Review of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Horses

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is becoming an increasingly important pathogen in horses worldwide. Infection with MRSA can be life threatening and difficult to treat. Additionally, veterinarians are at increased risk for zoonotic infection. Proper identification of MRSA infections and MRSA-colonized horses is critical for the treatment and control of this pathogen as well as the prevention of zoonotic spread to horse personnel. Authors’ address: Ontario Veterinary College, University of Guelph, Guelph, ON N1G 2W1 Canada, N1G 2W1; e-mail: mander01@uoguelph.ca (Anderson). © 2006 AAEP.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most important hospital-associated pathogens in human medicine, and it is emerging as an important cause of disease in people in the community.\(^1\)\(^-\)\(^4\) Perhaps concurrent with the movement of MRSA into people in the community, MRSA infection and colonization are increasingly reported in animals and people that work with animals. In particular, MRSA infection of horses and horse personnel seems to be an emerging problem.\(^4\)\(^,\)\(^5\) This has implications for both humans and horses, because disease can occur in either species and interspecies transmission can propagate MRSA. A basic understanding of the epidemiology of MRSA in horses and the means by which its transmission can be controlled is important for equine veterinarians all over the world.

2. Background

*Staphylococcus aureus* is a commensal bacterium of humans, and it is usually considered normal flora of skin and exposed mucosal surfaces, particularly within the nares; however, *S. aureus* has long been recognized as an opportunistic pathogen. It can cause diseases ranging from superficial soft-tissue infections to life-threatening bacteremia and toxic shock syndrome (TSS).\(^6\) Although the commensal microflora of the horse is poorly understood, nasal colonization (presence of *S. aureus* without any clinical disease) can occur in ≤7% of horses.\(^a\) The advent of penicillin in the 1920s had a significant impact on morbidity and mortality from infections caused by *S. aureus*. Unfortunately, penicillin resistance emerged not long after penicillin became widely available; resistance is caused by the production of bacterial β-lactamase that cleaves the β-lactam ring of penicillins and cephalosporins. This resistance led to the development of antimicrobials such as methicillin that are resistant to the effects of β-lactamase. Perhaps not surprisingly, it did not take long for methicillin-resistant bacteria to emerge in the early 1960s.\(^7\)\(^,\)\(^8\)
Methicillin resistance in *S. aureus* is mediated by the mecA gene, which encodes production of an altered penicillin-binding protein (PBP2a). When incorporated into the bacterial cell wall, PBP2a greatly reduces the ability of β-lactam antibiotics to bind to their site of action. This renders the bacteria resistant to all penicillins and cephalosporins, including those members of these classes that are β-lactamase resistant. Therefore, resistance to methicillin represents resistance to all β-lactam antimicrobials.

When it first emerged, MRSA disseminated slowly around the world; however, MRSA rates have increased dramatically over the last 10–20 yr, and MRSA is a major cause of morbidity and mortality in hospitalized humans. Recently, MRSA has emerged as a community-associated pathogen, sometimes causing rapidly fatal disease in people in the general population with no recognizable risk factors.9

### 3. Terminology

Molecular epidemiological analysis has been crucial in our understanding of the emergence and dissemination of MRSA and our evaluation of changes in clinical epidemiology. Unfortunately, the medical and veterinary communities have been slow to adopt a standard method for typing and consistent terminology. Different typing methods are appropriate for different objectives. For example, a method such as multi-locus sequence typing (MLST), which categorizes clones based on alleles found in several relatively stable housekeeping genes, is more useful in comparing isolates over a broad geographic range or over a long period of time. In contrast, pulsed-field gel electrophoresis (PFGE), which produces a band pattern based on macro-restriction enzyme digestion of *S. aureus* DNA, is much more sensitive to small variations that occur in the less conserved portions of the genome. Therefore, it is more useful for tracking strains within an outbreak in a given time and place.

Strains of MRSA can also be classified by their staphylococcal chromosomal cassette mec (SCCmec) type. This is the portion of the *S. aureus* genome that contains the mecA gene. Five main types of SCCmec have been identified. Types II and III often carry resistance genes to many other non-β-lactam antibiotics as well as mecA. Type IV, and less commonly, type V, are traditionally associated with community-acquired MRSA (CA-MRSA) strains as opposed to hospital-acquired MRSA (HA-MRSA) strains, and they are usually associated with resistance to no or few antimicrobial classes besides β-lactams.10

It is becoming increasingly common to name isolates based on sequence type-methicillin phenotype-SCCmec type. Therefore, an MRSA isolate possessing SCCmec type IV and being of sequence type 8 would be designated ST8-MRSA-IV.

Another virulence factor is the Panton-Valentine leukocidin (PVL) gene, which has been associated with the ability of the bacteria to destroy cutaneous tissue.11 In humans, soft-tissue infections of PVL-positive CA-MRSA can occur without any previous wounds and initially may appear very similar to an insect bite.11,12

### 4. Diagnosis of MRSA in Horses

Laboratory identification of *S. aureus* from clinical specimens is relatively straightforward, but identification of MRSA requires additional testing to identify phenotypic resistance or the presence of mecA or PBP2a. Like any culture-based technique, MRSA screening can take 3–7 days depending on whether enrichment techniques are used and what confirmation tests are employed. This timeframe can be a concern in infection-control programs, and in human medicine, new techniques such as real-time polymerase chain reaction (RT-PCR) are being employed to cut this turnaround time to as little as 1–2 h.13 Although no such technique has yet been validated in horses, similar developments are likely on the horizon in equine medicine.

It is important to ensure that the diagnostic lab to which clinical specimens are sent tests all *S. aureus* isolates for methicillin resistance. This is typically performed by assessing susceptibility to oxacillin, which is more stable than methicillin in vitro. Oxacillin-resistant *S. aureus* are MRSA.

Colonization of horses with MRSA is usually determined by culture of a nasal swab inserted into one nare ~8–10 cm and withdrawn in contact with the nasal mucosa. Multi-site colonization has been found in humans and is likely occurs in horses as well, although this has never been objectively evaluated. The bacteria can survive for several days or longer on a refrigerated culture swab. Clinical infections in other areas of the body are determined by culture of standard specimens as per the specific disease presentation.

### 5. Emergence of MRSA in Horses

Recent evidence suggests that horses may be particularly pre-disposed to MRSA infection and colonization, either through biology or management, and MRSA seems to be an important emerging issue in equine medicine.4,5 Initial reports of MRSA infection in horses in the late 1990s were limited to case reports or case series. Hartmann et al.10 reported a post-operative MRSA wound infection in a horse at a veterinary hospital in the United States and speculated that it originated from a human source. The hypothesis that equine MRSA was an aberrant and uncommon effect of direct infection of horses by colonized personnel was also present in a subsequent report of MRSA infections in 11 horses over 13 mo in another American veterinary teaching hospital, and the theory was strengthened by isolation of indistinguishable MRSA isolates from three hospital personnel.16 All horses developed infections at the
sites of therapeutic intervention, including surgery, joint invasion, and vaccination. Weese et al. were the first to study CA-MRSA in horses after detection of a cluster of MRSA cases at a Canadian veterinary teaching hospital. Colonization was later identified in horses that had no direct contact with a veterinary clinic or hospital, indicating that equine MRSA has become a community-associated pathogen as well as a hospital-associated threat. The vast majority of equine MRSA isolates identified in North America have been classified using PFGE as subtypes of Canadian epidemic strain CMRSA-5 (also known as USA500 and British eMRSA5), which is relatively uncommon in humans. This suggests that this strain is somewhat adapted to survival in horses. Unlike CA-MRSA in humans, these equine isolates were PVL negative and tended to be resistant to multiple classes of antimicrobials, despite having other characteristics of community-associated strains including SCCmec type IV.

Regional differences in the prevalence of equine MRSA seem to be marked and important in risk assessment for MRSA colonization and infection. Additional precautions must be taken with horses in or being moved from high-prevalence to low-prevalence areas and farms. In the original community-based study by Weese et al., zero prevalence of MRSA was found in horses from farms without a history of prior MRSA infection or colonization, suggesting that there might be a close link between amplifying sites (i.e., veterinary hospitals and farms with endemic infection) and subsequent dissemination on farms but restricted true community-associated transmission between farms. A prevalence study in the Netherlands reported no MRSA colonization in 200 clinically normal horses, and a similar survey of 300 horses in Slovenia also failed to identify MRSA. Additionally, a study of 20 S. aureus isolates from horses in the Netherlands reported no MRSA. Nonetheless, sporadic infections and outbreaks of MRSA have been reported in horses in many countries. The reported rate of nasal colonization of equine patients on admission to one Canadian veterinary hospital was found to be 5.3%; the rate of community-acquired colonization was estimated at 2.7% of admissions. Of additional concern is the apparent frequency of transmission of MRSA between horses and people, and zoonotic MRSA infections have been reported in people working with infected horses.

6. Risk Factors for Equine MRSA

Some of the more commonly reported risk factors for MRSA infection or colonization in humans include frequent or recent contact with the healthcare system, admission to a long-term care facility, hospitalization in an intensive care unit, surgery, and treatment with antimicrobials, particularly fluoroquinolones. Similar risk factors such as hospitalization, immunosuppression, and chronic or debilitating disease may be relevant in horses, but less objective information is available. In one study carried out on horse farms in Canada and the United States, the presence of >20 horses on the farm was identified as a risk factor for MRSA colonization. Similarly, the only significant risk factor identified for horse personnel in the same study was regular contact with >20 horses. In another study, risk factors for colonization at the time of admission to a veterinary teaching hospital were identified as age <1 mo, Thoroughbred breed, admission to the medicine service, previous identification of MRSA on the horse, and antimicrobial use within 30 days. Administration of cefotiofur or aminoglycosides has also been reported as a risk factor for hospital-associated colonization in horses.

7. Treatment of Clinical MRSA Infections

Clinical infections reported in horses range from simple skin and soft-tissue infections to bacteremia/septicemia, pneumonia, surgical-implant infection, septic arthritis, osteomyelitis, and omphalophlebitis. One of the most significant problems associated with the emergence of MRSA is treatment failure caused by empirical treatment of presumed S. aureus infections with β-lactam antimicrobials. Without proper identification of the MRSA isolate by culture and antimicrobial-sensitivity testing, such treatment can result in a prolonged delay in administration of effective therapy and a subsequent increase in morbidity and mortality.

There is currently no objective information regarding management of clinical MRSA infections in veterinary species. Treatment is based on general principles of treatment of the specific condition (i.e., pneumonia or incision infection) and consideration of antimicrobial-susceptibility testing results and pharmacokinetic data. Concurrent application of infection-control practices is critical to reduce the likelihood of re-infection or infection of other animals or people. This is of particular concern in veterinary hospitals because of the number of different animal contacts and contact with presumably high-risk animals (immunosuppressed, antimicrobial-treated, and surgically incised animals).

8. Eradication of Equine MRSA

Early identification of patients carrying MRSA is the key component to controlling the spread of this pathogen in veterinary hospitals or on farms. Because MRSA can be transmitted by human and equine carriers, a large number of colonized individuals may be present before the first clinical infection is identified. Horses being admitted to large stables should undergo preliminary quarantine and screening to avoid spreading pathogens, including MRSA, to other animals on the premises. Strict application of basic infectious-disease control protocols alone, including repeated MRSA-colonization screenings, cohorts of colonized and uncolonized animals, barrier precautions when handling colonized horses, and treatment with antimicrobials with proven activity against MRSA, is critical to control the spread of infection.
horses, and thorough disinfection of contaminated equipment, has been used successfully to eradicate or greatly decrease the prevalence of MRSA colonization on horse farms where the pathogen had become endemic.31

9. Management of Colonized Horses
The optimal approach to handling colonized horses is currently unclear. Strict application of infection-control practices, particularly hand hygiene, is likely critical for reducing the risk of transmission. At this point, there is no indication that antimicrobial therapy is useful for decolonizing horses. The risk of further emergence of antimicrobial resistance and the apparent ability of infection-control measures to eradicate MRSA on farms suggest that there is not a role for decolonization therapy in horses. At this point, the authors do not advocate treating horses that do not have signs of clinical infection.

10. MRSA in Horse Personnel
One area of particular concern is the ability of MRSA to be transmitted between humans and horses. Weese et al.4 found an unusually high prevalence of MRSA colonization among horse farm personnel (13%). Additionally, this study identified at least one colonized person on every farm that had colonized horses, and interspecies transmission was considered likely because horses and humans on the same farm carried the same strains. Zoo-notic MRSA infections have also been reported, which is another very concerning situation. An MRSA tattoo-site infection was reported in a veterinarian treating an infected horse.4 More concerning, MRSA skin infections were reported in three people working with a colonized foal in a veterinary teaching hospital.23 Disturbing aspects of this report are the fact that the foil did not have clinical infection, affected personnel wore gloves and coveralls when handling the foil, and infected personnel had only worked with the foil for a 4-h period. A recent study carried out at the 2005 convention of the American College of Veterinary Internal Medicine examined the prevalence of nasal MRSA colonization in 417 veterinary personnel: 9 of 239 (3.8%) small-animal veterinarians and 13 of 94 (13.8%) large-animal veterinarians were colonized. Working with large animals was the only risk factor identified using multivariate analysis (OR = 4.3; CI = 1.9–10.2). Furthermore, 11 of 13 (84.6%) of the large-animal veterinarians carried the horse-associated CMRSA-5 strain.32

Although risk factors for interspecies transmission have not been adequately evaluated, those individuals in the equine community thought to be at highest risk for transmission of MRSA from horses are breeding-farm personnel and veterinary practitioners. Because transmission from humans to horses is possible, a high prevalence of MRSA colonization in people who work with horses puts animals under colonized persons’ care at higher risk for colonization or infection. Veterinarians play a particularly important role in this scenario, because they are most often in contact with sick, wounded, or otherwise compromised animals that would be more pre-disposed to acquiring infections such as MRSA. The fact that veterinarians are in contact with numerous horses on different farms also creates an increased risk of exposure and wide-spread dissemination. Further characterization of the prevalence and epidemiology of MRSA in horses and horse personnel will help identify if there are particularly high-risk contacts between horses and people that can be avoided or during which infectious-disease control precautions may be used to help control the spread of this pathogen.

References and Footnote


