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INTRODUCTION

Resistance is resistance, right? The first thing to clear up about antimicrobial resistance is the definition of resistance. Clinicians are concerned about clinical resistance, based on clinically applicable breakpoints. Approved veterinary breakpoints are developed and approved by the Clinical and Laboratory Standards Institute Veterinary Antimicrobial Susceptibility Testing Subcommittee (CLSI VAST) based on the following.

- Clinical outcomes coupled with pathogen MIC distributions
- MIC distributions of wild type isolate collections
- Pharmacokinetic/pharmacodynamic modeling

These breakpoints are intended to give guidance on the probability of an antimicrobial working within the context of a combination of pathogen, antimicrobial, disease, animal species, and specific treatment regimen. Deviation from any of these factors greatly diminishes the predictive value of the breakpoint. It is incredibly important that we understand which breakpoints actually have a reasonable link to antibiotic resistance and which ones don’t.

The second type of “resistance” is related to changes in population profiles of “wild type” susceptibility distributions. Instead of a clinical breakpoint, these are now referred to as an “epidemiological cutoff”. These cutoffs are defined to indicate a change from the original population minimal inhibitory concentration (MIC) distribution, and may indicate the appearance of resistance genes. While the wild type cutoff is a component of a clinical breakpoint, without consideration of the other two components of the CLSI breakpoint process they are not necessarily correlated to clinical response. One of the outcomes of using both epidemiological cutoffs and clinical breakpoints in different monitoring systems may be declaring “resistance” at different MICs. This situation is complicated even further by the potential for resistance genes to be present that are not detected by phenotypic testing.

RESISTANCE CHALLENGES IN HUMAN MEDICINE

This session is about resistance challenges in veterinary medicine, but it helps us to see how challenges in human patients parallels our challenges. Therefore, understanding the resistance challenges in human medicine may inform our interaction with resistance challenges in veterinary medicine.

In 2013, the Centers for Disease Control and Prevention (CDC) released a report describing the major antibiotic resistance threats to human health. In this report, the major
threats were classified as threat levels of urgent, serious, and concerning. The urgent threats are high-consequence because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission. The urgent threats are *Clostridium difficile*, carbapenem-resistant Enterobacteriaceae, and drug-resistant *Neisseria gonorrhoeae*. *Clostridium difficile* is included because of the increasing (in both prevalence and severity) incidence of pseudomembranous colitis in patients treated with antimicrobials.

The CDC serious classification includes threats that for various reasons are not considered urgent (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), but which will worsen and may become urgent without ongoing public health monitoring and prevention activities. These organisms are multidrug-resistant *Acinetobacter*, drug-resistant *Campylobacter*, fluconazole-resistant *Candida*, extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *Pseudomonas aeruginosa*, drug-resistant non-typhoidal *Salmonella*, drug-resistant *Salmonella typhi*, drug-resistant *Shigella*, methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae*, and drug-resistant tuberculosis.

The CDC classification of “concerning” includes bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response. These organisms are vancomycin-resistant *Staphylococcus aureus* (VRSA), erythromycin-resistant Group A *Streptococcus*, and clindamycin-resistant Group B *Streptococcus*.

**RESISTANCE CHALLENGES IN VETERINARY MEDICINE CLOSELY MIRROR THOSE IN HUMAN MEDICINE**

Weese published a review of antimicrobial resistance issues in companion animals (2008), identifying these major organisms of concern. This would still be a good list for resistance challenges in veterinary medicine.

- *Staphylococcus aureus* and *Staphylococcus pseudintermedius*: both methicillin susceptible and resistant.
- Enterococci: *Enterococcus faecium* and *Enterococcus faecalis*.
- *Streptococci*: *Strep. zooepidemicus* and *Strep. Equi* in horses, *Strep. canis*
- *Escherichia coli*
- *Salmonella*
- *Pseudomonas*

**Methicillin-Resistant Staphylococcus aureus**

While *Staphylococcus pseudintermedius* is a very real resistance concern in veterinary medicine, methicillin resistant *Staphylococcus aureus* (MRSA) highlights issues of zoonotic interactions in multiple veterinary species. A 2008 review article summarized MRSA occurrence in cattle, dogs, cats, sheep, chickens, horses, rabbits, seals, and psittacine birds. Significant research has demonstrated the potential for exchange of isolates between people and their pets. Kottler, et al., evaluated the prevalence of MRSA in people and pets in the same household. The sample consisted of one human nasal swab and one dog or cat nasal and fecal
swab from 586 households. There was no difference in MRSA prevalence in households with human healthcare workers, veterinary healthcare workers, or without healthcare workers. The occurrence of MRSA in humans was 5.6%, with 3.4% in pets. In 4 of the 586 households (0.7%), the MRSA found in humans was the same strain as that found in the pet.

Faires, et al., evaluated the prevalence of concurrent infection in households where either a person or pet had a diagnosed MRSA colonization. In part 1 of the study, 22 households were identified as having an MRSA infection in a pet (19 dogs and 3 cats). In these households, 10 of 56 humans (17.9%) were also colonized with MRSA. In part 2 of the study, 8 households were identified where humans had MRSA cultures from dermal abscesses. In only 1 of these households was MRSA also isolated from a pet. In almost all cases of co-colonization or infection, the isolates were indistinguishable by PFGE.

O’Mahony, et al., evaluated MRSA isolates from dogs, horses, a cat, a rabbit, and a seal in Ireland along with isolates from 10 caregivers. The PFGE results for the equine MRSA isolates were indistinguishable from the results for those isolates originating from the caregivers for the horses.

Several studies have evaluated risk factors for infection with MRSA in companion animals. Faires, et al., evaluated risk factors for 40 MRSA infected dogs compared with 80 MSSA infected dogs. The highest prevalence of both infections was in ears and skin. The statistically significant risk factors for MRSA infection as compared to MSSA infection included the use of any antimicrobial prior to diagnosis (odds ratio 2.84), use of fluoroquinolones (OR 3.58), use of β-lactams (OR 3.58), or intravenous catheterization (OR 3.72).

A retrospective study in horses in Canadian and American referral hospitals evaluated MRSA infections in 115 horses. The infections originated both in the referral hospitals and in the community, with the frequency of both being approximately equal. Community acquired infections were significantly associated with previous hospitalization and previous gentamicin therapy. Hospital-acquired MRSA infections were significantly associated with infected incision sites.

Increasing attention in the literature has been paid to MRSA in swine and potential zoonotic concerns. While swine workers and veterinarians have been demonstrated to have nasal carriage of the MRSA type found in swine herds, epidemiological studies suggest that colonization is primarily limited to those working with the swine and further transmission is limited to familial communities of these exposed workers. In the U.S., the human community-acquired outbreak strains are different from animal strains. In the Netherlands, a type of MRSA (ST 398) is epidemiologically associated with pig and cattle farmers and is said to be > 20% of carriage in humans. MRSA has also been identified in bovine mastitis isolates. The authors of a 2012 study using single nucleotide polymorphisms (SNPs) to evaluate 89 CC398 MRSA isolates proposed that this MRSA originated in humans as a methicillin-susceptible isolate and then acquired tetracycline and methicillin resistance in livestock, but also lost phage-carried human virulence genes. MRSA CC398 has been documented to cause disease in humans, although it is not a major player in MRSA-associated disease in humans and appears to be a poor long-term colonizer.
Carbapenemase-Producing Enterobacteriaceae

MRSA is an example of a resistant organism (which may also be multi-drug resistant) that brings the issue of treating our veterinary patients together with concerns about the effect of this pathogen’s presence on our clients. A more recently emerging issue of shared resistance between human and animal pathogens is that of carbapenemase-producing enterobacteriaceae (CRE).

Human cases of CRE have been in the news lately where multidrug resistant pathogens have displayed resistance to this class of antimicrobials previously considered to be omnipotent. And, once again, the situation in veterinary medicine is mirroring the antimicrobial resistance challenges in human medicine. Carbapenemase-producing isolates of *Klebsiella pneumoniae* and *E. coli* have been identified in dogs from a single hospital in Germany, with the clonal nature of the isolates suggesting nosocomial spread.\(^{16}\) Carbapenem producing E. coli have also been confirmed in clinical isolates derived from dogs and cats in the United States.\(^{17}\) An analysis of the literature related to potential sources of these organisms cites detection in dairy cows (France), horses (Belgium), a wild raptor (Germany), poultry and swine (China), dogs and cats (Germany and USA), and multiple instances in water and sewage throughout the world.\(^{18}\) The pattern reasonably supports a hypothesis of spread to multiple veterinary species through environmental dissemination of human sources; this is further supported by no labeled carbapenems for food animals, a cost structure which makes extralabel use in food animals highly unlikely, and limited use in companion animals. While certainly not yet ubiquitous in occurrence, confirmation of these isolates in veterinary species strongly supports the need for continued evaluation of our use of carbapenems in veterinary species, and the potential for the occurrence of these organisms in clinical practice.

Bovine Respiratory Disease Pathogens – An example of looking to the future of therapy in food animals

Lubbers and Hanzlicek published a retrospective analysis of *Mannheimia haemolytica* susceptibility results during 2009-2011 from the Kansas State Diagnostic Laboratory.\(^{19}\) The percentage of isolates showing resistance to at least 3 of our main classes of antibiotics used for BRD were 42%, 46%, and 63% in 2009, 2010, and 2011 respectively. These data represent diagnostic laboratory isolates primarily from cattle of types associated with high risk for respiratory disease and do not represent a random sample across all cattle. However, these data represent isolates from cattle where the attending veterinarian felt the need to submit samples for susceptibility testing, and the trend in multidrug resistance in this population of cattle is concerning. While the data from the paper encompass 2009-2011, Dr. Lubbers provided this update through 2013.
In this figure, the X axis is the number of antimicrobials to which the isolate is resistant. The Y axis is the percent of *Mannheimia haemolytica* isolates. The 5 antibiotics represented are florfenicol, spectinomycin, enrofloxacin, tilmicosin, and oxytetracycline. Ceftiofur consistently tests as susceptible; however, that breakpoint is set at 2 µg/ml and the MIC90 of the wildtype population is typically around 0.03 to 0.06 µg/ml, requiring at least a 7 dilution jump to be called intermediate. Tilmicosin results closely agree with tulathromycin results. Of 179 M. haem isolates in 2011, 152 (85%) were direct matches, 14 were susceptible for tulathromycin and intermediate for tilmicosin, 10 isolates displayed resistance for one and intermediate for the other. The difference between 4 and 5 resistance findings is typically absence or presence of resistance to florfenicol.

When looking back at single drug trends in *Mannheimia haemolytica* at the Kansas State Diagnostic Laboratory a consistent trend is evident from 2005-2014.
The top dilution tested for tilmicosin up through mid-2007 was 32 µg/ml, making the maximum concentration on the chart ≥ 64 µg/ml. In mid 2007, a concentration of 64 µg/ml was added, making the top concentration on the chart >64 µg/ml.
Summary

Many of the resistance concerns in veterinary medicine mirror the challenges in human medicine. While it is possible for the discussion to devolve into one of assigning blame to antimicrobial use practices in one arena or the other, the solution is to adopt well-designed antimicrobial use strategies for all applications of antimicrobials.