Short "Staph"ed: Dealing with Antibiotic Resistant Gram Positive Infections

Stephen Cole, VMD, MS
Clinical Microbiology Fellow

Objectives

(1) Review the pathogenesis, therapeutic approach and clinical epidemiology of *Staphylococcus spp*. and *Enterococcus spp.* from small animals.
(2) Describe the common mechanisms of antibiotic resistance amongst common companion animal pathogens.
(3) Be able to generate diagnostic and therapeutic approaches to managing resistant Gram positive infections.

Staphylococcus pseudintermedius

Staphylococcus pseudintermedius is arguably the single most important infectious agent of canine disease. It is the most common agent of canine pyoderma, otitis externa and post-surgical infections. It is also commonly associated with struvite urolithiasis and secondary bacterial infections of the respiratory tract. Traditionally, beta lactam antibiotics were considered the drug of choice for treating staphylococcal infections. These drugs included first-generation cephalosporins and potentiated penicillins (i.e amoxicillin-clavulanate). Other first line antimicrobials include clindamycin and potentiated sulfonamides (i.e. TMS) for staphylococcal infections. Treatment with non-potentiated penicillins (i.e. procaine penicillin G, amoxicillin) is no longer recommended because beta-lactamase production is common among clinical isolates.

In recent years several successful clones of Methicillin-Resistant *Staphylococcus pseudintermedius* (MRSP) have disseminated throughout the USA. In the PennVet microbiology lab about 50% of isolates are methicillin resistant. While many strains exist, one strain called ST68 is thought to be the predominant MRSP in North America. Isolates are determined to be "methicillin-resistant" when the MIC of the organism is equal to or greater than 0.5 for the drug oxacillin. **Isolates determined to be "methicillin-resistant" are considered resistant to ALL beta-lactam antibiotics REGARDLESS of the MIC for that particular drug.** For example, if the isolate is methicillin-resistant then it is also resistant to amoxicillin-clavulanate (Clavamox), cefpodoxime (Simplicef) and carbapenems. The main mechanism of resistance is by production of an enzyme called "penicillin-binding protein 2A". This enzyme allows for bacterial cell wall synthesis even in the presence of beta lactams (which typically inhibit this process). It is also common that MR staphylococci are also resistant to other classes such as quinolones and macrolides.

There are also other species of *Staphylococcus* that are clinically important in small animals. *Staphylococcus schleiferi* is also an agent of canine pyoderma and very common in canine otitis. Rates of methicillin-resistance in *S. schleiferi* can exceed 75%.

Enterococcus spp.

Enterococci are common and normal inhabitants of the gastrointestinal tract of many animals. They can cause opportunistic infections such as skin and soft tissue infections and urinary tract infections. They are also common isolates in cases of bacterial cholangiohepatitis. Formerly known as "Group D Streptococci" these organisms are also common contaminants in bacterial cultures. The two most common species isolated from companion animals are *Enterococcus faecalis* and *Enterococcus faecium*.

Enterococci are intrinsically resistant to many classes of antimicrobials including lincosamides, sulfonamides, cephalosporins and aminoglycosides. Resistance to the quinolones and tetracyclines is also common. In human medicine, vancomycin-resistant *Enterococcus faecium* is a major concern for nosocomial infections; however, resistance is not commonly reported among veterinary isolates.

Therapy Options

Not Treating
It is important to note that "more resistant" does not mean "more pathogenic." It is important for you, as a clinician, to determine whether CLINICALLY this animal requires systemic antimicrobials to manage the disease. Consider the presence of other pathogens and the role the organism may play. Isolation of an organism is not always indication to treat. Remember BOTH of these organisms are normal flora of our patients and may be contaminants in the culture. Also, in human medicine, the "60-90" rule states that 60% of resistant infections will still "respond to antimicrobials." This reminds us that the goal should be clinical resolution of disease. In veterinary medicine we have no evidence to support or dismiss this concept.

Topical Therapy
Many Gram positive infections are accessible from the "outside". Topical therapy allows for HIGHER concentration of antimicrobials to affect the organisms for LONGER periods of time. It can be considered as monotherapy OR as adjunctive to systemic therapy. Examples of common therapies that should be included in comprehensive approaches to MRSP infections are chlorhexidine, benzoyl-peroxide, nisin and silver-sulfadiazine. Mupirocin ointment is often useful for treatment of focal MRSP infections; however, it should be reserved for serious or refractory infections since resistance is emerging.

First-Line Therapies
For MRSP, it is important to reconsider first-line therapies (if lucky enough) such as clindamycin and TMS. Clindamycin is a generally safe, narrow spectrum drug. It is important to confirm that the isolate is also erythromycin sensitive to avoid treating strains that may be INDUCIBLY resistant. Some labs automatically test for this mechanism. TMS (or OMS) is associated with immune-mediated diseases (KCS, IMHA, IMPA etc) and should be avoided in patients with a history of these conditions. It should also be avoided in dobermans, samoyeds and miniature schnauzers due to higher risk for side-effects. For *Enterococcus,* penicillin or amoxicillin should be used if the strain is sensitive.

Tetracyclines
The tetracyclines can be effective against MRSP and *Enterococcus* but resistance can be common. In our lab approximately 30% of MRSP and 75% of *Enterococcus faecium* are resistant to tetracyclines. New laboratory breakpoints may also affect these rates. Tetracyclines are mainly excreted in the bile which makes there use for UTI limited. Use should be avoided in growing animals (enamel hypoplasia). Cats should only be given the liquid formulation or have a pill followed with water to avoid the risk of esophageal stricture. Minocycline is more lipophilic and thought to have better penetration to the skin.

Chloramphenicol

Chloramphenicol is a broad-spectrum antimicrobial with Gram positive, Gram negative and anaerobic coverage. It should be dosed at 50 mg/kg TID to treat skin infections in dogs. In cats, 12 mg/kg BID is recommended; however, the clinical experience of the presenter is that this drug is rarely well-tolerated in cats. It is important to instruct owners of the risks associated with this drug and how to handle it appropriately.

Nitrofurantoin

This first line human drug is considered second or third line in veterinary medicine. It is **urinary tract only drug** and should not be used in cases of pyelonephritis due to poor tissue penetration. Recommended dose is 4.4 m/kg TID. It should also be avoided in young animals. This drug has also been associated with a reversible, peripheral neuropathy in dogs. **NOT TO BE USED IN CATS.**