combination with aminoglycosides, fluoroquinolones, and macrolides.[60]

It is challenging to make conclusions from these and similar studies in that they often do not compare the same antimicrobial in monotherapy and in combination therapy. Usually, a more pharmacodynamically potent agent in monotherapy is compared to a combination of two less potent agents. Overall, despite the efforts to examine the issue of

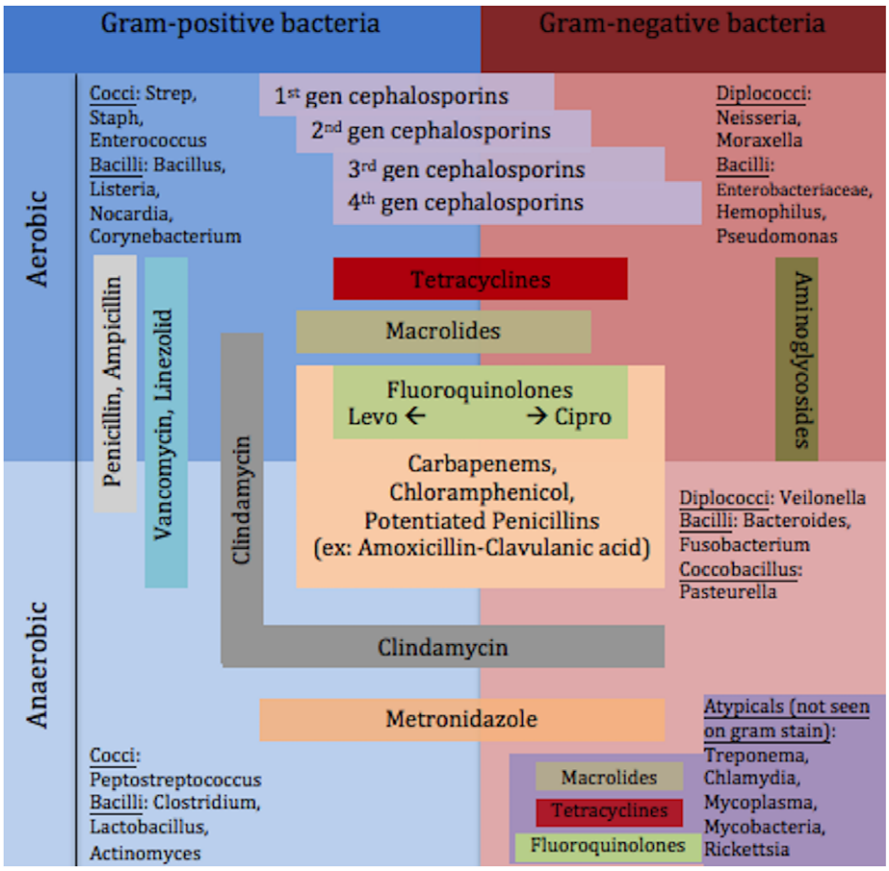

FIGURE 1 Antimicrobial spectra. Common antimicrobial susceptibilities illustrated over a 4 quadrant chart of bacterial pathogens based on their classification of Gram-positive versus Gram-negative and aerobic versus anaerobic. Pathogens that do not fit into this classification scheme (ie, atypicals) are documented in the lower right hand quadrant of the chart. For the antimicrobials in the center of the chart that provide 4-quadrant coverage it is important to be aware that there are organisms that fall into these classifications but might not have susceptibility to one of these antimicrobials (ie, *Pseudomonas* infections are commonly resistant to amoxicillin-clavulanic acid). Note that this chart does not account for antimicrobial resistance

combination therapy versus monotherapy, the results have been contradictory and the question has not yet been definitively answered. While waiting for appropriately designed randomized controlled trials, the combination of empiric antimicrobial therapy for several days with two drugs of different mechanisms of action can be considered appropriate for patients in septic shock. Monotherapy is reasonable for patients who are not critically ill and do not have a high risk of death.[41]

15 | ESCALATION AND DE-ESCALATION OF ANTIMICROBIAL THERAPY

Decisions regarding empiric antimicrobial therapy are based on 2 approaches: a judgment that the likely organism has a normal susceptibility and can therefore be treated as such with the possible need for escalation to second-line drugs after microbial identification;[7,11] or a judgment based on local microbiology patterns and clinical presentation, that the infecting organism may be MDR and should be treated as such, with possible de-escalation to a simpler antimicrobial regimen after antimicrobial susceptibilities are known. More frequently the latter approach is used in ICUs to ensure all possible causative organisms are initially covered.[7] More than 50% of isolates in human ICUs and 59% in veterinary ICUs have been shown to be resistant to at least one antimicrobial, suggesting that broad spectrum empiric therapy is more warranted in these units. Once the susceptibilities are known the spectrum can be de-escalated accordingly.[34,66]

There are no studies that have suggested that early narrowing of therapy is detrimental if the organism susceptibility is identified or if the patient is responding clinically well.[41] Several human studies have shown that de-escalation of antimicrobial therapy is associated with improved outcomes,[67–69] however one study showed that de-escalation may actually be feasible in <50% of cases.[70] Other studies on de-escalation have reported conflicting effects on outcome in various groups of critically ill patients.[71–73] In a veterinary ICU population, antimicrobial escalation rates have been reported to be around 22% and de-escalation rates around 31%.[34] It is recommended that de-escalation to a narrower spectrum should occur within 48–72 hours after initiation of treatment if a plausible pathogen is identified or if the patient stabilizes clinically to reduce the potential for antimicrobial resistance emergence.[27,39]

16 | OPTIMIZING THE OBTAINMENT OF PK/PD TARGETS

When treating infections improved outcomes are achieved when PK/PD targets associated with maximum antimicrobial activity are met. As discussed previously, early appropriate antimicrobial therapy is the central element in the management of septic shock, but clearance of pathogens will not begin until therapeutic levels of the antimicrobials in the circulation are reached.[41] The increased Vd that many antimicrobials may experience in critically ill patients can result in failure to achieve therapeutic levels at the target site when using standard dosing. There is emerging research showing that loading doses of some of these antimicrobial can prevent this, potentially yielding improved clinical outcomes.[74–76]

For time-dependent antimicrobials the key PK parameter for optimization of pathogen clearance is the T>MIC. There are relatively few studies in human medicine and none in veterinary medicine examining the role of T>MIC in serious infections, but those that have been performed in human medicine have been associated with improved bacterial eradication and clinical cure.[77] There are two main approaches used outside of standard antimicrobial dosing to increase the probability of achieving therapeutic targets in critically ill patients: the use of extended or continuous infusions of time-dependent antimicrobials,[7] and making dose adjustments during treatment guided by therapeutic drug monitoring. Some experts advocate using both approaches together.[11]

Several PK studies in humans investigating the use of beta-lactam antimicrobials have collectively suggested that extended infusions should be used in patients that are critically ill (either to 40–50% of the dosing interval or as a continuous infusion), as this method is more likely to achieve PK/PD targets than standard bolus dosing.[21,78–81] There have been a number of prospective studies that have repeatedly shown extended and continuous infusions to achieve higher steady state concentrations compared to trough concentrations with bolus dosing, however they have not always been correlated with a clinical advantage.[81–83] A reason for this may be that many of these studies were not stratified for patients with altered PK or reduced antimicrobial susceptibility. Many of these studies had a higher proportion of susceptible pathogens with lower MICs, allowing for standard regimens to more easily reach the desired PK/PD targets.[84]

A recent randomized controlled human trial showed a significantly higher clinical cure rate following administration of beta-lactam antimicrobials by extended infusion.[81] A more recent meta-analysis concluded that the administration of piperacillin-tazobactam or carbapenems by infusion, rather than bolus administration, was associated with a lower mortality rate.[85]

17 | THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) relies on direct measurement of serum antimicrobial concentrations with timely reporting back to the clinician. Adjustments can then be made to the antimicrobial treatment regimen by direct comparison of the measured value to a therapeutic target (ie, MIC). TDM has traditionally been used to minimize toxic effects, but in critically ill patients it can be used for the determination of antimicrobial dosing in the presence of severely altered PK.[86,87]

A randomized, controlled human trial showed that a dedicated TDM intervention in a general patient group significantly reduced their length of hospitalization compared to patients that did not have TDM (20.3 vs 26.3 days, respectively).[88] Studies with quinolones, β-lactams, glycopeptides, and linezolid have shown advantages in clinical cure, mortality, or both associated with achievement and maintenance of target PK/PD indices.[86,89–92]

TDM usually measures total drug concentrations (bound and unbound drug), sometimes making interpretation difficult. The concentration of unbound drug in a blood sample is important for accurate interpretation of drug exposure, as it is only the free drug that is microbiologically active. Knowledge of free concentrations is especially important for antimicrobials that are highly protein-bound in plasma.[93] Furthermore, because most infection occurs in tissue interstitial fluid, the antimicrobial concentration measured in the plasma is actually often only a surrogate for the true concentration at the site of infection and may over- or underestimate the actual interstitial fluid concentration.

Tissue penetration studies using microdialysis catheters suggest impaired tissue penetration by some antimicrobial agents in critically ill human patients. Low interstitial fluid concentrations, as much as one-tenth than is observed in plasma, have been described.[19] The clinical consequences of impaired penetration are yet to be defined, but may in part explain the findings of some clinical evaluations that have proposed that higher than previously considered necessary plasma antimicrobial concentrations may be required to achieve adequate interstitial fluid concentrations and therefore clinical cure in some critically ill patients.[16] TDM in veterinary medicine is routinely used for certain anticonvulsant and immunosuppressive drugs, however its use in antimicrobial dosing has not been evaluated and testing is not readily available. The aim of future studies should be to better determine the relationship between serum and interstitial fluid concentrations in critically ill veterinary patients and how to relate this to the use of TDM and clinical outcome.

18 | WHEN TO DISCONTINUE TREATMENT

Longer courses of antimicrobials are associated with MDR pathogen selection and spread, increased risk of toxicity, and higher costs. Antimicrobial courses that are too short risk inadequate bacterial eradication and the possibility of relapse. Current guidelines from the Surviving Sepsis Campaign[94] advise a 7–10 day course, unless clinically indicated otherwise (initial clinical failure, slow clinical response, undrainable foci of infection, immunologic deficiencies). Infections caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa* may also warrant prolonged courses to avoid treatment failure, early relapses, or metastatic complications. A meta-analysis of critically ill human patients showed no difference in microbial eradication, clinical cure,

or survival when using shorter antimicrobial regimens (5–7 days) compared to longer regimens (7–21 days).[95] Decisions regarding duration of antimicrobial therapy need to be determined on an individual basis, taking into consideration the severity of the illness, response to treatment, the type of infection, and whether adequate source control is able to be accomplished.[7,96–98] Ultimately, the decision to discontinue therapy is at the discretion of the attending clinician based on how the patient is doing clinically.[94]

19 | CONCLUDING REMARKS

Recent studies in human and veterinary medicine have provided an important glimpse into the relevance of PK/PD issues in the management of critically ill patients and challenges clinicians to move away from the "one dose fits all" strategy that has been traditionally employed in clinical medicine and towards a more personalized antimicrobial dosing that is individualized to the physiology of the patient being treated. These changes are often unpredictable and new techniques including direct measurement of drug concentrations and alternate dosing approaches may increasingly be employed to ensure doses are adequate.[11] There is a need for prospective, randomized, controlled studies in veterinary medicine on much of the information discussed in this review. With future investigations into these areas we could potentially weaken antimicrobial resistance progression, enhance the therapeutic effect of commonly used antimicrobial, and see improved clinical outcomes for our patients.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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