Empirical Antimicrobial Therapy and The Challenges of Resistance
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There are several important factors involved in selecting an antimicrobial agent. Some of these factors include: known or suspected pathogen, drug efficacy and safety, site of infection, and convenience of the dosing regimen. There is often more than one antimicrobial option when initiating antimicrobial therapy in a patient. Simple diagnostic tests (gram stain, cytology), infection location, clinical experience, and suspected pathogen(s) can help guide empirical therapy. Culture and susceptibility testing is not indicated for every infection but these tests can be helpful if the patient is not responding to the initial empirical therapy and/or has a resistant infection.

For skin infections, the most common bacterium involved is *S.pseudintermedius*. Antimicrobial agents for the empirical treatment of superficial pyoderma include amoxicillin-clavulanic acid, cephalosporins (cefovecin, cefpodoxime, cephalexin), clindamycin, potentiated sulfonamindes (eg. ormetoprim-sulfadimehoxine), and macrolides. For time dependent drugs, like penicillins and cephalosporins, maintaining concentrations above the MIC (T>MIC) for the majority of the dosing interval is associated with efficacy. Owner compliance is an important factor to consider in designing the treatment regimen. Studies have shown that there is better owner compliance with once a day therapy compared to medications that are administered multiple times a day (Adams et al, 2005). Cefovecin is a unique antibiotic in that it has a long half life resulting in drug concentrations above the MIC of susceptible bacteria for several days, optimizing the T>MIC, the parameter important for efficacy of time dependent drugs. It is important to consider topical therapy as an important component of treating skin infections and underlying conditions in dogs with superficial pyoderma.

Culture/susceptibility testing can identify the causative bacteria and assist the veterinarian in choosing an appropriate antimicrobial and potentially a dosing regimen. The agar disk diffusion (ADD) and broth microdilution test are two types of susceptibility testing. The ADD is a qualitative test because results are reported as the bacteria being susceptible, intermediate, or resistant to the various antimicrobials. The broth microdilution test is a quantitative test. This test reports MICs (minimum inhibitory concentrations). The MIC can assist in identifying the most appropriate drug and in the design of a dosing regimen. Even though most laboratories are now reporting MIC values, additional information (i.e. breakpoints) are required to compare MICs between drugs.

Antimicrobial Resistance

Antimicrobial drug resistance is an increasing problem in human hospitals and in the community. Several antibiotic classes used in human medicine have shown to be one of several risk factors in the selection of resistant organisms. Prudent use of antibiotics and good owner compliance are key components of successful treatments. Steps have been taken in human medicine to avoid and control the development of antimicrobial resistant bacteria. Some of the approaches include: antimicrobial rotation, restricted hospital formularies, standard treatment protocols, and required authorization from an infectious disease control committee for use of restricted drugs. There is not one specific class of drugs responsible for selecting for resistance, rather all, especially if used inappropriately, can select for resistant organisms.

In veterinary medicine, there is little available statistical data on antimicrobial drug use and resistance in companion animals. Therefore, it is difficult to quantify the magnitude or incidence of antimicrobial resistance. A few studies have investigated the prevalence of antimicrobial resistant bacteria but these studies often involve small sample sizes and samples sent to the laboratory may represent a skewed population because they usually represent the ‘treatment failure’ rather than the ‘treatment success’ case. Other problems faced in veterinary medicine include: lack of established breakpoints for veterinary bacterial species, variable collection and reporting procedures, and variable

laboratory methods for determining resistance. More information is needed on the incidence of drug resistance and antimicrobial usage.

Bacteria

Some bacteria are considered to be predictable. In other words, bacteria that have a predictable susceptibility to common antimicrobials. S*treptococcus* spp. (except *Enterococcus*), *Pasteurella* spp., and *Staphylococcus spp.* (except MRSA) isolated from small animals usually have good susceptibility to beta-lactamase resistant beta-lactam antibiotics (e.g. amoxicillin/clavulanic acid, cephalosporins (cefovecin, cefpodoxime, cephalexin, cefadroxil). Most staphylococci are also susceptible to the veterinary fluoroquinolones, clindamycin, and potentiated sulfonamides.

The bacteria commonly involved in drug resistant infections are classified as 'unpredictable bacteria'. These include SPICE organisms (*Serratia spp., Pseudomonas spp*., Indole positive *Proteus*, *Citrobacter*, and *Enterobacter*), *E. coli, Enterococcus*, and Methacilin Resistant *Staphylococcus*. These bacteria are known to have unpredictable susceptibility patterns and if identified on a gram stain, therapy should be based on culture and susceptibility results.

E.coli

There have been reports of resistant *E.coli* infections in dogs and cats in the literature. In a published study, the prevalence of antimicrobial resistant *E. coli* was determined from isolates obtained in 116 dogs hospitalized for a minimum of three days in the ICU of a veterinary school (Ogeer-Gyles J et al., 2006). The results showed an increase in rectal *E.coli* isolates resistant to antimicrobials as the duration of hospitalization increased. Another study showed indwelling urinary catheters where the most important risk factor for nosocomial UTI in the ICU (Ogeer-Gyles J et al, 2006). The results showed 19% of dogs with indwelling urinary catheters for 3 days developed a UTI. In addition, studies have reported incidences of E.coli resistance as high as 40% to fluoroquinolones (Boothe DM, 2006). Another study evaluated the possible selection of E. coli resistacet to extended spectrum cephalosporins after treatment with cephalexin (Damborg P et al., 2011). The results suggested a strong indication that cephalexin selects for E. coli producing plasmid-borne CMY-2 β-lactamase. (Damborg, P et al. Vet.Microbiology 2011)

Enterococcus

Based on clinical reports and evidence in the literature, there appears to be an increase in *Enterococcus* UTI in canine patients (Sequin MA, 2003). This is a bacterium that is not highly virulent but it is inherently resistant to many antimicrobials. The most common mistake seen in practice is when veterinarians treat these infections with a cephalosporin. *Enterococcus spp*. is inherently resistant to cephalosporins. Fluoroquinolones often show susceptible *in-vitro* but the minimum inhibitory concentration (MIC) is usually very high. Because fluoroquinolones are excreted in the urine, urine concentrations may be high enough to treat UTI caused by *Enterococcus*. The best approach for treatment is to base antimicrobial decisions on culture/susceptibilities results. In general, high dose beta lactam antimicrobials like amoxicillin and amoxicillin-clavulanic acid are recommended as first line agents. If the patient has a systemic *Enterococcus* infection then a combination of ampicillin plus an aminoglycoside is recommended.

Methicillin Resistant Staphylococcus (MRS)

Methicillin Resistant *Staphylococcus aureus* (MRSA) is an increasing resistance problem in human medicine. In a study published in the New England Journal of Medicine (Moran GJ et al., 2006), *S.aureus* was cultured in 76% of patients presenting with skin and soft tissue infections to hospital emergency rooms across the country (Moran G.J et al., 2006). Of these patients, 59% had a MRSA infection (Moran G.J et al., 2006). There are reports of methicillin resistant *Staphylococcus* infections in dogs and incidences where MRSA was spread from the pet dog or cat to its owner (Cefai C et al., 1994, Manian FA et al., 2003, Jones RD et al., 2007)

These *Staphylococcus spp.* have developed resistance mechanisms by altering their penicillin binding proteins. These methicillin resistant bacteria are resistant to all beta-lactam antimicrobial agents (penicillin and cephalosporins). Antimicrobials shown to be effective include potentiated sulfonamides (e.g. sulfadimethoxine-ormetoprim) and clindamycin. In addition, if the patient must be kept in the hospital, then isolation and disinfectant procedures should be instituted.

Ways to AVOID the Development of Antimicrobial Resistant Bacteria: Prudent use of Antimicrobial Agents

There are few studies evaluating the risk factors for developing resistant infections. Previous hospitalization and the exposure of bacteria to antimicrobial agents are likely risk factors (Sasaki T et al., 2007. Neinhoff et al. 2011). Therefore, animals with a chronic, recurrent, or relapsing infection that have been on multiple antimicrobials are more likely to develop a multiresistant bacterial infection than animals presenting for a first time infection without prior exposure to antimicrobials.

RIGHT indication

1. Use antimicrobial agents only when necessary
2. Identify the causative bacteria: gram stain, cytology, culture/susceptibility testing

RIGHT drug

1. If empirical therapy is initiated then reexamination of the choice of antimicrobial agent should be performed when culture/susceptibility results are available.
2. Choose a drug that will reach adequate concentrations at the site of infection for sufficient amount of time

RIGHT dose and frequency

1. Choosing the right dose is important for maximizing efficacy and reducing the incidence of resistance. An important cause of resistance is the lack of adequate concentrations at the infection site for sufficient duration of time.
3. Time dependent drugs (e.g. penicillins, cephalosporins): These drugs should be administered to maximize the time above the MIC. This may mean the drug has to be administered two or three times a day (e.g. cephalexin for pyoderma). For these antimicrobials it is imperative that the owner administers the drug as prescribed (i.e. every 12 hours or every 8 hours). If doses are skipped or frequency of dosing is prolonged therapeutic failure and risk for resistance increases. Owner compliance is often an issue with drugs that are administered multiple times a day. cefapodoxime is a drug that is labeled for use in dogs and is given once a day. The long half life of cefovecin allows for a single injection to be given to provide therapy for upto 14 days for superficial pyoderma.
4. Concentration dependent drugs (e.g. Fluoroquinolones, aminoglycosides). The area under the curve (AUC) to MIC ratio is emerging as preferred predictor of efficacy. Optimizing this ratio (>/= 125 (ideally >250) will help maximize efficacy and reduce the risk of bacterial resistance.. *Pseudomonas* and other resistant gram negative bacteria often require the dosages at the high end of the dosing range of fluoroquinolones to be effective.

RIGHT duration

1. Duration of therapy for most infections in veterinary medicine has not been established. There have been reviews that suggest 7-10 days for uncomplicated UTIs (Weese JS et al., 2011). In a study with cefovecin, over 90% clinical success was found after 2 weeks of therapy with a single injection of cefovecin compared to twice daily dosing of an oral cephalosporin.
2. Equally important is owner compliance. If a dosing regimen is interrupted or terminated early there is an increase risk of therapeutic failure, repeat visits (additional cost), and development of drug resistant bacteria. Research has shown owner compliance is improved with once a day and shorter course therapies (Kardas P et al., 2003)

For many years veterinarians relied on human approved products to treat disease in animal patients. Today, we have veterinary labeled products in most of the therapeutic categories. Some drugs on the culture/susceptibility panel are human drugs and the interpretive criteria have not been established for veterinary pathogens. A generic drug used today is the human approved fluoroquinolone, ciprofloxacin. Even though ciprofloxacin may be less expensive than the veterinary approved fluoroquinolones several factors should be considered prior to its use in dogs and cats. In some laboratories, ciprofloxacin is used as a class representative for veterinary fluoroquinolones. However, studies have shown ciprofloxacin does not predict the susceptibility of veterinary fluoroquiolones (Riddle C et al., 2003). Susceptibility to ciprofloxacin is based on human bacterial isolates and interpretive criteria do not exist for veterinary pathogens. Studies correlating an effective dose with clinical outcomes have not been performed; therefore, a scientific proven dose does not exist for companion animals. The pharmacokinetics of

ciprofloxacin differs between companion animals and humans where the amount of oral ciprofloxacin absorbed into systemic circulation is less in the dog and cat compared to humans (Nakamura S et al., 1990, Albarellos GA et al., 2004, Abadia AR et al., 1995). A recent study showed variable absorption among laboratory dogs when given ciprofloxacin as an oral tablet (Papich MG 2012). Comparatively, veterinary fluoroquinolones are well absorbed in dogs and cats and interpretive criteria have been established for veterinary pathogens for *in vitro* susceptibility testing.

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