A review of multidrug resistant surgical site infections

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Summary
Surgical site infections caused by bacteria that are resistant to multiple classes of antimicrobials are an important and increasing problem in veterinary medicine. Organisms such as methicillin-resistant staphylococci, extended spectrum beta-lactamase Enterobacteriaceae and multi-drug resistant Enterococcus, Acinetobacter and Pseudomonas spp. are among the current concerns; however, the emergence and dissemination of other multi-drug resistant organisms will likely follow. Despite the negative connotations that are associated with multi-drug resistant infections, most infections are potentially treatable if basic principles of infection treatment and infection control are followed.

Keywords
Nosocomial, antimicrobial resistance, surgical site infection

Introduction
Infectious diseases have been critically important causes of morbidity and mortality for millennia. Arguably, one of the most important discoveries in medicine was the identification of antimicrobials. It was not until the start of the ‘antibiotic era’ that human and veterinary medicine became equipped to successfully deal with various bacterial diseases. The introduction of antimicrobials had profound effects on patient morbidity and mortality and ushered in an era of great optimism. The optimism was so great that in 1967, the US Surgeon General declared that it was ‘time to close the book on infectious diseases’ (1). In hindsight, statements such as that seem ludicrous and the pendulum has swung in the opposite direction. Some people have expressed concern that the end of the ‘antibiotic era’ may be near (2) and questioned whether the continued emergence of multi-drug resistant (MDR) pathogens represents an ‘unwinnable war’ (3). Like most situations, reality likely lies between those two extremes, but concerns over the emergence and dissemination of MDR pathogens in human and veterinary medicine are significant.

Pathogens of concern
A variety of MDR pathogens may be encountered in veterinary surgical site infections (SSIs). Most are opportunistic pathogens that can be found in varying percentages of healthy animals. The prevalence of different pathogens likely varies between different geographic regions, between different animal species, and between veterinary practices. Most of the attention has been focused on a small number of pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), however other MDR bacteria can be as important from a clinical standpoint. Some of the more important pathogens are discussed in detail below.

**Methicillin-resistant Staphylococcus aureus (MRSA)**

Methicillin-resistant *S. aureus* is a critically important human pathogen and an emerging veterinary and zoonotic pathogen. MRSA strains are resistant to all beta-lactam antimicrobials (penicillins, cephalosporins, carbapenems) because they possess an altered penicillin-binding protein. Additionally, MRSA strains are often resistant to various other antimicrobial classes and treatment options may be very limited.

Recently, it was estimated that MRSA caused over 94,000 invasive infections in humans in the United States in 2005 with 18,600 deaths (4). MRSA is the most common cause of SSIs in some regions (5, 6). The incidence of MRSA SSIs in veterinary medicine is unclear but reports are increasing (7–15).

Clinical presentation of MRSA infections is not necessarily different from infections caused by a variety of other MDR and susceptible pathogens. Opportunistic infections, particularly surgical site, wound, skin and soft tissue infections, predominate in both animals and humans (8, 11, 15, 16, 4). Infections can range from mild and superficial to rapidly fatal, and can originate in the community, primary care veterinary clinics or referral hospitals.
Studies of risk factors for MRSA SSI have not been reported in animals, but antimicrobial use, originating from a farm with colonized horses and previous nasal colonization have been reported as risk factors for MRSA colonization in horses (17, 18). Colonization upon admission to hospital was also identified as a risk factor for development of clinical infection in horses (17). Similar information is not currently available for small animals.

There has been a lack of studies that have objectively evaluated different treatment regimens for MRSA (or any other MDR infection) in animals, however basic principles apply. Treatment is based on antimicrobial susceptibility as well as patient and infection factors. Penicillins, cephalosporins and carbapenems should not be used, regardless of in vitro susceptibility data. Fluoroquinolones should be avoided because in vitro data poorly predict in vivo response and because resistance quickly develops (19). Fortunately, there are typically one or more reasonable antimicrobial options for almost all MRSA infections, at least at this time. Obtaining an ‘expanded panel’ of antimicrobials may be required in order to identify appropriate treatment options. Chloramphenicol susceptibility is common and this drug has been successfully used to treat MRSA infections in different species, although emergence of resistance has been detected during treatment in horses (J.S. Weese, unpublished data). Human exposure issues must be considered when deciding whether this drug is appropriate. Trimethoprim-sulpha is often used in humans with community-associated MRSA infections (20), and may be useful in veterinary species. Aminoglycosides, particularly amikacin, may be useful in some situations, however gentamicin resistance appears to be common in horses (8, 21, 22). Vancomycin is widely used in human medicine, however there are concerns about the use of this critically important human drug in animals. Some veterinary facilities have implemented voluntary vancomycin restriction policies.

Topical application of antimicrobials (i.e. fusidic acid or mupirocin) or antiseptics, such as chlorhexidine, may also be useful. Local or regional therapy with antimicrobials, such as amikacin, may also be important treatment options.

An area of particular concern with MRSA is the potential for outbreaks and interspecies transmission. Both sporadic nosocomial MRSA infections and outbreaks have been encountered in small animals and horses. Additionally, veterinarians appear to have abnormally high rates of nasal MRSA colonization compared to the general public (23–26). This suggests that veterinarians may acquire MRSA occupationally, which could put them at risk for MRSA infection. Furthermore, colonized veterinary personnel have been implicated as sources of MRSA infection of their patients (11, 15, 27). Therefore, infection control precautions are important in order to reduce the risk of both human and animal exposure.

Other methicillin-resistant staphylococci

A variety of other MDR staphylococci may be encountered. Staphylococcus intermedius has typically been considered to be the main cause of staphylococcal infections in dogs and can also cause opportunistic infections in other species such as horses and cats. Methicillin-resistant strains (MRSI) are increasingly being reported (28–30); however recent evidence indicates that most, if not all, isolates identified as S. intermedius in dogs are actually the closely related species S. pseudointermedius (31, 32). The same may be true in other mammals. Regardless, whether an isolate is called MRSI or methicillin-resistant S. pseudointermedius (MRSP) is probably inconsequential. Staphylococcus schleiferi coagulans is another coagulase positive species and methicillin-resistant strains have been reported, primarily in dermatological disease in dogs (28, 29, 33). There is currently an absence of evidence that there are differences in clinical presentation with infections involving these different staphylococci.

Coagulase negative staphylococci (CoNS) are a broad group that include S. sciuri, S. lentus, S. capitus, S. epidermidis, S. haemolyticus, S. felis, S. simulans, S. saprophyticus, S. schleiferi schleiferi, S. warneri and S. vitulinus, among others (34). They are often considered as a group and speciation is rarely performed, which may be a reasonable approach because there is currently little evidence that speciation affects treatment or prognosis. CoNS are commonly found as commensal microflora of many body sites in a variety of species, and methicillin-resistant rates can be very high even in healthy animals in the community (34–37). CoNS are typically only pathogens of compromised hosts. Surgical site infections, wound infections, invasive device infections and bacteremia are most common.

Treatment of these MDR staphylococcal infections is the same as for MRSA, with less concern about interspecies transmission. Despite receiving less attention than MRSA, these organisms may be as, or more, difficult to treat. It has been anecdotally observed that MRSI/P isolates are often more drug resistant than MRSA.

Enterococci

Enterococci are opportunistic Gram-positive pathogens that are commonly found in the gastrointestinal tract of many animal species. The two species most often involved in disease are E. faecium and E. faecalis.

Antimicrobial resistance is very common in enterococci, and highly drug resistant strains can be encountered. Enterococci are inherently resistant to various antimicrobial classes, including cephalosporins, some penicillins, clindamycin and trimethoprim (38) and have a tendency to acquire and transmit other antimicrobial resistance determinants. This degree of resistance, combined with an ability to persist in a host longterm as part of the commensal microflora and survive in the hospital environment complicate control of MDR enterococci.

Most published reports in veterinary medicine have involved urinary tract infections (39), however SSIs do occur both sporadically and in clusters. At one veterinary teaching hospital, enterococci are most commonly implicated in catheter site, urinary tract, wound, and incision infections,
with smaller numbers of joint, respiratory and bloodstream infections (J. S. Weese, unpublished data).

Because of limited antimicrobial options, some enterococcal infections can be difficult to treat. Of particular concern are vancomycin resistant *Enterococcus* spp (VRE) infections (38), because there may be few antimicrobial options. VRE appears to be an emerging concern in veterinary medicine, both in veterinary clinics and in the general animal population. While currently uncommon, there are reports of VRE infection or colonization in various animal species (40, 41) and anecdotal information suggests VRE infections may be increasing.

Treatment of MDR enterococcal infections should be based on *in vitro* susceptibility testing, taking a few items into consideration. All enterococci are considered to be resistant to cephalosporins, regardless of *in vitro* results. A lack of correlation of *in vitro* and *in vivo* results can also be a problem with trimethoprim-sulpha and laboratories should not report susceptibility to trimethoprim-sulpha. Ampicillin can be effective for many multidrug resistant enterococcal infections (38). A combination of ampicillin and an aminoglycoside should be considered in more serious or invasive infections, even if aminoglycoside resistance is reported (38), because a synergistic effect exists, whereby cell wall damage by ampicillin facilitates entry of aminoglycosides into the bacterial cell. Aminoglycoside MIC results should be obtained if possible as this combination approach is directed at strains that are susceptible or with low-level aminoglycoside resistance, and may not be effective in cases where high aminoglycoside MIC’s are present. Chloramphenicol susceptibility is reasonably common among small animal and equine isolates (J. S. Weese, unpublished data) and this drug may be useful as long as human health risks are considered and manageable. Drugs such as linezolid and quinupristin/dalfopristin are often used in humans (42) yet their efficacy and safety have not been reported for other species, and there are ethical concerns regarding the use of drugs such as these in animals.

### Acinetobacter spp

Members of the Gram-negative genus *Acinetobacter* may be an important group of pathogens, particularly in hospital environments. *Acinetobacter baumannii*, *A. Iwoffii* and *A. anitratus* are commonly found in the environment and can be part of the normal commensal microflora (43–45). They are opportunistic pathogens that can cause a range of infections in various species, including dogs, cats and horses (46, 47). Hospital-associated infections are probably most common based on the opportunistic nature of *Acinetobacter* spp and the ability of this organism to persist in the hospital environment for prolonged periods of time.

Recently, much attention has been paid to *Acinetobacter baumannii* infections in humans; this is because of the increased incidence and very high level of antimicrobial resistance (2, 48, 49). *Acinetobacter* spp. tend to possess large collections of mobile resistance determinants and also have a high endogenous mutation rate that allows for *de novo* development of resistance (50). Emergence of resistance even during a single course of therapy has been reported (51). Some *Acinetobacter* spp. strains possess resistance mechanisms against all known antimicrobial classes (2, 51). While less has been published about *Acinetobacter* spp infections in animals, opportunistic infections including intravenous catheter and surgical drain infections, incision infections and wound infections appear to be most common (46) (J. S. Weese, unpublished data).

Prediction of *in vivo* response from *in vitro* susceptibility data is less clear than with most other organisms (2) and there are concerns about susceptibility testing methodology and interpretation (2). Amikacin, imipenem and enrofloxacin are often effective against equine and canine isolates *in vitro* (46, 47) (J. S. Weese unpublished data), however the degree of resistance in equine isolates and tendency to acquire resistance that has been reported in human medicine is concerning.

### Pseudomonas spp.

Multidrug resistance is a common problem in *Pseudomonas* spp. Members of this Gram-negative genus are opportunistic pathogens that are relatively ubiquitous in the environment. They can be particularly problematic in hospitals because of strong environmental persistence (especially in moist conditions) and innate resistance to many antiseptics (52, 53).

Primary community-onset infections are currently uncommon in humans, with most infections occurring in compromised hosts in hospitals (54, 55). Pan-resistant (resistant to most or all antimicrobials) *P. aeruginosa* has been reported in humans (52), with potentially dire consequences.

Less information is available about *Pseudomonas* spp infections in veterinary medicine. In horses, the most common community-associated *Pseudomonas* spp infection is likely ulcerative keratitis (56, 57), while incision, joint, invasive device and wound infections appear to be most common in hospitals (J. S. Weese, unpublished data). Otitis, pyoderma and urinary tract infections are common in small animals (58–60), however SSIs have been reported in dogs (61). The ability to *Pseudomonas* spp. to produce and survive in biofilms can complicate treatment, especially in cases of infections involving invasive devices or implants (54).

There is generally a good correlation between *in vitro* and *in vivo* susceptibility, but there may be few treatment options in some cases. Many equine isolates are still susceptible to fluoroquinolones and aminoglycosides, but highly resistant strains may be encountered, particularly in equine hospitals. Fluoroquinolone resistance and aminoglycoside susceptibility may be more common in isolates from small animals (J. S. Weese, unpublished data).
Extended spectrum beta-lactamase / extended spectrum cephalosporinase Enterobacteriaceae

The Enterobacteriaceae group contains a diverse range of Gram negative bacteria, including *E. coli*, *Klebsiella* spp and *Enterobacter* spp. The production of beta-lactamases is common amongst this group. Beta-lactamases confer resistance to beta-lactam antimicrobials (i.e. penicillins, cephalosporins) by hydrolyzing the antimicrobial’s beta-lactam ring. Some beta-lactamases have a relatively narrow range, while others confer resistance to a broad range of penicillins and cephalosporins (62). Extended spectrum beta-lactamases (ESBLs) confer resistance to a wide range of penicillins and cephalosporins, including third generation cephalosporins (63). ESBLs are not generally effective against cephemycins (i.e. cefoxitin) or carbapenems (i.e. imipenem) and can be inhibited by beta-lactamase inhibitors, such as sulbactam, tazobactam and clavulanic acid. A related group is the extended spectrum cephalosporinase (ESC) Enterobacteriaceae. Unlike ESBLs, these are active against cephemycins and refractory to beta-lactamase inhibitors, and therefore confer a broader range of resistance.

There has been minimal clinical or microbiological investigation of ESBLs and ESCs in veterinary medicine. ESBL and ESC *E. coli* and *K. pneumoniae* have been identified in horses (64). ESBL *Enterobacter* spp. have been implicated in opportunistic, including surgical site, infections in dogs (65). A review of antimicrobial resistance data from the Ontario Veterinary College, Canada, indicates that *E. coli* and *Klebsiella* spp isolates with resistance patterns consistent with ESBLs/ESC's have been isolated from wound and incision infections, urinary tract infections, peritonitis and bloodstream infections (J. S. Weese, unpublished data). Both hospital-associated and community-associated infections can occur.

Evaluation of *in vitro* susceptibility testing results is critical for case management, however there are concerns that *in vitro* data may suggest that a particular cephalosporin should be effective when in reality the drug may not be effective *in vivo*, particularly when a serious infection is present (63). Current susceptibility testing breakpoints may not be adequate to detect some ESBL organisms (66). Standard guidelines now recommend that all ESBL producing bacteria are reported as resistant to all penicillins and cephalosporins, regardless of *in vitro* results. This may be a problem in veterinary medicine, as testing for ESBLs is not widespread. In the absence of specific testing for ESBL and ESC strains, it is reasonable to consider all third generation cephalosporin-resistant Enterobacteriaceae to be resistant to all cephalosporins.

In humans, carbapenems are commonly and successfully used to treat ESBL/ESC infections (67), however it is prudent to attempt to limit the use of this class of antimicrobials in animals. Fluoroquinolones have been used with limited success in humans (67), and this class is likely to be most useful for the treatment of urinary tract infections because of the high urinary concentrations that are achieved. Fluoroquinolone resistance has emerged in humans (68) and it is not unreasonable to suspect that it could quickly become a problem in animals. Aminoglycosides, particularly amikacin (67), are often effective and represent a practical option in many cases.

Management of multidrug resistant infections

While efforts should be directed at reducing the incidence of MDR infections, it is inevitable that they will continue to occur. Therefore, development of plans to manage MDR infections is critical. A variety of areas need to be considered, including optimal patient care, prudent antimicrobial use practices, risks to owners, risks to veterinary personnel and risk to the veterinary hospital as a whole. Often, something that is beneficial for one area can be detrimental to another area, creating potential conflict.

Accurate diagnosis is critical, and involves a combined effort of the clinician and the diagnostic laboratory. MDR infections cannot be diagnosed without the submission of culture specimens. Culture and susceptibility testing should be a routine procedure, not one that is reserved for cases where initial treatment fails or severe disease is present. Failure to routinely culture post-operative infections can lead to suboptimal patient care and late identification of outbreaks or emerging issues. Proper sample collection is also essential, as results are only as good as the sample that was obtained. Proper testing by the laboratory is critical, and an area of concern in veterinary medicine. The author’s experiences with many commercial veterinary diagnostic laboratories is that, too often, there is inadequate identification of organisms (i.e. reporting ‘coagulase positive *Staphylococcus*’ instead of providing the actual species), misidentification of organisms, failure to test for relevant antimicrobials (i.e. oxacillin for staphylococci), failure to properly report results (i.e. reporting cephalosporin susceptibility for enterococci), and failure to follow standard testing and quality control guidelines. These problems are beyond the direct control of the clinician, however veterinarians should scrutinize the results that they receive, address any questionable result with the laboratory and pressure laboratories to correct any identified deficiencies.

Antimicrobial therapy is obviously an important component of treatment of MDR infections. An important aspect to remember is that general principles of patient and wound care apply equally to infections caused by MDR and susceptible pathogens. Patient (age, concurrent illnesses…), infection (location, local environment, blood supply…), drug (spectrum of activity, safety, pharmacokinetics…) and pathogen (susceptibility pattern, likelihood of development of resistance) factors must all be considered. *In vitro* susceptibility testing is a critical component, with the understanding that *in vitro* results are not always directly applicable to the *in vivo* situation. Laboratories should provide extended susceptibility panels for MDR bacteria to help direct appropriate treatment when options are limited. Consultation with experts in antimicrobial therapy, infectious diseases...
and infection control may be required in some situations.

Local therapy can be particularly important in the management of MDR infections. Local administration of antimicrobials can sometimes provide high enough drug levels that resistance is overcome and may be useful for administration of drugs that are not amenable to systemic therapy (69). Local administration of antiseptics, such as chlorhexidine, povidone iodine or acetic acid can also be a valuable tool in some infections. Topical administration of substances, such as tea tree oil have recently shown promise for treatment of MRSA infections (70).

Attention to patient housing in the clinic is important for the protection of other hospitalized animals and clinic personnel. Animals that are infected with MDR organisms should be isolated to reduce the risk of nosocomial and zoonotic transmission. The specific isolation protocols that are required may vary with the organism, severity of disease, animal species and hospital facility. Isolated animals should be housed in an area where there is no direct contact with other animals and where indirect contact can be prevented or severely restricted. Specific protocols should address patient management, personnel access, cleaning, disinfection and other relevant factors. The development of proper isolation protocols is an important part of the infection control program and should ideally be done proactively.

Infected animals should be handled using contact precautions (71, 72). This consists of the use of dedicated protective outerwear (i.e. barrier gown, lab coat that is not used elsewhere) and gloves, with the possible addition of other items, such as overboots. Contact precautions should be used when handling any animal with an MDR infection, even when the infected site will not be touched, as the animal could be concurrently colonized with the organism or its coat contaminated. Eye or face protection should be considered whenever there is a chance for splashing or aerosolization of infectious materials.

In addition to the use of contact precautions, wound care practices need to be considered. In human medicine, it is recommended that MRSA-infected wounds be covered with clean, dry bandages whenever possible (73). It is reasonable to extend this recommendation to all MDR infections in animals. Personnel must take care to avoid contaminating themselves, the environment, or medical items, during bandage changes. Any items handled during bandage changing or before removal of barrier items and disinfecting of hands should be considered potentially contaminated. Soiled bandage materials should be properly disposed of.

Surveillance is a critical aspect of any infection control program and is important for the prevention of MDR infections and outbreaks. The discussion of surveillance programs is beyond the scope of this review.

The cleaning and disinfection of potentially contaminated environments is important but is often poorly understood. Thorough discussion of this topic is not possible in this review, but basic principles of cleaning and disinfection must be followed, including proper cleaning in order to remove organic debris, the use of an appropriate disinfectant at the correct concentration and provision of adequate contact time (74).

Zoonotic concerns of MDR pathogens should not be overlooked. There is little doubt that MRSA can be transmitted between animals and humans. Considering that most of the other MDR pathogens encountered in veterinary medicine are also found in humans, it is possible if not likely that zoonotic transmission of those could also occur. It is therefore prudent to consider all MDR infections as potentially zoonotic.

Hand hygiene is a critical component of infection control [75]. Hand hygiene can consist of a thorough handwash or use of an alcohol-based hand sanitizer [75, 76]. Hand hygiene should be practiced before and after every animal contact, and after removing gloves.

Conclusion

Multidrug resistant infections will undoubtedly continue to become an important problem in veterinary medicine, particularly in surgical site infections. While it is unrealistic to think that all multidrug resistant infections can be prevented, increased awareness of the issues regarding these potentially important pathogens is needed. Application of general principles of prudent antimicrobial use, infection treatment and infection control are important to help reduce the risks posed by these organisms.

References


75. Boyce J, Pittet D, Unknown. Guideline for Hand Hygiene in Health-Care Settings: recommenda-
76. Traub-Dargatz J, Weese J, Rousseau J et al. Pilot study to evaluate 3 hygiene protocols on the reduc-