

Review on Methicillin-resistant *Staphylococcus aureus* (MRSA) in Dogs and Cats

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Abstract: Staphylococcal infection is of major importance in both Human and Animals. Some staphylococcal bacteria are Methicillin-resistant. This paper reviews the current information on Methicillin-Resistant *Staphylococcus aureus* (MRSA) in dogs and cats. *Staphylococcus aureus* is a Gram positive, non-spore forming coccus. It may be found singly, in pairs, in short chains, or in irregular clusters. The colonies are circular, smooth and glistening. *Staphylococcus aureus* is a major resident or transient colonizer of the skin and the mucosa of human and primates. These organisms occasionally live on domestic animals, although domestic animals are usually colonized by other species of Staphylococci. When *Staphylococcus aureus* gains entry into the host, it causes variety of infection, from mild skin infection to life threatening invasive infections. Methicillin resistance exhibited by these organisms is due to the acquisition of *mecA* gene, that encodes new protein designated PBP2a, belonging to the family of enzymes necessary in building the bacterial cell wall. The protein (PBP2a) has a very low affinity for β -lactams antibiotics and confers resistance to Methicillin and the other beta-lactams. In developed countries, companion animals have become an integral part of the household. More than 50% of households in the developed and developing countries have pets hence makes *Staphylococcus aureus* infection an important zoonotic disease. Methicillin resistance has been reported in Staphylococcal species such as *Staphylococcus aureus*, *Staphylococcus intermedius*, *Staphylococcus schleiferi* and *Staphylococcus sciuri*. Colonization and infection in-patients remain the major reservoir of MRSA in hospitals, while aerosols, inanimate objects, domestic animals and pets could act as reservoirs and transmit MRSA to humans. Conclusively, Methicillin resistant *Staphylococcus aureus* is a condition that needs to be given close surveillance due to the zoonotic importance of these bacterial organisms.

Keywords: Dogs and cats, methicillin resistance, *Staphylococcus aureus*

INTRODUCTION

Staphylococcal infection is of major importance in both human and Veterinary medicine. *Staphylococcus aureus* is a Gram positive, non-spore forming coccus. It may be found singly, in pairs, in short chains, or in irregular clusters (Bottone *et al.*, 1984). The colonies are circular, smooth and glistening (Bottone *et al.*, 1984). *Staphylococcus aureus* is a major resident or transient colonizer of the skin and the mucosa of human and primates. These organisms occasionally live on domestic animals, although domestic animals are usually colonized by other species of staphylococci. When *S. aureus* gains entry into the host, it causes variety of infection, from mild skin infection to life threatening invasive infections (Pantosti, 2012).

Staphylococcus aureus has the characteristic ability to rapidly develop resistance to virtually any antibiotic coming into clinical use (Pantosti *et al.*, 2007). Development of resistance to Methicillin and other beta-lactams by *Staphylococcus aureus* was first reported in 1961 which marked the appearance of

Methicillin-Resistant *S. Aureus* (MRSA). Methicillin resistance is due to the acquisition of *mecA* gene, that encodes new protein designated PBP2a, belonging to the family of enzymes necessary in building the bacterial cell wall. The protein (PBP2a) has a very low affinity for β -lactams antibiotics and confers resistance to Methicillin and the other beta-lactams (Pantosti *et al.*, 2007).

The *mecA* gene is located on a mobile genetic element, named staphylococcal cassette chromosome *mecA* (SCC *mec*) inserted in the *S. aureus* chromosome upstream *orf X* (Katayama *et al.*, 2000). Initially, reports of MRSA colonization in dogs and cats were infrequent. However, marked increment of case reports have been appearing in recent years (Boag *et al.*, 2004; Van Duijkeren *et al.*, 2004; Rich and Robert, 2004). Inter-transmission of MRSA between animals and humans has been reported (Manian, 2003; Weese and Rousseau, 2005). Companion animals have been indicated as potential reservoirs of MRSA (Cefai *et al.*, 1994; O'Mahony *et al.*, 2005). MRSA is becoming a public health concern because companion animals often

are in close physical contact through touching, petting and licking with their owners, hence exposing them to infection with pathogenic MRSA bacteria (Guardabassi *et al.*, 2004). The objective of this article is to review the epidemiology of Methicillin Resistant *Staphylococcus aureus* (MRSA) in companion animals with special emphasis on dogs and cats.

Historical background and natural habitat of MRSA: Staphylococci organisms were first observed in human pyogenic lesions by Von Recklinghausen in 1871. Pasteur obtained liquid cultures of cocci from pus and produced abscesses by inoculating them into rabbits in 1880. Sir Alexander Ogston, a Scottish surgeon in 1880 also established conclusively the role of cocci as a causative agent of abscesses and other suppurative lesions in various animal species. He also gave the name *Staphylococcus* (Staphyle, in Greek means “bunch of grapes”, Kokkos, means “berry”) due to the typical occurrence of the cocci in grape like clusters in pus and in cultures. Ogston had noticed that non-virulent staphylococci were also present on skin surfaces. Most Staphylococcal strains from pyogenic lesions were found to produce golden yellow colonies and the strains from normal skin produced white colonies on solid media. Rosenbach, named these organisms *Staphylococcus aureus* and *Staphylococcus albus* respectively in 1884. Later *Staphylococcus albus* was renamed as *Staphylococcus epidermidis*. These species are coagulase negative, mannitol nonfermenters and usually non pathogenic strain (Murray *et al.*, 2003).

Staphylococci organisms are wide spread in nature although they are mainly found as normal flora on the skin, skin glands and mucous membrane of mammals and birds. They may be found in the mouth, blood, mammary glands, intestines, genitourinary and upper respiratory tracts of various animals. *Staphylococcus aureus* generally have a benign or symbiotic relationship with their host; however they may be pathogenic, if they gain entry into the host tissue as a result of trauma of the cutaneous barrier, inoculation by needles or direct implantation of medical devices to susceptible host. Infected tissues of the host support large populations of Staphylococci organisms and in some situations persist for long periods. The presence of enterotoxigenic strains of *Staphylococcus aureus* in various food products is regarded as a public health hazard, because of the ability of these strains to produce intoxication or food poisoning. *Staphylococcus aureus* are major species of primates, although specific serovars or biotypes can be found occasionally living on different domestic animals or birds (Murray *et al.*, 2003).

The history of Methicillin Resistant *Staphylococcus aureus* (MRSA) started with the development of antibiotics. Hailed as a super drug that was designed to treat infections, penicillin was discovered in 1928 by

Alexander Fleming and quickly put into production. The 1940s saw penicillin being commonly used to treat a number of different infections. It also spawned the development of other antibiotics, like streptomycin, erythromycin, tetracycline and amoxicillin. Over time and use, the *Staphylococcus* bacteria naturally developed resistance to this drug, primarily due to the adaptive nature of the bacteria and the rampant overuse of the antibiotics in their early stages. Penicillin was used in the 1940s to treat infection from *Staphylococcus* organisms, but by the 1950s, the organisms developed resistant to many of the antibiotics that were already used (Centers for Disease Control and Prevention, 2004)

Methicillin was developed to treat *Staphylococcus* infections, with the widespread use of the drug beginning in 1959. In 1961, a hospital in the United Kingdom, reported finding a strain of *Staphylococcus* that had developed resistance to Methicillin, this led to the emergence of Methicillin Resistant *Staphylococcus aureus* (MRSA). The case reports of Methicillin resistant *Staphylococcus aureus* in the United Kingdom slowly increased in numbers, but did not reach an outbreak level. The first case of Methicillin Resistant *Staphylococcus aureus* (MRSA) in the United States was reported in Boston in 1968. The Methicillin Resistant *Staphylococcus aureus* (MRSA) cases seem to have been diagnosed in patients hospitalized with immunodeficiency syndrome conditions. The first reported case of Methicillin resistant *Staphylococcus aureus* (MRSA) outbreak was in Eastern Australia during the 1970s and culminated in the spread of the infection to most of the European countries, infecting many of their health care centers and hospitals, especially in Eastern Europe (Centers for Disease Control and Prevention, 2004).

Methicillin Resistant *Staphylococcus aureus* (MRSA) in companion animals: In developed countries, companion animals have become an integral part of the household. More than 50% of households in the USA have pets and 25% of households in the United Kingdom have dogs (Chomel and Sun, 2011). In general, Methicillin Resistant *Staphylococcus aureus* (MRSA) strains recovered from companion animals (cats, dogs, or horses) are different from those recovered from food animals. The first case of strains reported are usually similar to human HA-MRSA, while the second case appear to belong to specific animal-adapted clones, unrelated to most common HA-MRSA. Other Staphylococcal species that share with *Staphylococcus aureus* the ability to acquire Methicillin resistance, specifically *S. intermedius*, *S. pseudintermedius* and *S. schleiferi*, are more common in pets (Hanselman *et al.*, 2008, 2009). Reports of Methicillin Resistant *Staphylococcus aureus* (MRSA) isolated from pets were sporadic until the late 1990s

Table 1: Principal MRSA clones shared between human and animals

Lineage	Clones	Companion animals	Horses	Pigs	Poultry	Cattle	Human
CC1	ST1			°		°	°
CC5	ST5 (USA100)	°		°	°	°	°
CC8	ST8 (USA500)		°				°

(Pantosti, 2012)

and were mostly related to clinical infections. In addition, before the identification of *S. intermedius* and *S. pseudintermedius*, some misclassification may have occurred (Devriese *et al.*, 2005). The emergence of CA-MRSA in the last decade and the importance of tracing antibiotic-resistant organisms also in the community, have prompted many studies on MRSA in pets and its possible transmission to pet owners. According to studies performed in various countries, especially in the UK and Australia, Methicillin Resistant *Staphylococcus aureus* (MRSA) colonization is rare in healthy pets. No MRSA was found in healthy cats in several studies (Baptiste *et al.*, 2005; Loeffler *et al.*, 2005; Hanselman *et al.*, 2009), although in a recent study 2.1% of cats presented to Veterinary clinics in Greater London area were colonized by MRSA (Loeffler *et al.*, 2011). In dogs in a household or at admission to a Veterinary hospital, colonization rates varied from 0 to 2.1% (Bagcigil *et al.*, 2007; Boost *et al.*, 2008; Hanselman *et al.*, 2008, 2009; Loeffler *et al.*, 2011). In some particular settings, e.g., dogs in a rescue shelter (Loeffler *et al.*, 2010) or in a veterinary hospital (Loeffler *et al.*, 2005), a high MRSA colonization rate, up to 9%, was found.

Methicillin-Resistant *Staphylococcus aureus* (MRSA) infections in pets are mainly represented by skin and soft tissue infections and are sometimes associated with Veterinary surgeries. In a large study in the UK, MRSA was recovered from 1.5 % of samples from infected animals (Rich and Roberts, 2004). In several studies, dogs appear to have more MRSA infections than cats (Morgan, 2008), but as there are no direct comparative studies, any implication of different susceptibility to MRSA infections between these animal species should be verified. The Methicillin Resistant *Staphylococcus aureus* (MRSA) types recovered from cats and dogs are similar to those affecting humans, with a similar regional distribution, for instance, in the USA the most common MRSA type in pets is the clone identified as USA100 (ST5), which is also the most common HA-MRSA clone in humans (McDougal *et al.*, 2003). In the United Kingdom the most common clones are those identified as EMRSA-15 (ST22) and EMRSA-16 (ST36) that are prevalent in UK hospitals (Ellington *et al.*, 2010). Recently, dogs have been found to be colonized by the livestock-associated (LA)-MRSA clone characteristic of food animals and identified as ST398 (Loeffler *et al.*, 2009).

Epidemiology of MRSA in domestic animals: The first documented case of MRSA infection in a domestic

animal was reported in a dairy cow in 1972 (Devriese *et al.*, 1972) (Table 1). Since then, MRSA has been found in a variety of other domestic species including horses, chickens, dogs and cats (Cefai *et al.*, 1994; Rich and Roberts, 2004). The occurrence of MRSA in a dog was first described in Nigeria in 1972 (Loeffler and Lloyd, 2010), but more widespread occurrence was not reported until 1999, including cases in the United States (Gortel *et al.*, 1999), in the UK (Tomlin *et al.*, 1999) and in South Korea (Pak *et al.*, 1999). Canine infection has been subsequently reported in Canada (Oughton *et al.*, 2001) and in the Netherlands (Van Duijkeren *et al.*, 2003). MRSA was first described in healthy cat (Scott *et al.*, 1988). Staphylococcal flora of 148 cats in Brazil was also reported (Lilenbaum *et al.*, 1998). In the UK, recent reports of MRSA isolation from small animals (Rich and Robert, 2004; Boag *et al.*, 2004) suggest that MRSA is much more prevalent in small animal veterinary practice than has been hitherto recognized. MRSA carriage can be a hazard to owners, especially if they have increased susceptibility to infection. However, it should be noted that pet animals appear to become reservoirs of MRSA through exposure to infected humans and thus probably do not constitute the primary reservoir for MRSA but act as a small secondary reservoir (Guardabassi *et al.*, 2004).

Methicillin resistance is also recognized in *S. intermedius*, coagulase-negative Staphylococci and coagulase-variable species such as *Staphylococcus schleiferi*. Lilenbaum *et al.* (1998) described the occurrence of Methicillin-resistant *Staphylococcus intermedius* and coagulase-negative Staphylococci in clinically healthy Brazilian cats. In the USA, Frank *et al.* (2003) reported the isolation of Methicillin-resistant *Staphylococcus schleiferi* from 11 dogs with recurrent pyodermas. Although infection in man is uncommon, *S. schleiferi* is increasingly recognized as the cause of nosocomial infections.

Staphylococcal species reported in dogs and cats:

While *Staphylococcus aureus* can be recovered from both dogs and cats, in neither species, it is the most common staphylococcal strain. A variety of coagulase-positive and coagulase-negative Staphylococci have been identified in dogs and cats (Scott *et al.*, 1988). The most prevalent canine isolate in the majority of studies is the coagulase-positive species *Staphylococcus intermedius* (Kaszanyitzky *et al.*, 2003), although a recent study in Japan reported that the coagulase-negative species *Staphylococcus sciuri* was most prevalent (Nagase *et al.*, 2002). *Staphylococcus felis*

and *S. intermedius* appear to be the most prevalent coagulase-negative and coagulase-positive species, respectively, isolated from cats (Lilenbaum *et al.*, 1998; Patel *et al.*, 1999, 2002). The frequency of *Staphylococcus aureus* carriage on the skin and mucous membranes of dogs and cats is low; isolates are generally recovered from less than 10 percent of samples (Biberstein *et al.*, 1984; Kaszanyitzky *et al.*, 2003). However, other studies isolated *Staphylococcus aureus* from 17% of canine samples (Cox *et al.*, 1984), from 90% (9/10) and 40% (4/10) of healthy dogs and cats, respectively (Krogh and Kristensen, 1976) and 50% (16/32) of cats with pyodermas (Medleau and Blue, 1988).

Transmission of Methicillin-Resistant *Staphylococcus aureus* (MRSA) between humans and companion animals:

Colonization and infection in-patients remain the major reservoir of MRSA in hospitals, while transient carriage of the organism on the hands of healthcare workers accounts for the primary means of nosocomial infection (Nicolle *et al.*, 1999). Studies have also shown that MRSA can be transmitted through direct contact in the community (Nicolle *et al.*, 1999), aerosols (Shiomori *et al.*, 2001) and inanimate objects (Bures *et al.*, 2000). More recently, concern has been expressed that domestic pets could act as reservoirs and transmit MRSA to humans (O'Rourke, 2003). Transmission of bacterial strains between companion animals and their owners has been demonstrated in several instances where Molecular analyses have shown the presence of indistinguishable MRSA strains in pets and humans living in the same household and have suggested, but not definitely proved, the direction of transmission (Weese, 2010). As the isolates from cats and dogs resemble nosocomial MRSA, it is usually assumed that companion animals acquire MRSA from humans. Both humans and animals are more often colonized than infected and both can act as reservoirs of MRSA for recirculation of strains inside the household (Morgan, 2008). According to a study performed in Canada and in the US, the owners of companion animals have a MRSA colonization rate (18%) significantly higher than the general population (1–2%) although they do not appear to be at an increased risk for MRSA infections (Faires *et al.*, 2009). In a nursing home for the elderly in UK patients, staff and the resident cat were all colonized by the same MRSA strain. The cat harbored the MRSA strain on the fur and paws and was the most probable vehicle of MRSA transmission in the nursing home (Scott *et al.*, 1988). In a veterinary hospital the transmission of an EMRSA-15 (ST22) strain from infected dogs to staff members has been demonstrated by molecular typing methods (Baptiste *et al.*, 2005). Pets can be also colonized by CA-MRSA, as the spread of a PVL-positive CA-MRSA strain in a household in the

Netherlands was shown to involve also the family dog (Van Duijkeren *et al.*, 2005).

Geographic distribution of Methicillin-Resistant *Staphylococcus aureus* (MRSA):

MRSA can be found worldwide, but its prevalence varies (Weese *et al.*, 2006a; Cuny *et al.*, 2006). Human-adapted, hospital-associated strains of these organisms are rare among people in the Netherlands and Scandinavian countries, where extensive control programs have been conducted for years (Leonard and Markey, 2008; Kluytmans, 2010; Otter and French, 2010). Community-associated strains can occur even where hospital-associated strains have been controlled (Otter and French, 2010). One or two clonal complexes tend to predominate in an area (Cockfield *et al.*, 2007). CC398 has been detected among livestock in many European countries (Van den Broek *et al.*, 2009; Tenhagen *et al.*, 2009; Denis *et al.*, 2009; Battisti *et al.*, 2010; Catry *et al.*, 2010). MRSA in this clonal complex has recently been recognized among pigs in North America (Khanna *et al.*, 2008; Van den Broek *et al.*, 2009; Harper *et al.*, 2010; Catry *et al.*, 2010); Singapore (Sergio *et al.*, 2007). The specific isolates found in horses vary with the geographic area (Leonard and Markey, 2008).

Pathogenesis: *Staphylococcus aureus* are commensals that colonize the nares, axillae, vagina and pharynx or damaged skin surfaces. It causes superficial lesion (boils, furunculosis), deep-seated and systemic infection (endocarditis, osteomyelitis), and toxic syndromes (food poisoning by releasing enterotoxin in food, toxic shock syndrome by release of superantigens into the blood stream, localized and generalized exfoliation by the production of exfoliative toxins) (Lipsky and Stoutenburgh, 2005). In pyogenic infections the pathogenesis results from the combined action of a variety of factors (Gosden *et al.*, 1997). Infection is initiated when a breach of the skin or mucosal barrier allow *Staphylococci* access to adjacent tissues or to the bloodstream. Whether an infection is contained or spreads depends on a complex interplay between *Staphylococcus aureus* virulence determinants and host defense mechanisms.

Adherence to host tissue: The nose is the main ecological niche of *Staphylococcus aureus* and about 20% (range 12-30%) of individuals are persistent *Staphylococcus aureus* nasal carriers, increasing risk of acquiring an infection with this pathogen. *Staphylococcus aureus* adheres to cells and extra cellular matrix components by the joint action of MSCRAMM (microbial surface component recognizing adhesive matrix molecules) and secreted expanded repertoire adhesive molecules. MSCRAMMs bind molecules such as collagen, fibronectin and fibrinogen and different MSCRAMMs may adhere to the same

host-tissue component. Thus, these molecules act in initiation of endovascular infections, endocarditis and bone and joint infections. By the heterogeneity of MSCRAMMs types, different *Staphylococcus aureus* strains may be predisposed to causing certain kinds of infections (Clarke and Foster, 2006). Coagulase is an extracellular protein, belonging to the secreted expanded repertoire adhesive molecules class, which binds to prothrombin to form a complex called staphylothrombin. The protease activity of the thrombin complex is activated, resulting in the conversion of fibrinogen to fibrin. Coagulase is produced by almost all clinical isolates of *Staphylococcus aureus*; thus it is a traditional marker for identifying *S. aureus* in clinical microbiology laboratory.

Invasion of host tissues: The invasion of host tissues by staphylococci involves the production of a large number of extracellular proteins such as

The α , β , delta-Toxins: The α -toxin is expressed as a monomer that binds to the eukaryotic cell membranes, the subunits oligomerize to form heptameric rings with a central pore through which cellular contents leak. This toxin also induces the death of innate and acquired immunity cells, interferes with the metabolism of Arachidonic acid, exocytosis and induces dysfunctions in contractility, leading to bacterial spread and alterations of the hemostasis (Bhakdi and Trantum-Jensen, 1991). The β -toxin or sphingomyelinase C is a haemolysin, which targets lipid-rich membranes. It causes lysis of erythrocytes and mononuclear cells and also induces a strong inflammatory response. The majority of human isolates of *Staphylococcus aureus* do not express β -toxin, but it is frequently found among strains responsible for bovine mastitis (Marshall and Bohach, 2000). The delta-toxin consisting of a peptide 26aa, but its role in disease is unknown.

Phospholipase C: *Staphylococcus aureus* secretes phospholipase C, which specifically hydrolyses membrane lipid and protein-containing glycosyl phosphatidyl inositol (Daudherty and Low, 1993).

Metalloproteases: The aureolysin, member of the thermolysines family, is an extracellular and zinc dependent metalloprotease. This enzyme destroys host defence molecules (Banbula and Potempa, 1998).

Hyaluronidase and hyaluronate lyase: These enzymes digest hyaluronic acid, polymer present in the vitreous humour, skin, bones and synovial fluid, promoting the infection process by dispersal and tissue degradation (Farrell and Taylor, 1995).

Exfoliative toxins: There are two major biologically and serologically distinct *Staphylococcus aureus* exfoliative toxin isoforms, exfoliative toxin A and

exfoliative toxin B, that are primarily responsible for the skin manifestations of staphylococcal scalded skin syndrome and bullous impetigo. 5% of clinical *S. aureus* isolates produce either exfoliative toxin A, exfoliative toxin B or both toxins. They cleave the stratum granulosum from the stratum spinosum by targeting desmosomes (Amagai and Yamaguchi, 2002).

Epidermal cell differentiation inhibitor: The epidermal cell differentiation inhibitors which are mono-ADP ribosyltransferases belonging to the Rho family, are found in 8% of disease strains and in 3.7% of nasal carrier strains under 3 isoforms: epidermal cell differentiation inhibitors-A, B and C. Although epidermal cell differentiation inhibitor-A inhibits the differentiation of keratinocytes *in vitro*, the role of epidermal cell differentiation inhibitors in human diseases is not established (Yamaguchi and Nishifuji, 2002).

Avoidance of host defenses: The *Staphylococcus aureus* wall consists of two major components, peptidoglycan and lipoteichoic acid, both analogous to the lipopolysaccharide in gram-negative bacteria. They are able to induce the release of cytokines by macrophages, the activation of the complement system and the platelets aggregation, thus triggering a disseminated intravascular coagulation (Lowy, 1988).

Enterotoxins: *Staphylococcus aureus* can produce a large diversity of exoproteins belonging to the family of super antigens, stimulating polyclonal T-cell proliferation through co-ligation between Major Histocompatibility Complex (MHC) class II molecules on antigen-presenting cells and the variable portion of the T-cell antigen receptor β chain or α chain with no need for prior antigen-presenting cells processing. T-cell/ antigen-presenting cells activation by these toxins leads to the release of large amounts of various cytokines/lymphokines which are deleterious for the host (Dinges *et al.*, 2000). Twenty different enterotoxins have been described, among them, Staphylococcal toxic shock syndrome toxin (TSST-1), Staphylococcal enterotoxin A, B, C or enterotoxins coded by egc cluster (Jarraud and Peyrat, 2001). Beside their super antigenic properties, they are also pyrogenic and enteropathogenic for the majority, thus explaining their implication in both staphylococcal Toxic Shock Syndrome (TSS) and food poisoning. The enterotoxins have also been implicated in a number of autoimmune disorders (Rheumatic arthritis, etc.) and other abnormal immunologic states such as psoriasis, atopic dermatitis and Kawasaki syndrome (McCormick and Yarwood, 2001).

Protein A: Protein A is a multifunctional virulence factor produced by almost all clinical isolates: it inhibits opsonophagocytosis via binding of immunoglobulin Fc

fragment, it is also a B cell “superantigen” promoting B cell activation. It is a MSCRAMM, allowing the attachment of Von willebrand factor which is present on the injured endothelium. Finally, protein A plays a pro-inflammatory role, via the activation of the Tumor Necrosis Factor Receptor (TNFR1) present on the respiratory epithelium (Turnidge and Bell, 1998).

The fatty acid modifying enzyme and lipases: More than 80% of strains of *Staphylococcus aureus* express fatty acid modifying enzyme which modify antibacterial lipids and thus may contribute to bacterial survival, including in abscesses (Turnidge and Bell, 1998).

V8 Protease: The V8 protease is an extracellular serine protease which possesses many structural similarities with exfoliative toxin. It cleaves the peptide bonds, inactivating *in vitro* and *in vivo* the action of antibodies and may protect against antimicrobial peptides such as neutrophil defensin proteins and bactericidal platelet proteins thus contributing to tissue proteins destruction during the invasion (Postier *et al.*, 2004).

Leukocidins: These toxins consist of two separately secreted and non-associated proteins (class S and class F components) acting synergistically and promoting eukaryotic cell lysis. They are: γ -haemolysin, Pantone Valentine Leukocidin (PVL) and leukocidins Luk D/E and Luk M/F. The γ haemolysin is produced by almost all ($\geq 99\%$) *Staphylococcus aureus* strains (Von Eiff and Friedrich, 2004).

The panton-valentine leukocidin: This is a pore forming toxin which damages human neutrophils, recovered from less than 2% of *Staphylococcus aureus* strains. It has been epidemiologically linked to primary skin and soft tissue infections and to deep seated infections such as necrotizing pneumonia and severe recurrent osteomyelitis occurring in young immunocompetent patients. The genes coding for leukotoxins LukE-Luk D were detected in a high prevalence (82%) among blood isolates and 61% among nasal isolates (Von Eiff and Friedrich, 2004).

Clinical signs: Methicillin Resistant *Staphylococcus aureus* (MRSA) has been found in asymptomatic carriers including pigs, dogs, cats, horses, calves and other animals (Floras *et al.*, 2010; Velebit *et al.*, 2010; Aarestrup *et al.*, 2010; Graveland *et al.*, 2010; Loeffler and Lloyd, 2010; Catry *et al.*, 2010; Cuny *et al.*, 2010). *Staphylococcus aureus* can cause a wide variety of suppurative infections in animals (Lee, 2003; Catry *et al.*, 2010). *Staphylococcus aureus* (MRSA) has been isolated from various skin and wound infections including abscesses, dermatitis including severe pyodermas, exudative dermatitis in pigs, post operative

wound infections, fistulas and intravenous catheter or surgical implant infections (Catry *et al.*, 2010; Loffler and Lloyd, 2010; Pomba *et al.*, 2010; Faires *et al.*, 2010; Floras *et al.*, 2010). It has also been found in other conditions including pneumonia, rhinitis, sinusitis, otitis, bacteremia, septic arthritis, osteomyelitis, omphalophlebitis, metritis, mastitis (including gangrenous mastitis) and urinary tract infections (Catry *et al.*, 2010; Loffler and Lloyd, 2010; Fessler *et al.*, 2010; Spohr *et al.*, 2010; Floras *et al.*, 2010).

Bordetella Bronchiseptica And *Staphylococcus aureus* (MRSA) were isolated from the nasal and oropharyngeal tract of puppies after an outbreak of fatal respiratory disease; the role of *Staphylococcus aureus* (MRSA) in the outbreak was uncertain (Floras *et al.*, 2010). In addition to causing mastitis in dairy cattle (Van den Broek *et al.*, 2009; ; Fessler *et al.*, 2010; Spohr *et al.*, 2010), one study suggested that *Staphylococcus aureus* (MRSA) in milk was associated with higher somatic cell counts than Methicillin sensitive *Staphylococcus aureus* (Spohr *et al.*, 2010). *Staphylococcus aureus* (MRSA) was also isolated from a suppurative area in chicken meat and from the joints of chicken with signs of arthritis (Lee, 2003). In a recent study, most equine MRSA infections at *Staphylococcus aureus* Veterinary hospitals were opportunistic (Anderson *et al.*, 2009).

Diagnosis: *Staphylococcus aureus* infections, including colonization, are diagnosed by culture. MRSA can colonize more than one site and the best site for detecting carriers among dogs and cats is unknown (Kottler *et al.*, 2010). Nasal and rectal sampling should both be done whenever possible (Kottler *et al.*, 2010). In swine, one study reported that nasal swabs detected most colonized pigs, but some animals carried MRSA in both locations and a few carrier pigs (all weanlings) could only be found using rectal swabs (Khanna *et al.*, 2008). Enrichment media, as well as selective plates for MRSA, are available. Detection of the organism in clinical specimens can vary, depending on the isolation method used (Graveland *et al.*, 2009). On blood agar, they are usually beta hemolytic (Bottone *et al.*, 1984). Young colonies are colorless; older colonies may be shades of white, yellow or orange (Bottone *et al.*, 1984). Biochemical tests such as the coagulase test are used to differentiate *Staphylococcus aureus* from other Staphylococci. *Staphylococcus aureus* can also be identified with the API Staph Identification system. If *Staphylococcus aureus* is isolated from an infection, genetic testing or antibiotic susceptibility testing can identify Methicillin resistant strains (Centers for Disease Control and Prevention, 2009). Genetic tests to detect *mecA*, such as PCR, are the “gold standard” for identification (Lee *et al.*, 2004; Van Duijkeren *et al.*, 2004; Weese and Rousseau, 2005; Loffler and Lloyd,

2010). Polymerase Chain Reaction (PCR) methods to detect *mecA* in *Staphylococcus aureus* isolates from humans are commercially available (Warren *et al.*, 2004; Paule *et al.*, 2007). A real-time Polymerase Chain Reaction (PCR) test validated for the detection of human nasal carriage had poor agreement with culture results in horses (Anderson and Weese, 2007). A latex agglutination test can be used to detect PBP2a (Lee *et al.*, 2004; Weese and Rousseau, 2005; Löffler and Lloyd, 2010). Antibiotic susceptibility tests such as the agar screen test, disk diffusion test, or MIC determination can also be used to identify Methicillin Resistant *Staphylococcus aureus* (MRSA) (Lee, 2003; Lee *et al.*, 2004; Van Duijkeren *et al.*, 2004; Weese and Rousseau, 2005). Most antibiotic susceptibility tests use Oxacillin or Cefoxitin, as Methicillin is no longer commercially available in the U.S (Weese and Rousseau, 2005). Antibiotic susceptibility testing has some drawbacks compared to detection of *mecA* or PBP2a. Methicillin-susceptible and resistant subpopulations can coexist *in vitro*; although the entire colony carries the resistance genes, only a small number of bacteria may express resistance in culture (Weese and Rousseau, 2005). The expression of resistance in phenotypic tests can also vary with growth conditions such as temperature (Lee *et al.*, 2004). Clones or strains of MRSA are differentiated by genetic tests such as PFGE, MLST, SCC *mec* typing, spa typing and other assays (Weese and Rousseau, 2005; Leonard and Markey, 2008; Catry *et al.*, 2010). These techniques are usually used for epidemiological studies, such as tracing outbreaks (Catry *et al.*, 2010). Some isolates may be untypeable by certain methods (Catry *et al.*, 2010; Cony *et al.*, 2010). Notably, PFGE cannot identify CC398. PFGE and MLST typing tends to be congruent, but unrelated lineages can sometimes contain similar spa types (Golding *et al.*, 2008; Cuny *et al.*, 2010). Additional genetic testing can resolve such discrepancies (Golding *et al.*, 2008). Spa typing can distinguish strains that are indistinguishable by Multilocus Sequence Typing (MLST) or Pulse Field Gel Electrophoresis (PFGE) (Catry *et al.*, 2010). A combination of methods may be necessary to identify a strain.

Treatment: Antibiotic therapy should be based on susceptibility testing; however, all MRSA strains are considered to be resistant to penicillin's, cephalosporin's, cephems and other β -lactam antibiotics (such as ampicillin-sulbactam, amoxicillin-clavulanic acid, ticarcillin-clavulanic acid, piperacillin-tazobactam and the carbapenems) regardless of the susceptibility testing results (Seguin *et al.*, 1999; Lee, 2003).

Methicillin Resistant *Staphylococcus aureus* (MRSA) isolated from animals vary in their antibiotic susceptibility (Fessler *et al.*, 2010; Catry *et al.*, 2010). Most CC398 MRSA are resistant to tetracyclines and

many are also resistant to trimethoprim (Kadlec *et al.*, 2009; Catry *et al.*, 2010). However, the precise susceptibility patterns of these isolates can vary widely. Methicillin Resistant *Staphylococcus aureus* (MRSA) CC398 isolates from bovine mastitis cases in Germany demonstrated 10 different antibiotic resistance patterns, with approximately 41% of isolates resistant only to beta-lactam antibiotics and tetracycline's (Fessler *et al.*, 2010). Another study reported 22 different antibiotic resistance patterns among CC398 isolates from pigs (Kadlec *et al.*, 2009). Susceptibility to fluoroquinolones and resistance to tetracycline has been identified as characteristic of the epidemic MRSA strain CMRSA5 (CC8 lineage; USA500), found among horses especially in Canada (Anderson *et al.*, 2009). Some MRSA can appear sensitive to clindamycin during routine sensitivity testing, but carry a gene that allows them to become resistant during treatment (Faires *et al.*, 2009). In one study, inducible clindamycin resistance was very common among erythromycin-resistant, clindamycin-susceptible MRSA isolates from dogs and cats in Canada (Faires *et al.*, 2009). Some antimicrobials such as vancomycin, tigecycline and certain other drugs are considered to be critically important antimicrobials for use, sometimes as a last resort, in human MRSA infections (Catry *et al.*, 2010). These drugs are controversial for the treatment of MRSA-infected animals (Catry *et al.*, 2010). Using them may place selection pressure for antibiotic resistance on MRSA that may also infect humans (Catry *et al.*, 2010).

Antibiotics and other measures have been used successfully in case reports in animals (Leonard *et al.*, 2006; Catry *et al.*, 2010). In some cases, surgical implants were also removed (Leonard *et al.*, 2006). One dog with MRSA septic arthritis was treated successfully with a surgically implanted, absorbable gentamicin-impregnated sponge (Owen *et al.*, 2004). Local treatment with antiseptic compounds such as chlorhexidine, povidone iodine or glycerol may be helpful in some types of infections (Catry *et al.*, 2010). Meticulous wound management without antimicrobials was successful in at least one case in a dog (Catry *et al.*, 2010). Animals treated with topical therapy alone must be monitored closely for signs of localized progression or systemic spread (Catry *et al.*, 2010).

Prevention: Good Veterinary hospitals should establish guidelines to minimize cross-contamination by MRSA and other Methicillin-resistant Staphylococci (Duquette and Nuttall, 2004). Good hygiene including hand washing and environmental disinfection is important in prevention (Durand *et al.*, 2006; Catry *et al.*, 2010). Dedicated clothing that can be laundered at the clinic should be worn and gloves and other personal protective measures should be used when there is a risk of contact with body fluids (Leonard and Markey, 2008). Good infection control measures should be

employed, especially with invasive devices such as intravenous catheters and urinary catheters (Catry *et al.*, 2010). Barrier precautions should be practiced when treating animals with recognized MRSA infections and these animals should be isolated (Leonard and Markey, 2008; Catry *et al.*, 2010). MRSA-infected wounds should be covered whenever possible (Leonard and Markey, 2008; Catry *et al.*, 2010). Although colonized people can transmit MRSA to animals, one study suggests that there may be only a small risk of transmission from colonized surgical personnel if infection control protocols are followed (McLean and Ness, 2008). In this study, MRSA wound infections occurred in four of 180 surgical cases in which the primary surgeon was persistently colonized and none of 141 cases seen by a surgeon who was not colonized; this difference was not statistically significant (McLean and Ness, 2008).

Researchers have recommended that veterinary hospitals initiate surveillance programs for MRSA infections, particularly in horses (O'Rourke, 2003; Duquette and Nuttall, 2004). Screening at admission allows prompt isolation of MRSA carriers and the use of barrier precautions to prevent contact with other animals (Weese *et al.*, 2006b). It also allows clinical cases to be recognized rapidly. Routine screening of all admitted animals may be costly and it may be practical only for referral practices (Leonard and Markey, 2008; Catry *et al.*, 2010). For this reason, some authors recommend screening targeted populations, including animals with non-antibiotic responsive, non-healing or nosocomial infections and animals belonging to healthcare workers or known MRSA-positive households (Leonard and Markey, 2008; Catry *et al.*, 2010). Animals that have been in contact with MRSA cases or infected/ colonized staff should also be tested (Catry *et al.*, 2010). If staff are screened for any reason (e.g., during an outbreak), this must be undertaken only with full consideration of privacy and other concerns.

There are currently no proven, completely reliable methods to decolonize animals and the efficacy of decolonization in animals is unknown. Various measures have been used successfully in individual cases. Colonization in dogs, cats and horses often seems to be transient and some animals have spontaneously eliminated MRSA when the environment was regularly cleaned and disinfected and re-infection was prevented (Catry *et al.*, 2010; Loeffler *et al.*, 2010). Captive dolphins and walrus colonized at a marine park also cleared the carriage with only infection control procedures, although long term carriage (15 months) was reported in one dolphin (Faires *et al.*, 2009). Whether all MRSA types can be eliminated in all species with similar measures is still uncertain (Catry *et al.*, 2010). Routine decolonization with antimicrobials is currently not recommended for pets, but it may be considered in individual cases to control transmission to humans or other animals (e.g., when an animal remains a persistent carrier or infection control

measures are impossible) (Catry *et al.*, 2010). In rare cases where an entire family is being decolonized, kenneling an animal, preferably in isolation, might allow it to spontaneously eliminate MRSA without additional measures (Catry *et al.*, 2010). A variety of antimicrobials have been used to decolonize animals in individual cases, but the efficacy of the various drugs is still unknown. Oral doxycycline and rifampin eliminated MRSA carriage in one asymptotically colonized dog (Van Dujkere *et al.*, 2005). Rifampin and ciprofloxacin, or fusidic acid and chlorhexidine were successful in two other dogs (Catry *et al.*, 2010; Loeffler *et al.*, 2010). Topical treatment (e.g., mupirocin) to eliminate nasal carriage has been considered to be impractical in pets (Van Duijkeren *et al.*, 2004). Mupirocin resistance can occur in some MRSA isolates (Duquette and Nuttall, 2004; Catry *et al.*, 2010).

A combination of techniques has been used to control MRSA in some infected facilities. On two horse farms, the use of enhanced infection control measures, segregation of carriers and repeated screening, without antimicrobial treatment, eliminated colonization in many animals. People who had been colonized were referred to a physician for decolonization. Intranasal amikacin was used to eliminate long term carriage in two horses that remained colonized after 100 days. Amikacin was unsuccessful in one horse, which was then treated with two courses of oral chloramphenicol. This animal eventually eliminated the MRSA by 30 days after the end of treatment. Once MRSA was eliminated, screening of new horses and periodic testing of residents was established to prevent its reintroduction (Weese and Rousseau, 2005).

Management techniques may affect MRSA colonization on a farm (Van Rijen *et al.*, 2008). In some cases, MRSA appears to be introduced when buying new stock and to be spread during livestock movements (Van Rijen *et al.*, 2008). Biosecurity measures, such as dedicated clothing and showering in, may decrease the risk of MRSA introduction to a farm by visitors, or reduce transmission between units. Infection control measures, including improved hygiene, might also decrease transmission between farms (Catry *et al.*, 2010). Because MRSA CC398 has been detected in rats living on pig farms or mixed pig/veal operations, rats should be considered in control programs (Van den Eede *et al.*, 2009). Whether MRSA in manure poses a risk when used as fertilizer and the effectiveness of measures such as composting or heat treatment in prevention, are unknown. It is possible that avoiding routine antimicrobial use in food animals, to decrease selection pressures, might decrease the prevalence of MRSA among livestock (Catry *et al.*, 2010).

CONCLUSION

MRSA is a global problem, considering the trend of *Staphylococcus aureus* diagnosis in domestic animals, particularly dogs and cats. Initial reports

indicated low frequency of carriage, but recent reports indicated high frequency of occurrence in domestic and companion animals. MRSA infections in companion animals are mostly associated with exposure to hospitals, human contact, extensive wound, prolonged hospitalization and immunosuppression.

RECOMMENDATIONS

Pet owners should be advised to avoid unnecessary contact with their pets and to undertake proper hygienic precautions and also minimize indiscriminate use of antibiotics to prevent the development of Staphylococcal bacterial resistance. Veterinary and Medical personnel should be aware of MRSA infection occurrence in animals. Improved control measures are required to limit transmission in hospitals and research effort should be targeted at ascertaining the true prevalence of MRSA in healthy dogs and cats.

REFERENCES

- Aarestrup, F.M., L. Cavaco and H. Hasman, 2010. Decreased susceptibility to zinc chloride is associated with Methicillin resistant *Staphylococcus aureus* CC 398 in Danish swine. *Vet. Microbiol.*, 142(3-4): 455-457.
- Amagai, M. and T. Yamaguchi, 2002. Staphylococcal exfoliative toxin B specifically cleaves desmoglein. *J. Invest. Dermatol.*, 118(5): 845-850.
- Anderson, M.E. and J.S. Weese, 2007. Evaluation of a real-time polymerase chain reaction assay for rapid identification of Methicillin-resistant *Staphylococcus aureus* directly from nasal swabs in horses. *Vet. Microbiol.*, 122(1-2): 185-189.
- Anderson, M.E., S.L. Lefebvre, S.C. Rankin, H. Aceto, P.S. Morley, J.P.R.D. Caron, T.C.T.C. Welsh, B. Holbrook Moore, D.R. Taylor and J.S. Weese, 2009. Retrospective multicentre study of Methicillin-resistant *Staphylococcus aureus* infections in 115 horses. *Equine Vet. J.*, 41(4): 401-405.
- Bagcigil, F.A., A. Moodley, K.E. Baptiste, V.F. Jensen and L. Guardabassi, 2007. Occurrence, species distribution, antimicrobial resistance and clonality of methicillin-an erythromycin resistant staphylococci in the nasal cavity of domestic animals. *Vet. Microbiol.*, 121: 307-315.
- Banbula, A. and J. Potempa, 1998. Amino-acid sequence and three-dimensional structure of the *Staphylococcus aureus* metalloproteinase at 1.72 resolution. *Structure*, 6(9): 1185-1193.
- Baptiste, K.E., K. Williams, N.J. Williams, A. Wattret, P.D. Clegg, S. Dawson, J.E. Corkill O'Neill and C.A. Hart, 2005. Methicillin-resistant staphylococci in companion animals. *Emerg. Infect. Dis.*, 11: 1942-1944.
- Battisti, A., A. Franco, G. Merialdi, H. Hasman, M. Iurescia, R. Lorenzetti, F. Feltrin, M. Zini and F.M. Aarestrup, 2010. Heterogeneity among Methicillin-resistant *Staphylococcus aureus* from Italian pig finishing holdings. *Vet. Microbiol.*, 142 (3-4): 361-366.
- Bhakdi, S. and J. Trandum-Jensen, 1991. Alpha-toxin of *staphylococcus aureus*. *Microbiol. Rev.*, 55(4): 733-751.
- Biberstein, E.L., S.S. Jang and O.C. Hirsh, 1984. Species distribution of coagulase-positive staphylococci in animals. *J. Clin. Microbiol.*, 19: 610-615.
- Boag, A., A. Loeffler and D.H. Lloyd, 2004. Methicillin resistant *Staphylococcus aureus* isolates from companion animals. *Vet. Rec.*, 154: 411-415.
- Boost, M.V., M.M. O'Donoghue and A. James, 2008. Prevalence of *Staphylococcus aureus* carriage among dogs and their owners. *Epidemiol. Infect.*, 136: 953-964.
- Bottone, E.J., R. Girolami and J.M. Stam., 1984. Schneierson's Atlas of Diagnostic Microbiology. 9th Edn., Abbott Laboratories, Abbott Park IL, pp: 10-13.
- Bures, S., J.I. Fishbain, C.F.T. Uyehara, J.M. Parker and B.W. Berg, 2000. Computer keyboards and faucet handles as reservoirs of nosocomial pathogens in the intensive care unit. *Am. J. Infect. Control*, 28: 465-471.
- Catry, B., E. Van Duijkeren, M.C. Pomba, C. Greko, M.A. Moreno, S. Pyörälä, M. Ruzauskas Sanders, E.J. Threlfall, F. Ungemach, K. Törneke, C. Munoz-Madero and J. Torren-Edo, 2010. Scientific Advisory Group on Antimicrobials (SAGAM): Reflection paper on MRSA in food-producing and companion animals: Epidemiology and control options for human and animal health. *Epidemiol. Infect.*, 138(5): 626-644.
- Cefai, C., S. Ashurst and C. Owens, 1994. Human carriage of Methicillin-resistant *Staphylococcus aureus* linked with pet dog. *Lancet*, 344: 539-540.
- Centers for Disease Control and Prevention (CDC), 2004. Community - associated Methicillin - resistant *Staphylococcus aureus* infection among healthy newborns: Chicago and Los Angeles County. *MMWR Morb Mortal Weekly Rep.*, 55(12): 329-332.
- Centers for Disease Control and Prevention (CDC), 2009. Methicillin-resistant *Staphylococcus aureus* skin infections from an elephant calf--San Diego, California, 2008. *MMWR Morb Mortal Weekly Report* 6, 58(8): 194-198.
- Chomel, B.B. and B. Sun, 2011. Zoonoses in the bedroom. *Emerg. Infect. Dis.*, 17: 167-172.
- Clarke, S.R. and S.J. Foster, 2006. Surface adhesions of *Staphylococcus aureus*. *Adv. Microb. Physiol.*, 51: 187-224.

- Cockfield, J.D., S. Pathak, J.D. Edgeworth and J.A. Lindsay, 2007. Rapid determination of hospital-acquired Methicillin-resistant *Staphylococcus aureus* lineages. J. Med. Microbiol., 56(5): 614-619.
- Cox, H.U., S.S. Newman, A.F. Roy and J.D. Hoskins, 1984. Species of *Staphylococcus* isolated from animal infections. Cornell Vet., 74: 124-135.
- Cuny, C., J. Kummerle, C. Stanek, B. Willey, B. Strommenger and W. Witte, 2006. Emergence of MRSA infections in horses in a veterinary hospital: Strain, characterisation and comparison with MRSA from humans. Euro Surveill., 11(1): 10-15.
- Cuny, C., A. Friedrich, S. Kozytka, F. Layer, U. Nübel, K. Ohlsen, B. Strommenger, B. Walther, L. Wieler and W. Witte, 2010. Emergence of Methicillin-resistant *Staphylococcus aureus* (MRSA) in different animal species. Int. J. Med Microbiol., 300(23): 109-117.
- Daudherty, S. and M.G. Low, 1993. Cloning expression and mutagenesis of phosphatidylinositol-specific phospholipase C from *Staphylococcus aureus*: A potential staphylococcal virulence factor. J. Infect Immunol., 61(12): 5078-5089.
- Denis, O., C. Suetens, M. Hallin, B. Catry, I. Ramboer, M. Dispas, G. Willems, B. Gordts, P. Butaye and M.J. Struelens, 2009. Methicillin-resistant *Staphylococcus aureus* ST398 in swine farm personnel, Belgium. Emerg. Infect. Dis., 15(7): 1098-1099.
- Devriese, L.A., L.R. Vandamme and L. Fameree, 1972. Methicillin (cloxacillin-resistant *Staphylococcus aureus* strains isolated from bovine mastitis) cases. Zbl. Vet. Med. B, 19: 590-605.
- Devriese, L.A., M. Vancanneyt, M. Baele, M. Vaneechoutte, E. De Graef, C. Snauwaert, I. Cleenwerck, P. Dawyndt, J. Swings, A. Decostere and F. Haesebrouck, 2005. *Staphylococcus pseudintermedius* sp. nov., a coagulase-positive species from animals. Int. J. Syst. Evol. Microbiol., 55: 1569-1573.
- Dinges, M.M., P.M. Orwin and P.M. Schlievert, 2000. Exotoxins of *Staphylococcus aureus*. Clin. Microbiol. Rev., 13: 16-34.
- Duquette, R.A. and T.J. Nuttall, 2004. Methicillin-resistant *Staphylococcus aureus* in dogs and cats: An emerging problem. J. Small Anim Pract., 45(12): 591-597.
- Durand, G., M. Bes, H. Meugnier, M.C. Enright, F. Forey, N. Liassine, A. Wenger, K. Kikuchi, G. Lina, F. Vandenesch and J. Etienne, 2006. Detection of new Methicillin-resistant *Staphylococcus aureus* clones containing the toxic shock syndrome toxin 1 gene responsible for hospital- and community-acquired infections in France. J. Clin. Microbiol., 44(3): 847-853.
- Ellington, M.J., R. Hope, D.M. Livermore, A.M. Kearns, K. Henderson, B.D. Cookson, A. Pearson and A.P. Johnson, 2010. Decline of EMRSA-16 amongst Methicillin-resistant *Staphylococcus aureus* causing bacteraemia in the UK between 2001 and 2007. J. Antimicrob. Chemoth., 65: 446-448.
- Faires, M.C., K.C. Tater and J.S. Weese, 2009. An investigation of Methicillin-resistant *Staphylococcus aureus* colonization in people and pets in the same household with an infected person or infected pet. J. Am. Vet. Med. Assoc., 235(5): 540-543.
- Faires, M.C., M. Traverse, K.C. Tater, D.L. Pearl and J.S. Weese, 2010. Methicillin-resistant and susceptible *Staphylococcus aureus* infections in dogs. Emerg. Infect. Dis., 16(1): 69-75.
- Farrell, A.M. and D. Taylor, 1995. Cloning, nucleotide sequence determination and expression of the *Staphylococcus aureus* hyaluronate lyase gene. FEMS Microbiol. Lett., 130 (1): 81-85.
- Fessler, A., C. Scott, K. Kadlec, R. Ehricht, S. Monecke and S. Schwarz, 2010. Characterization of Methicillin-resistant *Staphylococcus aureus* ST398 from cases of bovine mastitis. J. Antimicrob. Chemoth., 65(4): 619-625.
- Floras, A., K. Lawn, D. Slavic, G.R. Golding, M.R. Mulvey and J.S. Weese, 2010. Sequence type 398 Methicillin-resistant *Staphylococcus aureus* infection and colonization in dogs. Vet. Rec., 166(26): 826-827.
- Frank, L.A., S.A. Khnia, K.A. Hnilica, R.P. Wilkes and O.A. Bemis, 2003. Isolation of *Staphylococcus schleiferi* from dogs with pyoderma. J. Am. Vet. Med. Assoc., 222: 451-454.
- Golding, G.R., J.L. Campbell, D.J. Spreitzer, J. Veyhl, K. Surynicz, A. Simor and M.R. Mulvey, 2008. A preliminary guideline for the assignment of Methicillin-resistant *Staphylococcus aureus* to a Canadian pulsed-field gel electrophoresis epidemic type using spa typing. Can. J. Infect. Dis. Med. Microbiol., 19(4): 273-281.
- Gortel, K., K.L. Campbell, I. Kakoma, T. Whittam, D.J. Schaeffer and R.M. Weisiger, 1999. Methicillin resistance among staphylococci isolated from dogs. Am. J. Vet. Res., 60(12): 1526-1530.
- Gosden, P.E., B.C. Reeves, J.R. Osborne, A. Turner and M. Millar, 1997. Retrospective study of outcome of patients treated for *Staphylococcus aureus* bacteraemia. Clin. Microbiol. Infect., 3: 32-40.
- Graveland, H., E. Van Duijkeren, A. Van Nes, A. Schoormans, M. Broekhuizen-Stins, I. Oosting-Van Schothorst, D. Heederik and J.A. Wagenaar, 2009. Evaluation of isolation procedures and chromogenic agar media for the detection of MRSA in nasal swabs from pigs and veal calves. Vet. Microbiol., 139(1-2): 121-125.

- Graveland, H., J.A. Wagenaar, H. Heesterbeek, D. Mevius, E. Van Duinkerken, D. Heederik, 2010. Methicillin resistant *Staphylococcus aureus* ST398 in veal calf farming: Human MRSA carriage related with animal antimicrobial usage and farm hygiene. PLoS One, 5(6): 109-190.
- Guardabassi, L., S. Schwarz and D.H. Lloyd, 2004. Pet animals as reservoirs of antimicrobial-resistant bacteria. J. Antimicrob. Chemoth., 54: 321-332.
- Hanselman, B.A., S. Kruth and J.S. Weese, 2008. Methicillin-resistant Staphylococcal colonization in dogs entering a Veterinary teaching hospital. Vet. Microbiol., 126: 277-281.
- Hanselman, B.A., S.A. Kruth, J. Rousseau and J.S. Weese, 2009. Coagulase positive Staphylococcal colonization of humans and their household pets. Can. Vet. J., 50: 954-958.
- Harper, A.L., D.D. Ferguson, K.R. Leedom Larson, B.M. Hanson, M.J. Male, K.J. Donham and T.C. Smith, 2010. An overview of livestock-associated MRSA in agriculture. J. Agromedicine., 15(2): 101-114.
- Jarraud, S. and M.A. Peyrat, 2001. Ege, a highly prevalent operon of enterotoxin gene, forms a putative nursery of super antigens in *Staphylococcus aureus*. J. Immunol., 166(1): 669-677.
- Kadlec, K., R. Ehricht, S. Monecke, U. Steinacker, H. Kaspar, J. Mankertz and S. Schwarz, 2009. Diversity of antimicrobial resistance phenol and genotypes of Methicillin-resistant *Staphylococcus aureus* ST398 from diseased swine. J. Antimicrob. Chemoth., 64(6): 1156-1164.
- Kaszanyitzky, E.J., S. Janosi, Z. Egyed, O. Agost and O. Semjen, 2003. Antibiotic resistance of Staphylococci from humans, food and different animal species according to data of the Hungarian resistance monitoring system in 2001. Acts Vet. Hungaria., 5: 451-464.
- Katayama, Y., T. Ito and K. Hiramata, 2000. A new class of genetic element, *Staphylococcus* cassette chromosome mec, encodes Methicillin resistance in *Staphylococcus aureus*. Antimicrob. Agents Ch., 44(6): 1549-1555.
- Khanna, T., R. Friendship, C. Dewey and J.S. Weese, 2008. Methicillin resistant *Staphylococcus aureus* colonization in pigs and pig farmers. Vet. Microbiol., 128(3-4): 298-303.
- Kluytmans, J.A., 2010. Methicillin-resistant *Staphylococcus aureus* in food products: Cause for concern or case for complacency. Clin. Microbiol. Infec., 16(1): 11-15.
- Kottler, S., J.R. Middleton, J. Perry, J.S. Weese and L.A. Cohn, 2010. Prevalence of *Staphylococcus aureus* and Methicillin resistant *Staphylococcus aureus* carriage in three populations. J. Vet. Inter. Med., 24(1): 132-139.
- Krogh, H.V. and S. Kristensen, 1976. A study of skin diseases in dogs and cats. II. Microflora of the normal skin of dogs and cats. Nordisk Vet. Med., 28: 459-463.
- Lee, J.H., 2003. Methicillin (Oxacillin)-resistant *Staphylococcus aureus* strains isolated from major food animals and their potential transmission to humans. Appl. Environ. Microb., 69(11): 6489-6494.
- Lee, J.H., J.M. Jeong, Y.H. Park, S.S. Choi, Y.H. Kim, J.S. Chae, J.S. Moon, H. Park, S. Kim and S.K. Eo, 2004. Evaluation of the Methicillin-resistant *Staphylococcus aureus* (MRSA) Screen latex agglutination test for detection of MRSA of animal origin. J. Clin. Microbiol., 42(6): 2780-2782.
- Leonard, F.C. and B.K. Markey, 2008. Methicillin-resistant *Staphylococcus aureus* in animals: A review. Vet Rec., 175(1): 27-36.
- Leonard, F.C., Y. Abbott, A. Rossney, P.J. Quinn, R. O'Mahony and B.K. Markey, 2006. Methicillin resistant *Staphylococcus aureus* isolated from a Veterinary surgeon and five dogs in one practice. Vet Rec., 158(5): 555-559.
- Lilenbaum, W., E.L.C. Nunes and M.A.I. Azeredo, 1998. Prevalence and antimicrobial susceptibility of staphylococci isolated from the skin surface of clinically normal cats. Lett. Appl. Microbiol., 27: 224-228.
- Lipsky, B.A. and U. Stoutenburgh, 2005. Daptomycin for treating infected diabetic foot ulcers: Evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillin's for complicated skin and skin-structure infections. J. Antimicrob. Chemoth., 55: 240-245.
- Loeffler, A., A.K. Boag, J. Sung, J.A. Lindsay, L. Guardabassi, A. Dalsgaard, H. Smith, K.B. Stevens and D.H. Lloyd, 2005. Prevalence of Methicillin-resistant *Staphylococcus aureus* among staff and pets in a small animal referral hospital in the UK. J. Antimicrob. Chemoth., 56: 692-697.
- Loeffler, A., A.M. Kearns, M.J. Ellington, L.J. Smith, V.E. Unt, J.A. Lindsay, D.U. Pfeiffer and D.H. Lloyd, 2009. First isolation of MRSA ST398 from UK animals: A new challenge for infection control teams. J. Hosp. Infect., 72: 269-271.
- Loeffler, A. and D.H. Lloyd, 2010. Companion animals: A reservoir for Methicillin-resistant *Staphylococcus aureus* in the community. Epidemiol. Infect., 138: 595-605.
- Loeffler, A., D.U. Pfeiffer, J.A. Lindsay, R. Soares-Magalhaes and D.H. Lloyd, 2010. Lack of transmission of Methicillin-Resistant *Staphylococcus aureus* (MRSA) between apparently healthy dogs in rescue kennel. Vet. Microbiol., 147: 178-181.

- Loeffler, A., D.U. Pfeiffer, J.A. Lindsay, R.J. Magalhaes and D.H. Lloyd, 2011. Prevalence of and risk factors for MRSA carriage in companion animals: A survey of dogs, cats and horses. *Epidemiol. Infect.*, 139: 1019-1028.
- Lowy, F.D., 1998. *Staphylococcus aureus* infections. *New Engl. J. Med.*, 339(8): 520-532.
- Manian, F.A., 2003. Asymptomatic nasal carriage of mupirocin resistant, Methicillin-Resistant *Staphylococcus aureus* (MRSA) in a pet dog associated with MRSA infection in household contacts. *Clin. Infect. Dis.*, 36(2): 26-28.
- Marshall, M.J. and G.A. Bohach, 2000. Characterization of *Staphylococcus aureus* beta-toxin induced leukotoxicity. *J. Nat. Toxins.*, 9 (20): 125-138.
- McCormick, J.K. and J.M. Yarwood, 2001. Toxic shock syndrome and bacterial superantigens: An update. *Annu. Rev. Microbiol.*, 55: 77-104.
- McDougal, L.K., C.D. Steward, G.E. Killgore, J.M. Chaitram, S.K. McAllister and F.C. Tenover, 2003. Pulsed-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: Establishing anationaldatabase. *J. Clin. Microbiol.*, 41: 5113-5120.
- McLean, C.L. and M.G. Ness, 2008. Meticillin-resistant *Staphylococcus aureus* in a Veterinary orthopaedic referral hospital: Staff nasal colonisation and incidence of clinical cases. *J. Small Anim. Pract.*, 49(4): 170-177.
- Medleau, L. and J.L. Blue, 1988. Frequency and antimicrobial susceptibility of *Staphylococcus* spp isolated from feline skin lesions. *J. Am. Vet. Med. Assoc.*, 193: 1080-1081.
- Morgan, M., 2008. Methicillin-resistant *Staphylococcus aureus* and animals: Zoonosis or humanosis. *J. Antimicrob. Chemoth.*, 62: 1181-1187.
- Murray, P.P., E.J. Baron, J.H. Jorgensen, M.A. Pfaller and R.H. Tenover, 2003. *Manual of Clinical Microbiology*. 8th Edn., American Society for Microbiology. Washington, DC, pp: 20-25.
- Nagase, N., A. Sasaki, K. Yamashita, A. Shimizu, S. Wakita Kitai and J. Kawano, 2002. Isolation and species distribution of *Staphylococci* from animal and human skin. *J. Vet. Med. Sci.*, 64: 245-250.
- Nicolle, L.E., B. Dyck, O. Thompson, S. Roman, A. Kabani, P. Plourde, M. Fast and J. Embil, 1999. Regional dissemination and control of epidemic Methicillin resistant *Staphylococcus aureus*. *Infect. Cont. Hosp. Ep.*, 20: 202-205.
- O'Mahony, R., Y. Abbott, F.C. Leonard, B.K. Markey, P.J. Quinn, P.J. Pollock, S. Fanning and A.S. Rossney, 2005. Methicillin-Resistant *Staphylococcus aureus* (MRSA) isolated from animals and veterinary personnel in Ireland. *Vet Microbiol.*, 109(3-4): 285-296.
- O'Rourke, K., 2003. Methicillin-resistant *Staphylococcus aureus*: An emerging problem in horses. *J. Am. Vet. Med. Assoc.*, 223: 1399-1400.
- Otter, J.A. and G.L. French, 2010. Molecular epidemiology of community-associated Methicillin-resistant *Staphylococcus aureus* in Europe. *Lancet Infect. Dis.*, 10(4): 227-239.
- Oughton, M., H. Dick and B.M. Willey, 2001. Methicillin-Resistant *Staphylococcus aureus* (MRSA) as a cause of infections in domestic animals: Evidence for a new humaniotic disease. *Can. Bact. Surveill. Netw. Newsl.*, Vol. April 2001, pp: 1-2.
- Owen, M.R., A.P. Moores and R.J. Coe, 2004. Management of MRSA septic arthritis in a dog using a gentamicin-impregnated collagen sponge. *J. Small Anim. Pract.*, 45(12): 609-612.
- Pak, S.I., H.R. Han and A. Shimizu, 1999. Characterization of Methicillin resistant *Staphylococcus aureus* isolated from dogs in Korea. *J. Vet. Med. Sci.*, 61: 1013-1018.
- Pantosti, A., 2012. Methicillin-resistant *staphylococcus aureus* Associated with animal and its relevance to human. *J. Microbiol.*, 3: 137-139.
- Pantosti, A., A. Sanchini and M. Monaco, 2007. Mechanisms of antibiotic resistance in *Staphylococcus aureus*. *Future Microbiol.*, 2: 323-334.
- Patel, A., O.H. Lloyd and A.I. Lamport, 1999. Antimicrobial resistance of feline *Staphylococci* in southeastern England. *Vet. Dermatol.*, 10: 257-261.
- Patel, A., O.H. Lloyd, S.A. Howell and W.C. Noble, 2002. Investigation into the potential pathogenicity of *Staphylococcus felis* in a cat. *Vet. Rec.*, 150: 668-669.
- Paule, S.M., D.M. Hacek, B. Kufner, K. Truchon, R.B.J. Thomson, K.L. Kaul, A. Robicsek and L.R. Peterson, 2007. Performance of the BD gene on Methicillin-resistant *Staphylococcus aureus* test before and during high-volume clinical use. *J. Clin. Microbiol.*, 45(9): 2993-2998.
- Pomba, C., L.R. Baptista, F.M. Couto, N.F. Loução and H. Hasman, 2010. Methicillin-resistant *Staphylococcus aureus* CC398 isolates with indistinguishable *Apal* restriction patterns in colonized and infected pigs and humans. *J. Antimicrob. Chemoth.*, 65(11): 2479-2481.
- Postier, R.D., S.L. Green, S.R. Klein, E.J. Ellis-Grosse, E. Loh, 2004. Tigecycline 200 study group. Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients. *Clin. Ther.*, 26: 704-714.
- Rich, M. and L. Roberts, 2004. Methicillin-resistant *Staphylococcus aureus* isolates from companion animals. *Vet. Rec.*, 154: 310-312.

- Scott, G.M., R. Thomson, J. Malone-Lee and G.L. Ridgway, 1988. Cross-infection between animals and man: Possible feline transmission of *Staphylococcus aureus* infection in humans? J. Hosp. Infect., 12: 29-34.
- Seguin, J.C., R.D. Walker, J.P. Caron, W.E. Kloos, C.G. George, R.J. Hollis, R.N. Jones and M.A. Pfaller, 1999. Methicillin-resistant *Staphylococcus aureus* outbreak in a Veterinary teaching hospital: Potential human-to-animal transmission. J. Clin. Microbiol., 37(5): 1459-1463.
- Sergio, D.M., T.H. Koh, L.Y. Hsu, B.E. Ogden, A.L. Goh and P.K. Chow, 2007. Investigation of Methicillin-resistant *Staphylococcus aureus* in pigs used for research. J. Med. Microbiol., 56(8): 1107-1109.
- Shiomori, T., H. Miyamoto and K. Makishima, 2001. Significance of airborne transmission of Methicillin-resistant *Staphylococcus aureus* in an otolaryngology head and neck surgery unit. Arch Otolaryngol. Head Neck Surg., 127(6): 644-648.
- Spohr, M., J. Rau, A. Friedrich, G. Klittich, A. Fetsch, B. Guerra, J.A. Hammerl and B.A. Tenhagen, 2010. Methicillin Resistant *Staphylococcus aureus* (MRSA) in three dairy herds in Southwest Germany. Zoonoses Public Hlth., 58(4): 252-261.
- Tenhagen, B.A., A. Fetsch, B. Stührenberg, G. Schleuter, B. Guerra, J.A. Hammer, S. Hertwig, J. Kowall, U. Kämpe, A. Schroeter, J. Bräunig, A. Käsbohrer and B. Appel, 2009. Prevalence of MRSA types in slaughter pigs in different German abattoirs. Vet. Rec., 165(20): 589-593.
- Tomlin, J., M.J. Peard and D.H. Lloyd, 1999. Methicillin resistant *Staphylococcus aureus* infections in 11 dogs. Vet. Rec., 144: 60-64.
- Turnidge, J.D. and J.M. Bell, 1998. The Sentry Western Pacific plus Participants: Multi-Resistant Oxacillin-Resistant *S. aureus* (MORSA) as Major Nosocomial Pathogens in Asia. Result from the SENTRY Program, Australia and South Africa.
- Van den Broek, I.V., B.A. Van Cleef, A. Haenen, E.M. Broens, P.J. Van der Wolf, M.J. Van den Broek, X.W. Huijsdens, J.A. Kluytmans, A.W. Van De Giessen and E.W. Tiemersma, 2009. Resistant *Staphylococcus aureus* in people living and working in pig farms. Epidemiol. Infect., 137(5): 700-708.
- Van den Eede, A., A. Martens, U. Lipinska, M. Struelens, A. Deplano, O. Denis, F. Haesebrouck, F. Gasthuys and K. Hermans, 2009. High occurrence of Methicillin-resistant *Staphylococcus aureus* ST398 in equine nasal samples. Vet. Microbiol., 133(1-2): 138-144.
- Van Duijkeren, E., A.T. Box and J. Mulder, 2003. Methicillin Resistant *Staphylococcus aureus* (MRSA) infection in a dog in the Netherlands. Tijdschr. Diergeneesk., 128: 314-315.
- Van Duijkeren, E., M.J. Wolfhagen, A.T. Box, M.E. Heck, W.J. Wannet and A.C. Fluit, 2004. Human-to-dog transmission of methicillin-resistant *Staphylococcus aureus*. Emerg. Infect. Dis., 10(12): 2235-2257.
- Van Duijkeren, E., M.J. Wolfhagen, M.E. Heck and W.J. Wannet, 2005. Transmission of a Pantone-Valentine leukocidin-positive, methicillin-resistant *Staphylococcus aureus* strain between humans and a dog. J. Clin. Microbiol., 43: 6209-6211.
- Van Rijen, M.M., P.H. Van Keulen and J.A. Kluytmans, 2008. Increase in a Dutch hospital of methicillin-resistant *Staphylococcus aureus* related to animal farming. Clin. Infect. Dis., 46(2): 261-263.
- Velevit, B., A. Fetsch, M. Mirilovic, V. Teodorovic and M. Jovanovic, 2010. MRSA in pigs in Serbia. Vet. Rec., 167(5): 183-184.
- Von Eiff, C. and A.W. Friedrich, 2004. Prevalence of genes encoding for members of the staphylococcal leukotoxin family among clinical isolates of *Staphylococcus aureus*. Diagn. Microbiol. Infect. Dis., 49(3): 157-162.
- Warren, D.K., R.S. Liao, L.R. Merz, M. Eveland and W.M.J. Dunne, 2004. Detection of Methicillin-resistant *Staphylococcus aureus* directly from nasal swab specimens by a real-time PCR assay. J. Clin. Microbiol., 42(12): 5578-5581.
- Weese, J.S., 2010. Methicillin-resistant *Staphylococcus aureus* in animals. ILAR J., 51: 233-244.
- Weese, J.S. and J. Rousseau, 2005. Attempted eradication of Methicillin-resistant *Staphylococcus aureus* colonization in horses on two farms. Equine Vet. J., 37(6): 510-514.
- Weese, J.S., H. Dick, B.M. Willey, A. McGeer, B.N. Kreiswirth, B. Innis and D.E. Low, 2006a. Suspected transmission of Methicillin-resistant *Staphylococcus aureus* between domestic pets and humans in veterinary clinics and in the household. Vet. Microbiol., 115(1-3): 148-155.
- Weese, J. S., F. Caldwell, B.M. Willey, B.N. Kreiswirth, A. McGeer, J. Rousseau and D.E. Low, 2006b. An outbreak of Methicillin-resistant *Staphylococcus aureus* skin infections resulting from horse to human transmission in a veterinary hospital. Vet. Microbiol., 114: 160-164.
- Yamaguchi, T. and K. Nishifuji, 2002. Identification of the *Staphylococcus aureus* and pathogenicity island which encodes a novel exfoliative toxin, ETD and EDIN-B. Infect. Immun., 70(10): 5835-5845.