MAKING THE BEST FIRST CHOICE ANTIBIOTIC SELECTIONS

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INTRODUCTION

What is the best antimicrobial to select as an initial choice for treatment of bacterial infections in small animals? What is the best drug for a skin infection? For a urinary tract infection? For pneumonia? The answer is that there is not a single best drug, but usually several drugs that are considered appropriate. Selection is made on the basis of the activity of the drug against the organism, the activity of the drug at the site of infection (in the urine for example), the safety of the drug in the patient, and the ability to achieve good compliance when a dosing regimen is prescribed. For initial treatment, especially for common infections, veterinarians will select empirical treatment that is based on their experience and clinical history. The treatment can be simplified by localizing the infection to a site or organ and considering the most likely bacteria that cause infections in these tissues.

BACTERIAL SUSCEPTIBILITY

For initial treatment, most veterinarians will select antimicrobial treatments without the benefit of a culture and susceptibility test. Most bacteria that cause infections come from the following list: Staphylococcus intermedius, (and occasionally other staphylococci) Escherichia coli, Klebsiella pneumoniae, Pasteurella multocida, beta-hemolytic streptococci, Pseudomonas aeruginosa, Proteus mirabilis (and occasionally indole-positive Proteus), Enterobacter spp and Enterococcus spp. If the bacteria are accurately identified, antibiotic selection is simplified because the susceptibility pattern of many organisms is predictable. For example, if the bacteria is likely to be Pasteurella, Streptococcus, or Actinomyces, susceptibility is expected to penicillin or an aminopenicillin such as ampicillin, amoxicillin, or amoxicillin-clavulanic acid (Clavamox). Even when the bacteria are not accurately identified, a cytology specimen from the infection site can be helpful: a gram-negative bacilli is most often E. coli and a gram-positive cocci is most often Staphylococcus. The clinical history for the infection can be helpful: pyodermia in dogs is usually caused by Staphylococcus intermedius; urinary tract infections are most often caused by E. coli; and bite wounds in cats are often Pasteurella. Based on this evidence initial therapy can be considered.

SUSCEPTIBILITY PATTERNS

Gram-positive Cocci

Staphylococcus isolated from small animals is most likely to be S. intermedius rather than S. aureus. S. intermedius will usually have a predictable susceptibility to b-lactamase resistant b-lactam antibiotics such as amoxicillin combined with a b-lactamase inhibitor (Clavamox), or first-generation cefazolin or cephalaxin. Staphylococcus also is susceptible to many other cefazolin such as the third-generation cefazolin

cefepoxide. Staphylococcus also is susceptible to oxacillin and dicloxacillin but these are not used as commonly in small animal medicine. Reports of studies on S. intermedius have shown that, despite frequent use of the above mentioned drugs in small animals, the incidence of resistance has not increased (Lloyd, et al, 1996). Most staphylococci are also sensitive to fluoroquinolones and there appears to be little difference in the in vitro activity of the veterinary fluoroquinolones (enrofloxacin, difloxacin, marbofloxacin, orbifloxacin) against Staphylococcus. The majority of staphylococci are sensitive to lincomycin, lincosamides (clindamycin, lincomycin), trimethoprim-sulfonamides, or erythromycin, but resistance can occur in as high as 25% of the cases. Streptococci (but not enterococci) are usually susceptible to the same drugs that are active against staphylococci.

Anaerobic Bacteria

If the bacteria is an anaerobe (for example, Clostridium, Fusobacterium, Prevotella, Actinomyces, or Porphyromonas) predictable results can be attained by administering a penicillin, chloramphenicol, metronidazole, clindamycin, amoxicillin-clavulanic acid, or one of the second-generation cephalosporins such as cefotetan or cefoxitin. Metronidazole is consistently highly active against anaerobes including B. fragilis. The activity of first-generation cephalosporins, trimethoprim-sulfonamides/ormetoprim-sulfonamides, or fluoroquinolones for an anaerobic infection is unpredictable. Resistance is more common among the gram-negative anaerobes. In particular, if the anaerobe is from the Bacteroides fragilis group, resistance may be more of a problem because they produce a beta-lactamase that may inactivate 1st generation cephalosporins and ampicillin/amoxicillin. Some of these Bacteroides may also be resistant to clindamycin. More resistant strains of Bacteroides have been observed in recent years (Jang et al 1997).

Gram-Negative Bacilli

The most susceptible gram-negative bacilli (rods) are Pasteurella multocida and Proteus mirabilis. These bacteria may be encountered in wound infections, urinary tract infections, or pneumonia. Most common, first-line drugs such as amoxicillin, amoxicillin, cephalosporins, tetracyclines, or trimethoprim-sulfonamides should be active at standard recommended dosages.

If the organism is an enteric gram-negative bacilli (Enterobacteraceae), such as Enterobacter spp., Klebsiella pneumoniae, or Escherichia coli, resistance to many common antibiotics is possible and the choice of antibiotics requires a different strategy. If the infection is serious, a susceptibility test is advised. A report showed that among nonenteric E. coli, only 23% were sensitive to a 1st generation cephalosporin, and less than half were sensitive to ampicillin. In that same study, 13%, and 23% were intermediate or resistant to enrofloxacin, and orbifloxacin, respectively (Oluoch, et al 2001). Based on these data as well as other studies, for initial therapy we usually expect the gram-negative enteric bacteria to be susceptible to fluoroquinolones and aminoglycosides. Many of these bacteria are susceptible to amoxicillin-clavulanate.

Gram-Negative Bacteria (nonfermentors)

An extended-spectrum cephalosporin (second- or third-generation cephalosporin) usually is active against enteric gram negative bacteria, but will not be active against...
**Pseudomonas aeruginosa.** If the organism is a *Pseudomonas aeruginosa*, inherent resistance to many drugs is common, but it may be susceptible to fluoroquinolones, aminoglycosides, cefazidime (one of the few cephalosporins active against *Pseudomonas*), or an extended-spectrum penicillin such as ticarcillin or piperacillin. Carbapenems (eg, imipenem, meropenem) are consistently very active against *Pseudomonas*.

When administering a fluoroquinolone to treat *Pseudomonas aeruginosa* the high-end of the dose range is suggested. Of the currently available fluoroquinolones, (human or veterinary drugs) ciprofloxacin is the most active against *Pseudomonas aeruginosa*.

**CONSIDERATIONS FOR THE SITE OF INFECTION**

For most tissues, antibiotic drug concentrations in the serum or plasma approximate the drug concentration in the extracellular space (interstitial fluid). This is because there is no barrier that impedes drug diffusion from the vascular compartment to extracellular tissue fluid (Nix et al, 1991). Pores (fenestrations) or microchannels in the endothelium of capillaries are large enough to allow drug molecules to pass through unless the drug is restricted by protein binding in the blood. Tissues lacking pores or channels may inhibit penetration of some drugs (discussed below).

**Diffusion Into Tissues**

Diffusion of most antibiotics from plasma to tissues is limited by tissue blood flow, rather than drug lipid solubility. If adequate drug concentrations can be achieved in plasma, it is unlikely that a barrier in the tissue will prevent drug diffusion to the site of infection as long as the tissue has an adequate blood supply. Rapid equilibration between the extracellular fluid and plasma is possible because of high surface area:volume ratio (high SA:V). That is, the surface area of the capillaries is high relative to the volume into which the drug diffuses. Drug diffusion into an abscess or granulation tissue is sometimes a problem because in these conditions drug penetration relies on simple diffusion and the site of infection lacks adequate blood supply. In an abscess, there may not be a physical barrier to diffusion (eg, impenetrable membrane), but low drug concentrations, or slow equilibration occurs because in a cavitated lesion there is low surface area to volume ratio (low S:V ratio).

In some tissues a lipid membrane (such as tight junctions on capillaries) presents a barrier to drug diffusion. This has been called permeability-rate limited drug diffusion. In these instances, a drug must be sufficiently lipid-soluble, or be actively carried across the membrane in order to reach effective concentrations in tissues. These tissues include: the central nervous system, eye, and prostate. There also is a barrier between plasma and bronchial epithelium (blood:bronchus barrier). This limits drug concentrations of some drugs in the bronchial secretions and epithelial fluid of the airways. Lipophilic drugs may be more likely to diffuse through the blood-bronchus barrier and reach effective drug concentrations in bronchial secretions.

**Urinary Tract**

High antibiotic concentrations achieved in renal tubules and the urine after routine therapy with modest doses of antibiotics is often sufficient to cure lower urinary tract infections, even those that are caused by organisms identified on a susceptibility test as “intermediate” in sensitivity (Lees & Rogers, 1986; NCCLS, 2002). Urine concentrations of antibiotics are at least 100 x the corresponding plasma concentrations because of the tubular concentration. When the infection is confined to the lower urinary tract, these high concentrations are an advantage (Stamey, et al. 1974). Cures of urinary tract infections are possible, even when the antibiotic levels do not attain concentrations high enough for a systemic infection. However, clinicians should be aware that if the concentrating ability of the kidneys is compromised, antibiotic concentrations in the urine may be low. Patients may have dilute urine because of renal disease, or treatment with corticosteroids, fluid therapy, or diuretics.

When the renal tissue is involved, high urine drug concentrations offer no advantage. Drug concentrations in renal tissue – which are equivalent to the renal lymph concentrations – are correlated to plasma drug concentrations, not the drug concentrations in the urine. Therefore, consideration must be given to drugs that attain high concentrations in the renal tissue and that can be administered at doses and intervals that are optimum to achieve the pharmacokinetic-pharmacodynamic relationships for a clinical cure.

**Intracellular Infections**

Most bacterial infections are located extracellular, and a cure can be achieved with adequate drug concentrations in the extracellular (interstitial) space rather than intracellular space. Intracellular infections present another problem. For drugs to reach intracellular sites, they must be carried into the cell or diffuse passively. Generally, lipid-soluble drugs are best able to diffuse through the cell membrane for intracellular infections. Examples of drugs that accumulate in leukocytes, fibroblasts, macrophages, and other cells are fluoroquinolones, lincosamides (clindamycin, lincomycin), macrolides (erythromycin, clarithromycin), and the azalides (azithromycin) (Pasqual, 1995). β-lactam antibiotics and aminoglycosides do not reach effective concentrations within cells. Intracellular organisms such as *Brucella*, *Chlamydia*, *Rickettsia*, *Bartonella* and *Mycobacteria* are examples of intracellular pathogens. Staphylococci may in some cases become resistant to treatment because of intracellular survival. Fluoroquinolones and tetracyclines such as doxycycline are frequently administered to treat *Rickettsia* and *Ehrlichia* infections. There is good evidence for efficacy of doxycycline or fluoroquinolones (enrofloxacin is the only one tested) for treating *Rickettsia*, but only doxycycline should be considered for its efficacy for treating canine ehrlichiosis.

**LOCAL FACTORS THAT MAY IMPAIR ANTIBIOTIC EFFECTIVENESS**

Local tissue factors may decrease antimicrobial effectiveness. For example, pus and necrotic debris may bind and inactivate vancomycin or aminoglycoside antibiotics (gentamicin or amikacin), causing them to be ineffective. Cellular material also can decrease the activity of topical agents such as polymyxin B. Foreign material in a wound (such as material surgically implanted) can protect bacteria from antibiotics and phagocytosis by forming a biofilm (glocycalyx) at the site of infection (Habash & Reid, 1999). Cations can adversely affect the activity of antimicrobials at the site of infection. Two important drug groups diminished in activity by cations such as Mg++, Al³⁺, and Ca²⁺ are fluoroquinolones and aminoglycosides. (Cations such as magnesium, iron, and aluminum also can inhibit oral absorption of fluoroquinolones.)
**SUGGESTED EMPIRICAL TREATMENT BASED ON TISSUE SITE**

On the following table is a list that includes some (but not all) possible choices for common infections encountered in veterinary medicine. In this list the “first choice” is a drug with a high likelihood of success, low expense and few risks. If the first choice has not been effective, or if patient factors preclude using the first choice (e.g., allergy) the alternate choice should be considered.

**REFERENCES AND ADDITIONAL READING**


<table>
<thead>
<tr>
<th>Infection site</th>
<th>First choice drugs</th>
<th>Alternate choice drugs</th>
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<tbody>
<tr>
<td>Skin: pyoderma or other skin infection</td>
<td>Amoxicillin-clavulanate</td>
<td>Trimethoprim-sulfonamides</td>
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<td></td>
<td>Cephalosporin</td>
<td>Fluoroquinolone + Clindamycin</td>
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<td>Urinary tract</td>
<td>Cephalosporin</td>
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<td></td>
<td>Amoxicillin / Ampicillin</td>
<td>Fluoroquinolone</td>
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<td></td>
<td>Amoxicillin-clavulanate</td>
<td>Tetracycline</td>
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<td>Respiratory tract</td>
<td>Amoxicillin-clavulanate</td>
<td>Macrolide (erythromycin, azithromycin)</td>
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<td></td>
<td>Fluoroquinolone</td>
<td>Aminoglycosides (amikacin, gentamicin)</td>
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<td>Cephalosporin</td>
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<td>Septicemia</td>
<td>Amoxicillin-clavulanate</td>
<td>Extended-spectrum cephalosporin #</td>
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<tr>
<td></td>
<td>Cephalosporin</td>
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<td></td>
<td>Fluoroquinolone</td>
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<td>Bone and joint</td>
<td>Cephalosporins</td>
<td>Aminoglycoside</td>
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<td></td>
<td>Amoxicillin-clavulanate</td>
<td>Extended-spectrum cephalosporin</td>
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<td>+ Fluoroquinolone = enrofloxacin, difloxacin, marbofloxac or orbifloxacin</td>
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<tr>
<td># Extended spectrum cephalosporin = 2nd – or 3rd-generation drugs (eg, cefotetan, cefotaxime, cefpodoxime).</td>
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