CHAPTER 93

GRAM-POSITIVE INFECTIONS

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KEY POINTS

- Most gram-positive infections are caused by normal resident microflora of the skin, mucous membranes, and gastrointestinal tract.
- Critically ill hospitalized patients are at increased risk for infections with opportunistic gram-positive bacteria.
- *Streptococcus canis* is a well-recognized cause of various suppurative infections in animals, including toxic shock syndrome.
- Enterococci, traditionally viewed as commensal bacteria in the alimentary tract of animals, are known to be capable of causing life-threatening, multidrug-resistant infections in dogs and cats.
- As antibiotic-resistant staphylococci evolve, the ability to treat staphylococcal infections in companion animals with cephalosporins, penicillins, and fluoroquinolones is decreasing.

Since the early 1990s the epidemiology of pathogenic bacteria isolated from critically ill patients has shifted from gram-negative organisms to an increasing number of nosocomial infections caused by gram-positive isolates.[1,2] Increasing numbers of pathogenic, multidrug-resistant (MDR) gram-positive organisms now are being isolated from dogs and cats, paralleling the trend in antibiotic-resistant nosocomial and community-acquired infections in humans.[3,6] Awareness of emerging trends of resistance, particularly in *Enterococcus faecium* and various strains of staphylococci, militates against indiscriminate antimicrobial use and provides a basis for appropriately treating critically ill patients suffering from such infections.[7,8]

GRAM-POSITIVE CELL STRUCTURE AND PATHOGENICITY

Morphologically, gram-positive bacteria are composed of a cell wall, a single cytoplasmic membrane, and cytosol.[9-11] The cell wall is a thick, coarse structure that serves as an exoskeleton. Buried within the cell wall are enzymes called *transpeptidases,* commonly referred to as *penicillin-binding proteins (PBPs)*. PBPs are a group of enzymes responsible for the building and maintenance of the cell wall.[9,10]

In addition to a thick cell well, most gram-positive bacteria have other protective mechanisms. One of these mechanisms is an outer capsule or biofilm that extends beyond the cell wall and interfaces with the external milieu.[9,10] Hydrolase enzymes located within the cytoplasmic membrane, called *β-lactamases,* serve a protective role for the bacteria.[9,10] Once attacked by the hydrolases, the β-lactam antibiotics are no longer capable of binding to PBPs in normally susceptible bacteria.

Peptidoglycan is the basic structural component of the cell wall of gram-positive bacteria, accounting for 50% to 80% of the total cell wall content. Like endotoxin, peptidoglycan is released by bacteria during infection, reaches the systemic circulation, and exhibits pro-inflammatory activity.[9,10] Lipoteichoic acids found in the gram-positive cell wall have structural and epithelial adherence functions. Lipoteichoic acid induces a proinflammatory cytokine response, the production of nitric oxide, and may lead to cardiovascular compromise.

In addition to structural components, gram-positive organisms produce soluble exotoxins that may play a role in the pathogenesis of sepsis. Much attention is focused on the roles of superantigenic exotoxins that promote the massive release of cytokines, potentially leading to shock and multiorgan failure in human and veterinary patients.[6,9]

STREPTOCOCCAL INFECTIONS

The genus *Streptococcus* consists of gram-positive cocci arranged in chains.[11,12] These are fastidious bacteria that require the addition of blood or serum to culture media. They are nonmotile and non–spore forming. Most are facultative anaerobes and may require enriched media to grow.[9,12] Streptococci are generally commensal organisms found on the skin and mucous membranes and are ecologically important as part of the normal microflora in pets and humans.[11,12] However, several species of streptococci are capable of causing localized or widespread pyogenic infections in companion animals.[11]

Streptococci may be grouped superficially by how they grow on blood agar plates as either hemolytic or nonhemolytic.[9,13] The type of hemolytic reaction displayed on blood agar has been used to classify the bacteria as either α-hemolytic or β-hemolytic. β-Hemolytic species are generally pathogenic, and nonhemolytic or α-hemolytic members of the genera have been viewed traditionally as contaminants or unimportant invaders when isolated.

Streptococci also are classified serologically based on species-specific carbohydrate cell wall antigens, with groups designated A through L.[9,11,12] Group A streptococci *(Streptococcus pyogenes)* cause pharyngitis, glomerulonephritis, and rheumatic fever in humans.[11-13] Although dogs may become colonized transiently with this organism, group A streptococci rarely cause illness in dogs and cats.[11] Therapy generally is not indicated, but these organisms are susceptible to most β-lactam agents, macrolides, and chloramphenicol.

The group B streptococci, which are all strains of *Streptococcus agalactiae,* infrequently cause infections in dogs and cats.[11] Rare infections with *S. agalactiae* have been associated with metritis, fading puppy syndrome, and neonatal sepsis in dogs, and septicemia and peritonitis in parturient cats.[11] Similarly, group C streptococci are rare causes of illness in immunocompetent pets. Species included in this serologic group include *Streptococcus equi* ssp. *zooepidemicus* and *Streptococcus dysgalactiae.* Sporadic cases of endometritis, wound infections, pyelonephritis, lymphadenitis, and neonatal sepsis resulting from infection with β-hemolytic group C streptococci have been reported in dogs and cats. The number of reports of outbreaks of hemorrhagic pneumonia in dogs caused by *S. equi* ssp. *zooepidemicus* is limited but increasing. This acute, highly contagious, and often fatal disease most often is reported in dogs housed in shelters and

research kennels. Clinical findings include moist cough, sanguinous nasal discharge, fever, and acute respiratory distress.[6] Postmortem findings reveal fibrinosuppurative, hemorrhagic, and necrotizing pneumonia. Pleural effusion is also common.[6,11] As with most streptococci, isolates frequently were susceptible to ampicillin and amoxicillin. Some isolates were susceptible to doxycycline. Isolates of *S. equi* ssp. *zooepidemicus* were found to be susceptible in vitro to enrofloxacin.[6] However, many streptococci are intrinsically resistant to second-generation fluoroquinolones, and thus single-agent therapy with enrofloxacin is not recommended for any streptococcal infections.[14] The combination of penicillin and an aminoglycoside was found to be effective in one study.[15]

Group G streptococci are common resident microflora and are the cause of most streptococcal infection in dogs and cats.[9,11] The most common isolate is *Streptococcus canis.*[9,11] The main source of infection with this pathogen in dogs is the anal mucosa; young cats more commonly acquire infection from the vagina of the queen or via the umbilicus.[11] Infection spreads rapidly in neonatal kittens and is often fatal during the first week of life in affected cats. *S. canis* may be isolated from adult cats with abscesses, pyelonephritis, sinusitis, arthritis, metritis, or mastitis, and from kittens with lymphadenitis, pneumonia, or neonatal septicemia.

S. canis is generally an opportunistic pathogen of dogs and is isolated from an array of nonspecific infections, including wounds, mammary tissues, urogenital tract, skin, and ear canal.[10,11] *S. canis* is a cause of canine prostatitis, mastitis, abscesses, infective endocarditis, cholangiohepatitis, pericarditis, pyometra, sepsis, discospondylitis, and meningoencephalomyelitis.[11] *S. canis* has also been implicated in cases of fading puppy syndrome, causing polyarthritis and septicemia in affected pups.[11]

Despite 50 years of penicillin use in animals, no mechanism of resistance to the drug in β-hemolytic group G streptococci has been documented; penicillin G and ampicillin are therefore effective for most infections.[2,10,11] Erythromycin, clindamycin, potentiated sulfonamides (TMP-SMZ), and most cephalosporins are also usually efficacious. Susceptibility to veterinary-approved fluoroquinolones is negligible, and their use generally is discouraged for streptococcal infections.[14,16] *Streptococcus* spp. generally are not considered susceptible to aminoglycosides, owing to poor transport across the cytoplasmic membrane.[2] However, combination therapy with a β-lactam agent and an aminoglycoside is an appropriate treatment strategy for critically ill animals with streptococcal bacteremia or endocarditis.[2,14] Combination therapy is also recommended for cases of infective necrotizing fasciitis and myositis (NFM) (see Empiric Antibiotic Strategies), endocarditis, or when polymicrobial infections are suspected. Although long-term (at least 6 weeks) therapy is recommended for treating unstable patients with disseminated infection, in most clinical settings aminoglycosides are rarely prescribed for this duration due to concerns for drug-associated nephrotoxicity.

Over the past decade, streptococcal toxic shock syndrome (STTS), with or without necrotizing fasciitis and myositis (NFM) resulting from infection with *S. canis*, has emerged as a recognized syndrome in dogs (see Chapter 101).[9,11,17] The most common source for infection in animals with STTS appears to be the lung, with occasional reports of affected dogs suffering from acute or peracute suppurative bronchopneumonia. Some case histories have included failed attempts to treat patients with enrofloxacin and nonsteroidal antiinflammatory agents.[11,18] Cases of STTS-associated septicemia are often fatal, whereas most dogs with NFM alone survive with prompt, appropriate medical therapy and aggressive surgical resection (see Chapter 139).[11,18]

The most likely pathogenesis for STTS and NFM starts with minor trauma. The dog then licks its wounds and seeds *S. canis* from the oral mucosa into the wound. The bacteria proliferate, typically resulting in painful, rapidly developing cellulitis, skin discoloration, and often signs of systemic illness.[17] Prompt recognition and aggressive surgical debridement are imperative. Clindamycin has proven to be effective therapy in affected animals.[11,17] Aminopenicillins, erythromycin, and β-lactam antibiotics also may be effective.[11] Culture and susceptibility testing is important because similar toxic shock–like diseases in dogs may be caused by bacteria other than streptococci. Gram staining of tissues or fluids should be helpful in ascertaining the morphology of the infecting agent, particularly in acute infections. A similar syndrome in young cats with suppurative lymphadenopathy and multifocal ulcerative skin lesions caused by group G streptococci has been reported.[11]

ENTEROCOCCAL INFECTIONS

Enterococcus species are facultative anaerobic cocci that demonstrate intrinsic and acquired resistance to multiple antibiotics. Unlike streptococci and staphylococci, most enterococci do not produce reliably a set of proinflammatory toxins, but they are equipped with many genes that mediate adhesion to host tissues.[7] Enterococci (previously group D streptococci), as the name implies, are commensal bacteria that inhabit the alimentary tract of animals and humans.[9,12] Enterococcal infections previously were considered rare, and not especially virulent, in companion animals. Presently, enterococcal infections are a leading cause of nosocomial disease in human health care, and pathogenic and multidrug resistant (MDR) enterococci are recovered increasingly from hospitalized veterinary patients.[1,11]

Postoperative wound and urogenital infections are seen most commonly; however, enterococcal cholangiohepatitis, peritonitis, vegetative endocarditis, mastitis, and blood-borne infections have been reported in companion animals.[11,19] Many enterococci are intrinsically resistant to numerous antibiotics, and the development of MDR enterococci is thought to result from inappropriate antimicrobial usage and poor infection control measures in hospitalized patients.[11,12,19] The majority of clinical isolates belong to the species *Enterococcus faecalis,* although *Enterococcus faecium* remains the species that exhibits a disproportionately greater resistance to multiple antibiotics.[11,19]

E. faecium is increasingly resistant to vancomycin, which was effective for almost all penicillin-resistant enterococci until recently.[9,11,19] Strains that remain susceptible to vancomycin may be resistant to a wide range of drugs that are selected empirically for managing bacterial infection in critically ill patients.[11,19] *E. faecium* often possesses inherent and acquired resistance to many drug classes, including the fluoroquinolones, lincosamides, macrolides, and potentiated sulfonamides (TMP-SMZ).[7,11,19] Unlike most streptococci, enterococci are often inhibited, but not killed, by penicillins and are generally resistant to cephalosporins.[2] Moreover, although enterococci do not often intrinsically produce β-lactamases, production of these enzymes by the bacteria may be induced by exposure to β-lactamase–inhibitor drugs. As such, it is not appropriate to prescribe amoxicillin-clavulanate or ampicillin-sulbactam for an enterococcal isolate that is reported to be susceptible to ampicillin. Until recently, aminopenicillin monotherapy was successful for many enterococcal infections. However, this is no longer predictable. Presently, many isolates are resistant to aminopenicillins and many other antimicrobials that were previously effective in managing gram-positive infections.[2,11,19] One of the few effective modes of therapy takes advantage of antibiotic synergy. Penicillins alone only arrest bacterial growth, and aminoglycosides are without effect against enterococci, except at very high concentrations, but the combination of both drugs effectively kills the organism.[2,14] This high-dosage synergy approach is among the most effective pharmacologic means to clear infection. Unless there is documentation that other

potentially safer antibiotic regimens are effective in vivo and in vitro, the co-administration of gentamicin (but not amikacin) with a cell wall–active agent (generally ampicillin) is standard of care for serious enterococcal infections in critically ill patients and in those with osteomyelitis, endocarditis, sepsis or joint infections.[11,14,17]

Unfortunately, some enterococci are resistant to aminoglycosides, even when coadministered with ampicillin, leaving few alternatives for treating these infections.[7,11] In some cases, the only effective drugs are glycopeptides, such as vancomycin, but this drug should be viewed as a therapy of absolute last resort.[2] Vancomycin has a narrow spectrum and is potentially nephrotoxic (see Chapter 181). Clinical experience with vancomycin is limited in veterinary medicine.

STAPHYLOCOCCAL INFECTIONS

The broad distribution of staphylococci as normal flora of domestic animals is perhaps the most important epidemiologic factor in staphylococcal infections.[1,5,20,21] These organisms are often not inherently invasive and colonize intact epithelium of healthy animals without causing disease.[9,21] Subsequently, isolation of these bacteria may signify the presence of transient or long-term colonization of epithelial surfaces.[10,22]

Disease pathogenesis and lesion development are not fully understood but likely involve a breach of the host's mucosal barrier or other means of immunocompromise, in conjunction with numerous bacterial virulence factors such as staphylococcal toxins and enzymes that permit them to withstand phagocytosis by neutrophils.[5,11,21,22] Biofilm formation has been demonstrated for many staphylococci, increasing bacterial resistance to stressful environmental conditions and antimicrobial exposure. Biofilm formation may be particularly important for infections associated with implants and invasive devices such as indwelling catheters.[2,20,23] For many years, production of coagulase by staphylococci has been associated with virulence and tissue tropism. Almost all infections in humans, dogs, and cats were caused by coagulase-positive species, with coagulase-negative staphylococci viewed invariably as contaminants.[5,10,20] More recent studies implicate coagulase-negative staphylococci as a cause of significant morbidity in humans and companion animals.[1,2,20]

Pathogenic staphylococci may affect any organ system and are responsible for community-acquired and nosocomial infections.[5,20,21] Of approximately 35 species of staphylococcal organisms, three are of clinical importance in companion animals: *Staphylococcus pseudintermedius, Staphylococcus aureus,* and *Staphylococcus schleiferi* ssp. *coagulans.*[20,22,24] *Staphylococcus intermedius* previously was considered the most important staphylococcal species in dogs and cats. What was recognized previously as *S. intermedius* now is known to be the closely related *S. pseudintermedius.*[4,5,20,22] *S. pseudintermedius* is a common canine commensal, with colonization rates of 31% to 68% in healthy dogs, and is the leading pyogenic bacterium of dogs.[4,20,22] Although it is recognized as the most common etiologic agent of bacterial skin and ear infections, it also may cause systemic infections, including arthritis, osteomyelitis, cystitis, mastitis, wound infections, and bacteremia.[9,20,22] Sites of infection are similar in cats, although reports of disseminated disease are less numerous.[20]

Until recently, *S. pseudintermedius* isolates were generally susceptible to β-lactamase–resistant β-lactam antibiotics.[20] Infections with strains of *S. pseudintermedius* that are resistant to multiple antibiotics are becoming common, and since 2006 methicillin-resistant *S. pseudintermedius* (MRSP) has emerged as a significant health problem in veterinary medicine.[4,20,21,24,25] As with other staphylococci, the methicillin resistance of *S. pseudintermedius* is mediated by the *mecA* gene that encodes production of a modified penicillin binding protein (PBP).[4,21] Normally, β-lactam antibiotics bind to *S. pseudintermedius* to prevent cell wall development by the bacterium. The modified PBP of *S. pseudintermedius* has a low affinity for β-lactams, and therefore cell wall synthesis is not inhibited by these antimicrobials.

The treatment of infections with MRSP is a new challenge in veterinary medicine.[4,20,21,25] Determination of methicillin resistance for all staphylococci is based on in vitro resistance to oxacillin. Oxacillin is used as a surrogate for methicillin because it is sensitive and more stable. If staphylococci are resistant to oxacillin, they are inherently resistant to all other β-lactams, including cephalosporins and amoxicillin-clavulanate, regardless of the results of in vitro susceptibility testing.[4,24] MRSP isolates are often resistant to many other antimicrobials, including all of those licensed for use in companion animals.[3,20,24,25] Most *S. pseudintermedius* infections are not caused by MRSP, and infections with MRSP are clinically indistinguishable from infections caused by methicillin-susceptible *S. pseudintermedius* (MSSP).[20] Further, there is currently no indication that MRSP is more virulent than MSSP, and most reported MRSP infections have been treated successfully, albeit with fewer options for antimicrobial therapy.[3,21,25] Based on in vitro testing, the most useful systemic antibiotics include rifampicin, amikacin, chloramphenicol, and/or minocycline (see Empiric Selection).[4,20,25]

Similar antibiotic resistance patterns have emerged for pyoderma and systemic infections caused by *S. schleiferi.* Although this bacterium appears to be a less frequent cause of disseminated infections, results of clinical studies reveal that tissue tropism and antimicrobial susceptibility data are not predictable for this relatively novel species.[20]

S. aureus is well established as a significant community-acquired and nosocomial pathogen in humans, and infection with methicillin-resistant *S. aureus* (MRSA) is a relatively recent development in veterinary medicine.[1,20,21,26] The emergence of MRSA in dogs and cats appears to be a direct reflection of MRSA in the human population.[20,21] Unlike *S. pseudintermedius*, *S. aureus* is not a true commensal organism in dogs and cats.[20,27] Although dogs and cats are not natural reservoirs of *S. aureus,* they can become colonized, in all likelihood from humans.[20,21] Once colonized, pets may clear the organism, go on to develop infection, or remain asymptomatic carriers for an indeterminate period. *S. aureus* produces a similar range of infections as those caused by *S. pseudintermedius.*[20,21,27]

Infected animals should be isolated, and barrier contact precautions should be used when handling patients, food bowls, bandages, and all associated materials. Hand washing between patients is imperative. Such guidelines must be enforced (1) to minimize the risk of patient-to-patient spread of resistant clones and (2) to limit the likelihood of animal-to-human transmission. There is increasing evidence that interspecies transmission of MRSA occurs and that it may emerge as an important zoonotic and veterinary disease.[20,21,27]

In human hospitals, transmission of MRSA occurs mainly via the transiently colonized hands of health care workers.[2,20,26] Colonized veterinary personnel are thought to be the most likely vectors of MRSA in veterinary hospitals.[27,28] All personnel in contact with patients should be advised of appropriate precautions once MRSA infection is confirmed. Like other staphylococci, MRSA can survive for long periods on inanimate objects such as bedding and cages, and it is relatively resistant to heat. Thus it may be difficult to eliminate once introduced to the hospital environment. MRSA infections most often remain treatable, albeit by a small number of antibiotics.[20] Because MRSA may be transmitted between animals and humans, owners of infected or colonized animals should be informed of this potential. However, veterinarians are discouraged from making any recommendations regarding the diagnosis or treatment of MRSA, or any disease, in humans.

Treatment of deep or disseminated staphylococcal infections requires prompt systemic therapy. Drug choices should be based on in vitro susceptibility testing in combination with other factors (e.g., drug penetration, site of infection). Historically, uncomplicated

methicillin-susceptible staphylococcal infections were predictably susceptible to β-lactam-β-lactamase inhibitor combination drugs (e.g., amoxicillin-clavulanic acid) and first-generation cephalosporins (e.g., cephalexin, cefazolin).[20] These agents remain appropriate for treating uncomplicated and/or first-time staphylococcal infections in otherwise stable pets. This level of confidence does not extend to hospitalized patients with risk factors for MDR, such as those with a history of recent antibiotic use, indwelling devices, exposure to nosocomial pathogens, and protracted hospital stays. Clindamycin, potentiated sulfonamides (TMP-SMZ), doxycycline, and aminoglycosides are frequently, although not uniformly, effective for treating staphylococcal infections.[5,20,25] The role of fluoroquinolones in critically ill pets with staphylococcal infections is controversial, particularly with methicillin-resistant strains, as emergence of resistance and treatment failures are reported.[4,14,20] Inducible resistance to clindamycin is documented and generally is not identified with culture and susceptibility testing. However, *S. aureus* reported as susceptible to clindamycin but resistant to erythromycin should be inferred to be resistant to clindamycin.[4,20] Inducible clindamycin resistance is rare in *S. pseudintermedius*, but erythromycin-resistant strains similarly should not be managed with clindamycin.[20]

Commercial veterinary laboratories should test all β-lactam–resistant staphylococci for susceptibility to chloramphenicol, aminoglycosides, tetracyclines, TMP-SMZ, erythromycin, and clindamycin.[20,24,25] Duration of therapy depends on the site of infection and comorbid conditions that may impair host defenses or delay healing. When tolerated, therapy generally extends 2 weeks beyond the resolution of clinical signs of infection.

Vancomycin, linezolid, tigecycline, and daptomycin remain the only effective antimicrobials for resistant strains of staphylococcus in human health care settings; these drugs should be used only in exceptional circumstances in veterinary medicine.[20,25] It is argued that their use should be restricted in dogs and cats because avoidance of antibiotic use is a valid strategy to curtail antibiotic resistance.

Table 93-1 Antibiotics Used to Treat Gram-Positive Infections

Drug	Dosage
Amikacin	15 mg/kg IV q24h (dogs) 10 mg/kg IV q24h (cats)
Ampicillin	22 mg/kg IV q6-8h
Ampicillin-sulbactam	22 mg/kg IV q8h
Azithromycin	5 to 10 mg/kg IV q24h
Cefazolin	22 mg/kg IV q6-8h
Cefotetan	30 mg/kg IV q8h
Cefoxitin	30 mg/kg IV q6-8h
Chloramphenicol	25 to 50 mg/kg IV q8h (dogs) 15 to 20 mg/kg IV q12h (cats)
Clindamycin	10 mg/kg IV q12h
Enrofloxacin	15 to 20 mg/kg IV q24h (dogs) 5 mg/kg IV q24h (cats)
Gentamicin	10 mg/kg IV q24h (dogs) 6 mg/kg IV q24h (cats)
Imipenem-cilastatin	5 to 10 mg/kg IV q6-8h
Meropenem	8 to 12 mg/kg IV q8-12h
Ticarcillin-clavulanate	50 mg/kg IV q6-8h
Trimethoprim-sulfamethoxazole or trimethoprim-sulfadiazine	15 to 30 mg/kg PO/IV q12h
Vancomycin	15 mg/kg IV q8h (dogs) 10 to 15 mg/kg IV q8-12h (cats)

IV, Intravenous.

EMPIRIC ANTIBIOTIC STRATEGIES

In critically ill patients, prompt administration of broad-spectrum injectable antimicrobials is warranted when a polymicrobial infection is suspected or when the causative agent causing an infection is not known (Table 93-1). Wright-Giemsa and Gram-stained cytologic preparations of aspirates or impression smears should be examined to evaluate the morphologic and staining characteristics of bacterial pathogens.

Clinicians should be familiar with the gram-positive pathogens associated with severe infections in their hospital and choose therapy based on the prevalence and susceptibility patterns of these bacteria, as well as the site(s) of infection. Once culture and susceptibility data are available, therapy is streamlined to ensure eradication of the pathogen without promoting resistance secondary to inappropriate antimicrobial treatment.[14]

Although bacterial resistance to previously effective antibiotics is an ever-increasing concern in patients with gram-positive infections, first-choice recommendations for first time and non–life-threatening infections include a first-generation cephalosporin (e.g., cefazolin) or a β-lactam- β-lactamase inhibitor combination (e.g., amoxicillin-clavulanic acid, ampicillin-sulbactam). The first-generation cephalosporins have a similar spectrum of activity to ampicillin, with the notable difference that β-lactamase–producing staphylococci often remain susceptible to the cephalosporins.[14,20] However, methicillin-resistant, coagulase-positive staphylococci are resistant to all cephalosporins.[4,22,25] Sulbactam, like clavulanic acid, is an inhibitor of β-lactamases (the latter is more potent). β-Lactamase inhibitors have weak antibacterial activity by themselves, but they show extraordinary synergism when co-administered with ampicillin, amoxicillin, or ticarcillin owing to the irreversible binding of the β-lactamase enzymes of many resistant bacteria.[14] The aminopenicillins and first-generation cephalosporins have relatively short half-lives, and in the absence of renal impairment, they may be administered every 6 hours to take advantage of the well-described pharmacodynamic properties of most β-lactam agents. This recommendation is particularly relevant for patients with altered volumes of distribution (i.e., patients receiving intravenous fluids, parenteral nutrition, or blood products, and those with vascular leak or third-spacing syndromes).[14]

Alterations in drug clearance can occur rapidly. The clinician must consider these and other pharmacokinetic principles when determining dosages of all antibiotics to achieve the desired pharmacodynamic effects. Similarly, individualization of regimens based on prior antibiotic use may reduce the risk of therapeutic failure.

An important exception to the above therapeutic recommendations exists when a new infection is documented in a patient currently receiving antibiotics. Similarly, critically ill patients with a history of recent antibiotic use or presumed polymicrobial infection should be managed with broader-spectrum antibiotics, such as a carbapenem, alone or in conjunction with an aminoglycoside or fluoroquinolone, while culture and susceptibility results are pending. For treatment of infections caused by some enterococci or methicillin-resistant staphylococci, evaluation of susceptibility data is imperative to avoid treatment failures.[2,11,20,29]

Fluoroquinolones and aminoglycosides remain effective treatment for some staphylococci. Neither drug class is predictably active against streptococci. However, they are often active against gram-negative pathogens that may be contributing to patient morbidity.

These agents generally are administered once daily at the upper end of the dosage range. In cats, enrofloxacin should not be prescribed at a dose exceeding 5 mg/kg/day because its administration has been associated with temporary or permanent blindness in domestic felids.[14]

Among the aminoglycosides, gentamicin is reported to be more effective than amikacin for treatment of staphylococcal infections in humans.[25] The clinical relevance of this distinction among veterinary isolates is not clear. Both amikacin and gentamicin are associated with potential renal dysfunction, but both are frequently prescribed without incident for short-term therapy (<10 days) in well-hydrated patients without preexisting renal disease. Gentamicin, when administered with ampicillin, is effective for many serious enterococcal infections. This combination results in synergistic bactericidal activity against susceptible strains. Treatment options for enterococcal isolates with high-level gentamicin resistance are limited, since amikacin is not effective against enterococci. Clindamycin demonstrates in vitro activity against some staphylococci and streptococci, and may be particularly useful for managing patients with cellulitis or bone infections caused by susceptible strains.[1,20] All pathogenic enterococci are inferred to be intrinsically resistant to clindamycin.

Carbapenems, such as imipenem and meropenem, are highly active against most *Streptococcus* and *Staphylococcus* spp. However, they are uniformly ineffective for the treatment of methicillin-resistant pathogens and vancomycin-resistant enterococci. They are prescribed based on culture and susceptibility data or administered empirically to patients with risk factors for infection with MDR organisms. However, they should not be used liberally because excessive use of carbapenems is associated with β-lactamase production against other β-lactam antibiotics, especially cephalosporins.[2,30]

Chloramphenicol and potentiated sulfonamides generally are not used empirically in the critically ill patient, but some MDR staphylococci are susceptible to these agents. Both have been available for many years, and practitioners are encouraged to familiarize (or refamiliarize) themselves with the spectrum of activity of these medications and with the uncommon but potentially serious adverse events that may occur with their use. All enterococci are inherently resistant to potentiated sulfonamides. Vancomycin seldom is required to treat isolates of any of the gram-positive cocci in small animal veterinary medicine.

Pharmaceutical companies are devoting fewer resources to the development of new antimicrobials, and few novel drugs are in the pipeline. Therefore there are no known indications for veterinarians to prescribe any of the antibiotics for virulent MDR enterococci or staphylococci recently approved for human medicine. Daptomycin, quinupristin-dalfopristin, linezolid, ceftaroline, telithromycin, and tigecycline are the last lines of defense for patients with life-threatening infections[2,26] (see Chapter 181). A small number of human *E. faecium* and *S. aureus* isolates already possess documented resistance to some of these drugs, and clinicians thus are urged to use antibiotics rationally and wisely.

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