PRACTICAL APPLICATION OF ANTIBIOTIC USE GUIDELINES

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INTRODUCTION

Antimicrobial resistance “occurs when bacteria change in response to the use of antibiotics to treat bacterial infections (such as urinary tract infections, pneumonia, bloodstream infections) making [antibiotic treatment] ineffective,” according to the World Health Organization (WHO)\(^1\). The Centers for Disease Control and Prevention, the White House, the WHO and other local and global entities have sounded the alarm regarding emerging antimicrobial resistance and have made antimicrobial stewardship a top priority. The MN Department of Health has convened a One Health Antimicrobial Stewardship Collaborative initiative in which stakeholders in human, animal and environmental health have developed a 5-year strategic plan to combat antimicrobial resistance in Minnesota.\(^2\)

Compared to the human and food animal health fields, little attention has been paid to antimicrobial resistance in companion animal medicine, though we all have experienced it. One challenge in companion animal medicine has been the lack of evidence to support specific antibiotic protocols and the dearth of guidelines for antimicrobial use. In response to this unmet need, the International Society for Companion Animal Infectious Diseases (ISCAID) has gathered together panels of veterinarians to provide guidelines that combine evidence and expert opinion, where evidence is lacking, for antibiotic use in common small animal diseases. So far, guidelines for canine superficial bacterial folliculitis\(^3\) and canine and feline urinary tract infections\(^4\) have been published. Forthcoming are guidelines for respiratory disease and an update to the UTI guidelines. All published guidelines are available open access on the ISCAID website.\(^5\)

USING THE GUIDELINES IN PRACTICE

While the guidelines are meant to provide general recommendations, they will not apply to every clinical situation. For this reason, we seek in this session to highlight the antimicrobial stewardship ideas addressed in the guidelines and point out areas of contention as well as areas that require more evidence-based medicine to inform clinical practice. (Note: Areas in which we disagree or feel the guidelines need clarification are written below in italics).

Antimicrobial use guidelines for the treatment of urinary tract disease in dogs and cats

1. Simple Uncomplicated Urinary Tract Infections:

   Simple uncomplicated UTIs are rare or infrequent bacterial bladder infections in patients with normal urinary tract anatomy and function and no comorbid diseases that would predispose to UTI. The presence of lower urinary tract signs (stranguria, pollakiuria, urgency) alone does not indicate the presence of infection, though these signs are typically present with clinical UTIs and should initiate a work-up. Similarly, bacteriuria and pyuria do not always indicate a clinically significant UTI, especially in the absence of clinical signs (see more about asymptomatic bacteriuria below). Of note, urinary tract infections are rare in cats, and lower urinary tract signs are more likely due to feline idiopathic cystitis or urolithiasis.

   A urinalysis is considered part of a minimum database for simple UTIs and can provide information regarding potential comorbidities, but exert caution in interpretation due to potential contamination if stains are used. Ideally, an aerobic urine culture should be submitted to a diagnostic laboratory to determine colony-forming unit counts, speciation and sensitivity testing, with every UTI. The guidelines recommend that samples be collected via cystocentesis, with catheterization as a second
choice; free catch samples are discouraged. *We disagree with the guidelines here. A clean mid-stream sample in our practice is a suitable specimen, and unlikely to be contaminated in our experience, if collected appropriately. One recent study suggested that applying the cut-off of >100,000 CFU/ml to voided samples provided an overall sensitivity and specificity of 94%. This cut-off resulted in 4% false positives and 2% false negatives. It is important to note, however, that all dogs in the study had consistent lower urinary tract clinical signs. One milliliter of urine is plenty for urine culture, and 5 mls is sufficient for both urine analysis and culture. Using a sterile collection container, ensuring the sample is mid-stream, and not attempting to collect too much will help to prevent contamination. Owner-obtained samples should not be cultured, as these may be contaminated.*

The guidelines recommend that reasonable first line or empiric therapy choices for a simple uncomplicated UTI include amoxicillin or trimethoprim sulfonamide. If susceptibility results indicate that the isolate is resistant to the chosen empiric antibiotic, the decision to change the antibiotic should depend on the presence or absence of a clinical response. The guidelines suggest that if the patient is improving, changing the antibiotic may not be indicated. However, we recommend that the urine be recultured to ensure the perceived clinical response is a true microbiologic response. If the bacteria are still present, then the antibiotic should be stopped and replaced with an appropriate antibiotic based upon susceptibility testing.

The current guidelines state, in the absence of sufficient evidence to inform duration of therapy, 7 days of treatment is likely adequate. However, since the release of these guidelines, a couple of papers have started to address this question. One study found no difference in clinical cure rates in dogs treated with 3 days of trimethoprim-sulfamethoxazole or 10 days of cepha lexin. Another study found no difference in clinical cure rates in dogs with uncomplicated UTIs when treated with 3 days of high dose enrofloxacin versus 14 days of amoxicillin-clavulanic acid. Based on these studies, it is likely that the conventional 10-14 days of antibiotic therapy is not necessary in the majority of uncomplicated UTIs. Further prospective studies are needed to determine if short duration therapy with first tier drugs provides adequate clinical cure rates.

3. Complicated Urinary Tract Infections:

Complicated UTIs are those in which a functional or anatomic abnormality of the urinary tract or the presence of a comorbid condition results in chronic or recurrent infection. Recurrent infections are defined as three or more infections within a year. Diagnosis of recurrent infections should always be by urine culture. A thorough physical exam, including rectal and vulvar exams should be performed. Additionally, a minimum database (CBC, chemistry, urine analysis) and endocrine testing, if indicated, are used to determine predisposing factors. Radiographic or ultrasonographic evaluation of the urinary tract to look for abnormalities and uroliths should be performed. If these diagnostics do not reveal a cause for recurrent infections, referral to a specialist for cystoscopy may be necessary.

When possible, waiting for culture results prior to instituting antibiotic therapy is recommended. If the clinical signs require immediate initiation of treatment, then empirical therapy should be as for simple uncomplicated UTIs. The guidelines recommend using a first line drug from a drug class not previously used, *though no evidence is provided for this recommendation. Previous use of an antibiotic does not necessarily mean that the current infection is resistant to it.* Antibiotics excreted in the active form into the urine should be used. If more than one organism is cultured from the urine, therapy should be directed towards the pathogen(s) deemed clinically relevant. The guidelines state that anecdotally *Enterococcus* is likely to resolve once the other infecting organisms are cleared. *If susceptibility testing indicates that a third tier antibiotic is required, we would recommend referral.*

Again, there is little data to guide duration of therapy, though 4 weeks is often utilized. The guidelines suggest that shorter duration is likely to be effective, especially in non-recurrent infections complicated by comorbidities such as diabetes or hyperadrenocorticism. *Though not mentioned in the guidelines, in patients with immune compromise, bactericidal drugs are indicated. Regardless of the duration of therapy, culture 5-7 days after treatment initiation, as well as 7 days after cessation of therapy, is recommended.*
3. Asymptomatic Bacteriuria:

Asymptomatic bacteriuria, also called subclinical bacteriuria or clinically silent bacteriuria, is the presence of bacteria in the urine via culture in the absence of clinical (and sometimes cytological) signs. Since the guidelines have been published, two studies have addressed asymptomatic bacteriuria in dogs and cats. Both studies suggest that abstaining from treating patients without clinical signs despite positive urine cultures does not affect morbidity or mortality. In humans, asymptomatic bacteriuria, even in the presence of significant pyuria, is not treated unless the patient is pregnant or about to undergo urogenital surgery. Of note, multidrug resistant organisms do not require treatment without clinical signs, unless there is a high risk of pyelonephritis. Often the absence of antibiotic pressure will allow more susceptible organism to take over in time. We agree with this observation, and often withhold therapy in asymptomatic patients, especially those with asymptomatic Enterococcus bacteriuria.

Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis

1. Diagnosis of Superficial Bacterial Folliculitis:

*Staphylococcus pseudintermedius* (sometimes reported as *S. intermedius* group) is the most common organism associated with superficial bacterial folliculitis (SBF) in dogs, though *S. aureus* and the coagulase-variable *S. schleiferi* are sometimes implicated (very rarely *Streptococcus*, *Pseudomonas*, and other Gram negative organisms can be seen). Most often, the diagnosis of SBF is made based upon characteristic clinical signs. These include the presence of papules, pustules, crusts, epidermal collarettes, and patchy or “moth-eaten” alopecia. However, it is important to interpret these lesions in the context of the patient’s history and general physical examination findings because other skin disorders can present with lesions mimicking SBF (e.g. pemphigus foliaceus and cutaneous drug eruption).

Cytology is strongly recommended for every case; the presence of coccie is supportive of the diagnosis and patients can be screened for co-infection with *Malassezia*. The guidelines suggest that cytology is mandatory in the absence of typical lesions, the absence of expected clinical response to therapy, or whenever a culture is to be performed. Intracellular bacteria confirm infection, and large numbers of degenerate neutrophils and extracellular bacteria are also indicative of infection. Though leukocytes may be absent in severely immunocompromised patients, *we urge caution when interpreting large numbers of coccie in the absence of inflammatory cells, as this is likely to be bacterial overgrowth and not true infection*. Similarly, with atypical presentations or lack of response to treatment, investigations for differential diagnoses are recommended (for example, fungal dermatophyte culture and deep skin scraping for demodicosis).

While culture is always a good idea, there are circumstances in which the likelihood of an antimicrobial resistant infection dictates the need for culture and susceptibility testing. These include inadequate improvement (<50% reduction in lesions) or emergence of new lesions after 2 weeks of therapy, lesions remaining after 6 weeks of therapy, presence of rods on cytology, and history of having or being exposed to another animal with a methicillin-resistant and/or multi-drug resistant infection. Previous exposure to antibiotics increases the risk of methicillin-resistant *S. pseudintermedius* (MRSP). Ideally, pustules are sampled for culture. The guidelines include helpful tables to guide sampling and interpretation of microbiology results. Unlike urinary cultures while patients are on antibiotics (especially those that concentrate in the urine), current therapy with antibiotics does not have a significant effect on the ability to culture the causative agent in skin infections.

The guidelines point out a couple of caveats for interpretation of culture and susceptibility results. First, if the bacteria are resistant to erythromycin but susceptible to clindamycin, they may have inducible resistance to clindamycin. Additional tests can be performed to look for this inducible resistance. Second, ensure that the lab you are using differentiates between coagulase positive and negative *Staphylococcus*, as well as among *S. aureus* and veterinary coagulase positive *Staphylococcus* species. The antibiotic breakpoints differ between *S. aureus* and *S. pseudintermedius* and *S. schleiferi*. Additionally, *S. aureus* carries a greater zoonotic concern.
2. Treatment of Superficial Bacterial Folliculitis:

Treatment for SBF can be topical, systemic or a combination of the two. Localized or mild disease may only require topical therapy to clear infection. Medicated ointments, gels, creams, sprays, mousse, lotions and wipes are useful for localized infections, while shampoos, conditioners, and sprays are typically used for generalized disease. The guidelines suggest that the use of topical therapy as an adjunct to systemic antimicrobial therapy may shorten the duration of therapy needed. Treatment duration is typically 3 to 6 weeks, and the guidelines recommend treatment 1 week beyond clinical resolution to prevent relapse.

The guidelines recommend first generation cephalosporins (ex: cephalexin), clindamycin and amoxicillin-clavulanate as first tier antibiotics to be used for empiric therapy or as first choices when susceptibility testing indicates these will be effective. We differ from the guidelines in the recommendation of clindamycin for empiric therapy. As described above, staphylococci may have inducible resistance to clindamycin. Of note is the lack of consensus among members of the guideline working group regarding categorization of third generation cephalosporins (cefovecin/Convenia, and cefpodoxime/Simplicef) as first versus second tier antibiotics. A tenant of antimicrobial stewardship is using narrow spectrum antibiotics whenever possible. As most SBF infections are due to Gram-positive S. pseudintermedius, using an enhanced spectrum cephalosporin is not needed. Additionally, the authors cite concern that the use of cefovecin may select for highly resistant Gram-negative bacteria in the gut, causing the development of extended-spectrum β-lactamase-producing E. coli. In our practice, third generation cephalosporins are restricted to use only by pre-authorization. Third generation cephalosporins are drugs of human medical importance, and thus are not used for empiric therapy. There are rare occasions when the ability to provide an antibiotic as a single injection is desirable (animals in which oral medications are not possible, i.e., oral tumors).

When choosing empiric therapy, consider that there may be regional differences in antimicrobial resistance patterns. Your laboratory may provide regional antibiogram data. Rather than using regional resistance patterns to choose empirical therapy, we recommend that this information be used to guide the need for culture. For example, if your region’s antibiogram shows that 65% of S. pseudintermedius isolates are susceptible to cephalexin, you may choose to perform a culture right away to guide therapy.

Successful therapy is dependent not only on the use of appropriate antimicrobial agents, but also the resolution or adequate control of underlying or inciting disease processes, such as atopy. Thus, as with recurrent urinary tract infections, a thorough work-up may be required. Finally, as for any disease process, client education is paramount for successful therapy.

REFERENCES:


