INTRODUCTION

Penicillin and other β-lactam antimicrobials act by binding to a transpeptidase involved in cell wall peptidoglycan synthesis disrupting the bacterial cell wall resulting in death of the bacterium. One mechanism by which bacteria become resistant to β-lactam antimicrobials is through the production of enzymes such as β-lactamase that destroy the antimicrobial’s β-lactam ring rendering the drug ineffective. Shortly after the introduction of penicillin in the 1940s, this type of resistance became prevalent leading to the development of new synthetic β-lactam drugs such as methicillin that resisted β-lactamase. After only a few years of use, however, S. aureus became resistant to methicillin. Resistance to methicillin is not mediated through production of β-lactamase, but rather methicillin resistant staphylococci have acquired a mobile genetic element known as staphylococcal cassette chromosome mec (SCCmec). This SCC carries a gene known as mecA which encodes for an altered penicillin-binding protein (PBP2a or PBP2’). The PBP2a has a lower affinity for β-lactam antimicrobials than the normal PBP such that these antimicrobials are ineffective. Importantly, the SCC containing the mecA gene can spread between bacteria within staphylococcal populations. Furthermore, the SCC contains additional insertional DNA sequences that allow for incorporation of additional antimicrobial resistance markers. These insertional sequences explain why many methicillin-resistant staphylococci are resistant to non-β-lactam antimicrobials that act through mechanisms other than interference with bacterial cell wall synthesis (e.g., macrolides, fluoroquinolones), and thus why methicillin-resistant strains can be multi-drug resistant.

While methicillin resistance is often associated with Staphylococcus aureus, so-called MRSA, it can be commonly found in other non-S. aureus staphylococci most frequently classified as the coagulase-negative staphylococci (CNS), and there is speculation that MRSA may have acquired the mecA gene from CNS. The moniker methicillin-resistant stems from the original description of MRSA in 1961. However, routine diagnostic screening now employs testing for in vitro susceptibility to either oxacillin or cefoxitin as methicillin is no longer used in clinical practice. In addition to phenotypic characterization using susceptibility testing, molecular methods (polymerase chain reaction; PCR) that detect the mecA gene are now employed to confirm a diagnosis of mecA mediated resistance as bacteria expressing β-lactamase may be falsely identified as mecA positive when using phenotypic methods alone (conventional antimicrobial susceptibility testing). While the PCR test for confirming a diagnosis has been widely employed, recently mecA gene variants have been identified in some staphylococcal isolates from people and dairy cattle that are not detected using the current PCR test. Hence, these mecA variants may be misclassified as methicillin susceptible using the current PCR detection method. Therefore a combination of phenotypic (antimicrobial susceptibility testing) and genotypic (mecA PCR) identification methods is recommended.

Methicillin-resistant staphylococcal strains are not necessarily more virulent than their methicillin susceptible counterparts, but are more difficult to treat as they are often resistant to multiple classes of antimicrobial drug as illustrated above. Historically, MRSA was associated with hospital-acquired (HA-MRSA) infections. More recently, however, there has been an increased incidence of non-healthcare-associated, or so-called community-acquired MRSA (CA-MRSA) infections. Additionally, starting in the early 2000s, a new type of MRSA began to emerge, the so-called livestock-associated MRSA (LA-MRSA). In both humans and animals, inapparent colonization is far more common than outright infection, and colonization is more often transient than chronic. However, colonization does increase the host’s risk of MRSA infection.

MRSA IN LIVESTOCK

Methicillin-resistant staphylococci have been isolated from a number of animal hosts including cats, dogs, horses, cattle, chickens, rabbits, and pigs. As discussed above, colonization of healthy animals with either MRSA or non-S. aureus methicillin-resistant staphylococci appear to be far more common than overt infection.

Staphylococci are among the most common bacteria isolated from bovine milk and cause both clinical and subclinical mastitis. Staphylococcus aureus is a major contagious mastitis pathogen which is spread cow-to-cow, usually during milking. The coagulase negative staphylococci (CNS) are frequently isolated from milk, but are generally regarded as minor mastitis pathogens. Devriese et al. were the first to describe MRSA in animals in 1972 with the detection of MRSA in cattle with mastitis in Belgium. However, while S. aureus and CNS are commonly isolated from milk, methicillin-resistant staphylococci have been infrequently isolated from cases of clinical and subclinical bovine mastitis. Furthermore, the origin of MRSA intramammary infections in dairy cattle was historically difficult to define. Devriese and Hommez reported that MRSA infections in dairy cattle were most likely of human origin. At that time, however, molecular strain-typing techniques were not available. With the advent of multilocus sequence typing (MLST) and spa-typing (DNA-based strain-typing methods), the host range and transmissibility between hosts has been more easily assessed. For example, a Hungarian study recently reported that MRSA isolates from dairy cattle with subclinical mastitis and a farm worker were phenotypically and genotypically indistinguishable suggesting cross-species transmission, but still not definitively identifying the origin of infection. In addition to MRSA being associated with mastitis, a recent report documented methicillin-resistant Staphylococcus epidermidis being isolated from a cow with mastitis on an organic dairy farm, but it was unclear whether the isolate was of bovine or human origin. While S. aureus strains seem to be somewhat host specific, humans and animals may share similar Staphylococcus epidermidis strains further complicating who infected whom.
Some of the earliest reports of MRSA in veterinary hospitals involved equine nosocomial infections, specifically post-procedural wound infections.\textsuperscript{9} Metritis in a group of mares from Japan was also documented in the mid 1970’s.\textsuperscript{10} A study evaluating the occurrence of MRSA among \textit{S. aureus} isolated from patients at 7 veterinary teaching hospitals showed that MRSA accounted for 14\% of the \textit{S. aureus} infections with 89\% of the MRSA infections occurring in dogs (44.4\%) and horses (44.4\%).\textsuperscript{11} Studies from Ontario, Canada demonstrate that Canadian MRSA-5 (CMRSA), a strain rare in the human population, is the most frequent strain of MRSA isolated from horses and horse personnel.\textsuperscript{12} In contrast, in Atlantic Canada MRSA colonization was not detected despite colonization of 7.9\% of healthy horses with methicillin-resistant \textit{S. aureus} (MSSA).\textsuperscript{13} In Europe, other MRSA strains have been identified including ST398, a type believed to be of porcine origin. Other methicillin-resistant staphylococcal species have been isolated from horses. \textit{Staphylococcus pseudintermedius} is isolated from horses at a lower frequency than MRSA. In contrast, methicillin-resistant coagulase negative staphylococci (MRCNS) are more prevalent than MRSA, with 42\% of healthy horses colonized in a Canadian study and 22.5 or 50\% of horses colonized by MRCNS in two Danish studies.\textsuperscript{11,14-16} Finally, a Japanese study reported that 29.5\% of horses sampled were colonized with methicillin-resistant staphylococci, but MRSA was seldom isolated in the population.\textsuperscript{17} Importantly, MRCNS are thought to potentially serve as reservoirs for resistance genes leading to the emergence of new MRSA strains. Risk factors for methicillin-resistant staphylococci in horses have not been extensively studied. A Canadian study reported that previous colonization of the horse, existence of colonized horses on the farm, antimicrobial administration within the past 30 days, admission to the neonatal intensive care unit, and admission to a hospital service other than surgery were significant risk factors for horses being colonized with MRSA at the time of admission to a veterinary teaching hospital.\textsuperscript{18} While methicillin-resistant organisms are generally thought to be harbored by a mammalian host, evidence from another Canadian study suggests that the clinic environment and fomites can serve as potential reservoirs for colonization and infection with MRSA. A more recent multicentre study evaluated data from 115 horses admitted to 6 veterinary teaching hospitals and found that infection of surgical incisions was most common (38\%), and overall 84\% of cases survived until discharge. Survival of infected horses was inversely correlated with intravenous catheterization, CA-MRSA infection, and disseminated infection.\textsuperscript{19}

Reports of MRSA in swine populations first emerged in the Netherlands, but swine associated MRSA colonization and infection has now been detected across Europe, in North America, and Asia with rates of colonization among pigs as high as 49\% and among personnel caring for swine as high as 45\%. The most common strain associated with swine colonization and infection is ST398, a strain also found to colonize people who work with swine or veal calves. This strain has also now been isolated from other domesticated animals including dairy cattle, poultry, dogs, and horses.\textsuperscript{5} While on swine farms, pigs appear to be the major reservoir for MRSA ST398, a recent study reported that rats on farms can be colonized MRSA strain ST398 suggesting that farm rodent populations may play a role in dissemination and persistence of MRSA colonization and infection of swine operations. In addition, dust samples taken from swine operations have been found to harbor MRSA suggesting that environmental reservoirs of colonization and infection may exist. Recent reports from Europe have now shown that ST398 can establish in dairy herds, and both MRSA and methicillin susceptible variants of ST398 have been documented.\textsuperscript{3} Hence, while MRSA detected in bovine milk were once thought to be the result of incidental infection with human host-adapted strains, there is emerging evidence for LA-MRSA may be establishing in dairy cattle and thus be a potential reservoir for human infection.

Most recently a new \textit{mecA} variant MRSA has been identified in humans and dairy cattle in various locations throughout Europe. The strain accounts for <1\% of human MRSA in the UK and Denmark.\textsuperscript{5} Because the \textit{mecA} variant is not detected by routine PCR methods, some MRSA may be falsely identified as methicillin susceptible. The clinical significance and epidemiology of this variant are still not fully understood, but its detection in both humans and cattle illustrates the potential for inter-species transmission.

**MRSA in Dogs & Cats**

While dogs and cats may become contaminated, colonized, or infected with \textit{S. aureus}, including MRSA, dogs and cats are not considered reservoir hosts for \textit{S. aureus} and are more commonly colonized with other staphylococcal species.\textsuperscript{4} The most commonly isolated coagulase positive staphylococcus (CPS) from pets is \textit{S. pseudintermedius} (formerly misclassified as \textit{S. intermedius}). Despite poorer in vitro adhesion to feline cortonocytes, \textit{S. pseudintermedius} is common in cats as well as dogs. \textit{Staphylococcus schleiferi} subspecies \textit{coagulans} is another CPS frequently found on dogs. Dogs and cats are often colonized with a wide variety of CNS (several of which commonly possess methicillin resistance) including \textit{S. felis}, \textit{S. haemolyticus}, \textit{S. sciuri}, \textit{S. epidermidis}, \textit{S. warneri}, \textit{S. simulans}, \textit{S. saprophyticus}, and \textit{S. schleiferi subsp. schleiferi}. Methicillin-resistant \textit{S. pseudintermedius} (MRSP, a.k.a. MRSI) is found both on healthy pets and in association with infection. Prevalence of MRSP cultured from pet animals is usually <5\% but may be as high as 17\%.\textsuperscript{3} It has been speculated that the true prevalence of MRSP may be much higher than documented in the literature because these isolates are easily missed by routine disk diffusion or broth microdilution methods. Although MRSP is predominantly associated with infections of pet animals, people can also become infected. Human MRSP infection, which likely results from exposure to colonized or infected pets, results in difficult-to-treat infections and increased risk of mortality. Even when people do not become directly infected by exposure to pets with MRSP, concern exists that MRSP may provide the genetic source material to convert MSSA colonizing humans into MRSA through transfer of its mobile \textit{SCCmec}. Similarly, co-colonization with MSSA and MRCNS and may facilitate acquisition of \textit{SCCmec} by MSSA.

Although not the predominant CPS of pets, \textit{S. aureus} and MRSA can be found on healthy and infected dogs and cats. Colonization of healthy pets with MRSA is apparently uncommon, but evidence to date suggests that MRSA strains found in companion animals are identical to strains involved in epidemic human infections.\textsuperscript{3} Further investigation is necessary to identify risk factors for MRSA colonization or infection of pet animals. Ownership by a health care worker may or may not increase risk of MRSA colonization. Other factors, including prior antimicrobial use and frequency of human contact, have not been associated with an increased likelihood of MRSA colonization. Because \textit{S. aureus} is the predominant CPS commensal on humans, but not dogs and cats,
it is believed that pets most commonly acquire the organism from people. However, bidirectional transmission occurs. When methicillin-resistant staphylococcal infections occur in pets, they are typically associated with either pyoderma or post-operative wound infections, but otitis, urinary tract infections, and arthropathies due to MRSA and/or MRSP have also been reported in pet animals.

ZOONOSIS OR ANTHROPONOSIS?

By definition a zoonotic infection is an infectious disease in animals that can be transmitted to people and the natural reservoir for the infectious agent is an animal. The opposite of zoonosis, an athroponotic infection is one that is spread from humans to animals. While MRSA has been documented in people and animals, when a person or animal becomes colonized or infected with MRSA it is often asked where the infection originated? Can animals serve as a reservoir for human infection and vice versa? In general, S. aureus strains seem to be fairly host-specific and molecular strain-typing tools have allowed a better understanding of geographical distribution and host-specificity. The host-specificity of the CNS species is less well-defined.

As discussed, many domestic animal species can become colonized or infected with MRSA and might serve as a potential source of human infection. A variety of case reports document animals (primarily pets) as the possible culprits behind the spread of MRSA to humans. However, it was difficult, if not impossible, to determine whether the pathogen was spread from animal to man or vice versa. Dogs and cats are not believed to be a natural reservoir host for S. aureus, making it more likely that MRSA originates from a person than a pet. However, once colonized pets could certainly transmit the pathogen to people directly or indirectly. Additionally, pets might serve as a fomite if they become contaminated but not colonized with MRSA. For instance, MRSA was detected on the hands of an investigator after a dog became contaminated during a pet therapy visit. Transmission has even been documented between an elephant calf and its caretakers in a zoological park.

With the discovery of LA-MRSA, the assertion that MRSA colonization or infection in animals was primarily an anthroponosis has again been brought into question. Reports from the early 2000s suggest that pigs are a potential major zoonotic reservoir for MRSA, and farm workers and their families are at increased risk of infection and colonization with this strain of MRSA. Additional concern is now being voiced as dairy herds in northern Europe have now been shown to possess ST398 infected cattle and a mecA variant strains has been identified in dairy cattle and humans. That said, ST398 does not appear to be very virulent and colonization is most often detected due to routine screening rather than patients presenting with overt clinical disease.

Taken together with the equine data presented above, veterinary practitioners working with at risk livestock populations, including swine, horses, and possibly dairy cattle should exercise precautionary measures to prevent colonization and infection with MRSA such as hand-washing and barrier nursing procedures. Pet pigs do not appear to have been studied with regard to risk of MRSA colonization or potential for zoonotic transmission to humans, but certainly should be considered given the increased recognition of MRSA in commercial swine and because pet pigs tend to have closer relationships with their caretakers.

CONCLUSIONS

Methicillin-resistant staphylococci are an uncommon cause of livestock disease, but evidence suggests that MRSA are emerging as pathogens of veterinary importance. Both MRSA and methicillin susceptible S. aureus can cause a range of symptoms from asymptomatic colonization through to severe infection. MRSA strains are, however, more difficult to treat. Currently, bovine mastitis caused by MRSA does not appear to differ appreciably from that caused by methicillin susceptible strains. Coagulase negative staphylococci can commonly carry the mecA gene and may serve as a reservoir for gene transfer to S. aureus. While it appears that human strains can colonize or infect animals the opposite scenario may also exist, particularly if the infected or colonized animal is a pig, veal calf, or dairy cow. Pasteurization of milk and appropriate cooking of meat should kill S. aureus and MRSA in milk and meat, and hence food safety should be ensured unless people are drinking raw milk or consuming undercooked meat. Infection control, particularly hand hygiene, is important in preventing animal to human transmission and vice versa. Identification of persistently colonized personnel or animals may be necessary to prevent or alleviate some infections.

REFERENCES