

FECAVA LECTURE

Dealing with MRSA in Companion Animal Practice

D. H. Lloyd⁽¹⁾, A. K. Boag⁽¹⁾, A. Loeffler⁽¹⁾

SUMMARY

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a worldwide problem in human medicine that is now increasingly recognised as a cause of disease in small animal practice. Molecular studies indicate that the majority of isolates from dogs and cats are human hospital strains and point towards links with human healthcare institutions.

Treatment of MRSA infections relies on the same principles as the treatment of methicillin-susceptible *S. aureus* (MSSA) and fortunately most UK MRSA isolates infecting pets are sensitive to co-trimoxazole and tetracyclines, and to topical antimicrobials, including fusidic acid. MRSA can be carried by and exchanged between owners, veterinary surgeons and in-contact pets, and is able to survive for long periods in the environment. This poses risks to susceptible individuals. Decolonisation of both humans and animals can be attempted to reduce such risks but the key to control of this organism lies in prevention of transmission. There is a need for rigorous hygiene procedures to be instituted in veterinary practice to achieve this objective.

Key words: dog, cat, antimicrobial, resistance, MRSA

The origin and significance of MRSA

Staphylococcus aureus is a major cause of infection in both animals and man. The advent of large scale production of the penicillins in the 1940s, enabled *S. aureus* infections to be readily treated and greatly decreased both morbidity and mortality caused by staphylococci. However, resistance developed rapidly. At the end of the decade penicillin-resistant strains predominated in many hospitals. By 1950, 40% of all hospital *S. aureus* isolates were penicillin resistant; and by 1960, this had risen to 80% [1].

Staphylococcal resistance to penicillins is primarily mediated by the production of β -lactamase enzymes and the β -lactamase-resistant antibiotics were developed to counter such resistance. Methicillin (meticcillin), one of the earliest of these, was introduced in 1956 but by 1961 strains of *S. aureus* resistant to this antibiotic (methicillin-resistant *S. aureus*, MRSA) were already being recognised in continental Europe and in the UK. MRSA spread rapidly. By the 1980s it was recognised as a

worldwide problem in healthcare facilities and in 1983 dominant epidemic clones (EMRSA) capable of affecting large numbers of individuals within such institutions were described [2]. In the UK two clones, EMRSA-15 and EMRSA-16 are now responsible for more than 95% of hospital infections [3].

Resistance to methicillin and other β -lactam antibiotics in MRSA is conferred by the *mecA* gene, which is part of a 21- to 60-kb mobile genetic element, the staphylococcal chromosome cassette, *mec* (SCC*mec*). Expression of *mecA* yields PBP 2A which has a low affinity for β -lactam rings, the primary active-site of β -lactam antibiotics [4-6]. MRSA associated with hospital infections commonly possess resistance to a wide variety of antimicrobials, extending beyond the β -lactams (cephalosporins and penicillins) and, in the more resistant isolates, including all antibiotics in normal clinical use [7].

A worrying development in the MRSA story has been the

(1)Department of Veterinary Clinical Sciences, Royal Veterinary College, University of London, Hawkshead Lane, North Mymms, Hertfordshire GB-AL9 7TA. Corresponding author: David H. Lloyd E-mail: david-lloyd@ntlworld.com

emergence of community-associated strains (CA-MRSA) causing infection amongst young, healthy patients without significant contact with health care institutions. CA-MRSA do not display the multi-resistance of the healthcare-associated strains and generally induce skin and soft tissue infections. However, they can carry potent virulence factors leading to rapid, severe and lethal infections [8]. This is an important difference from the hospital-associated MRSA strains which do not show virulence greater than the methicillin-sensitive *S. aureus* (MSSA) [9].

Risk factors for MRSA acquisition in people

S. aureus, irrespective of its antimicrobial resistance pattern, is thought to colonise the human nose in 30-70% of the population [10]. Such commensal isolates are often involved in human staphylococcal infections but cross-contamination from other humans, animals or from the environment can also occur. Factors predisposing people to MRSA acquisition, as compared to methicillin-susceptible *S. aureus*, are well documented in human medicine and include contact with carriers, age, antimicrobial therapy, immunosuppression, chronic disease and visits to healthcare facilities or nursing homes. In addition to personal carriage of MRSA, risk factors for MRSA infection are, for example, antimicrobial treatment (cephalosporins and fluoroquinolones in particular), surgery and other invasive procedures, staying at hospitals in countries with a high MRSA prevalence and hospitalisation in intensive care units [11].

The correlation between the use of antimicrobials and selection for drug resistant *S. aureus* is well documented [12, 13], and healthcare-associated risk factors have also been explored in detail in many countries. However, the extent of the risk for MRSA acquisition in the healthy human community remains controversial, partly because little information exists on MRSA carriage rates amongst healthy people. Two small studies from the UK and an extrapolation study from the US suggest that less than 2% of healthy people are MRSA carriers [14, 15]. However, higher rates of up to 10% are reported in medical staff and, more recently, 10 to 20% carriage rates were found in veterinary staff in Canada, the UK and Ireland [16-21].

MRSA in dogs and cats

MRSA was first described in nasal isolates from two dogs by Ojo (1972) in Nigeria [22]. However it was not recognised in companion animals in Europe until 1988, when carriage by a ward cat was associated with recurrent MRSA infections amongst patients in contact with it [23]. Subsequently, in 1994, recurrent infection amongst two healthcare workers was linked to carriage of MRSA by their pet dog [24]. These reports provided the first links between animal carriage and human infection.

Clinical infections with MRSA in dogs and cats have tended to be associated with wounds and surgical procedures, as in man, but cannot be differentiated clinically from infections caused by *Missa* and *S. intermedium*. MRSA infection was first reported in dogs in 1999 by Tomlin *et al.* who made a retrospective analysis of 11 cases in North America and in the UK [25]. Infection

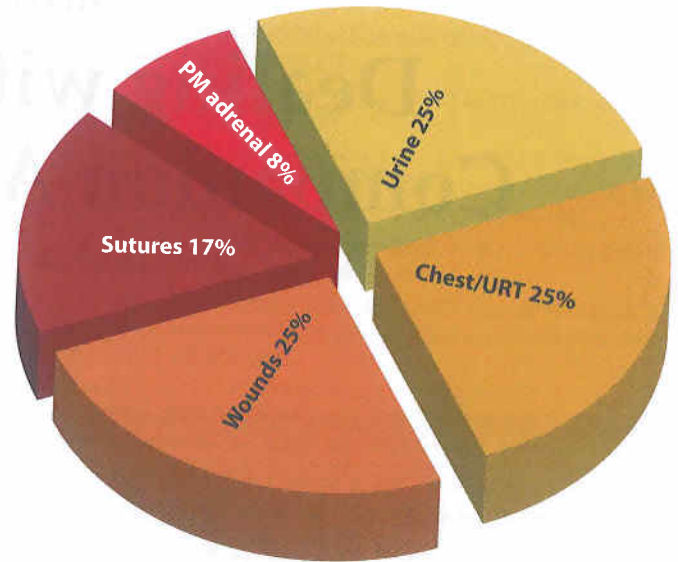


Fig 1: Pie chart showing the clinical presentations of 12 cases of MRSA infection seen in five cats and seven dogs at a small animal referral hospital in the UK between November 2003 and March 2004 (data of Boag, Loeffler and Lloyd 2004)[28]

was associated with surgical treatment, especially orthopaedic surgery, but infection following trauma and in cases of recurrent pyoderma was also seen. In the British Isles, two reports in 2004, provided warning that MRSA infection was becoming a problem in small animal practice. Rich and Roberts (2004) reported isolation of 95 MRSA from specimens submitted to a veterinary diagnostic laboratory during 2003 [26]. In March 2004, Boag *et al.* (2004) reported an increase in cases of MRSA infection seen at a small animal referral hospital [27]; 12 cases had been confirmed in dogs and cats over the previous 5-months. Five (42%) of these cases involved wounds or suture infections (Fig 1). Nasal swabs taken in five of these cases revealed concurrent MRSA colonisation of the nasopharynx.

A review of MRSA infection in dogs and cats in 2004 described it as an emerging problem [28] and since 2000 there have been increasing numbers of reports of MRSA in domestic animals, including more than 30 published articles from the US, Canada, Netherlands, Germany, Switzerland, the UK, Korea and Japan. Most of these have dealt with infection and or carriage by dogs and cats, although there is now a substantial number of reports of infection in horses and other veterinary species including a rabbit and a seal [21], and birds [29].

Little is known of the actual rates of carriage of MRSA by dogs and cats. Feline carriage was reported from Brazil in 1998, where MRSA was isolated from the skin of 3 (2%) of 148 normal cats but not from the saliva of 150 normal cats [30, 31]. In 2005, Loeffler *et al.* reported oral or nasal carriage in 9% of 45 dogs admitted to a small animal referral hospital [20]. However, a recent study failed to isolate MRSA amongst 200 dogs in Slovenia [32]. More detailed studies are now required to define the MRSA carriage status and the factors which influence such carriage amongst healthy pets.

How do animals acquire MRSA?

While *S. intermedius* remains the predominant organism in staphylococcal infections and at carrier sites in dogs and cats, the perceived increase in MRSA infections in companion animals and the zoonotic implications of staphylococcal disease have prompted extensive investigation into the origin of MRSA isolated from animals.

It is well documented that staphylococci, including *S. intermedius* and *S. aureus* (both resistant and susceptible to methicillin) can be transferred between humans and animals in both directions [33-36]. Furthermore, typing studies from several countries have shown that MRSA isolates from dogs and cats are identical with or closely related to the human epidemic hospital-acquired MRSA important in those countries [19-21, 25, 37-40]. This strongly suggests that the principal source for MRSA infection in pets is contact with humans infected with or carrying MRSA.

On the other hand, a few reports have also identified MRSA isolates from infected and healthy animals that are genetically distinct from human epidemic clones [41, 42]. This raises concern about animal-specific MRSA isolates developing, which may be particularly well adapted to animals and constitute another reservoir for human infection. As the *mecA* gene, which can confer broad resistance to methicillin, has also been identified in other staphylococcal species commonly found in animals, gene transfer between staphylococci on animals may also occur [43-46].

As MRSA can survive on dry surfaces for many months, [47] indirect transfer and acquisition of this organism from the pet's environment is also possible. Only a few studies have so far investigated the presence of MRSA in the veterinary environment revealing survival on up to 10% of sampled surfaces [20, 37, 48].

While the sources of animal infection have been studied extensively, the circumstances which facilitate transmission from humans to pets have not been investigated. It may be hypothesised that risk factors for MRSA infection in animals are similar to those known in humans such as contact with human or animal MRSA carriers, self MRSA-carriage, previous antimicrobial and immunosuppressive therapy, chronic disease and invasive veterinary procedures (such as surgery and implants).

Table 1. When to suspect MRSA infection in a pet.

When to suspect MRSA infection?
Post-operative and traumatic wound infections (non-healing wounds)
Implant infections (e.g. catheters, orthopaedic implants)
Unresponsive skin and soft tissue infections
Previous history of MRSA infection
Known owner infection or carriage
Cluster of MRSA infections recently diagnosed in the clinic

There are already indications that self carriage and contact with human MRSA carriers favour MRSA infection in pets. A recent study has demonstrated that staphylococcal carriage isolates and infection isolates are related in a high percentage of cases [49] and that horses colonised with MRSA on admission to hospital are 39 times more likely to develop MRSA infection than controls [50]. In addition, preliminary results from a case-control study investigating risk factors in animals showed that contact with a human MRSA carrier increases the risk that an animal will acquire MRSA rather than MSSA by at least 6-fold (Loeffler, data presented at the 1st International Conference on MRSA in Animals, Liverpool, 20th June 2006). These findings, together with the high MRSA carriage rates amongst pet owners and veterinary staff, indicate that cross-contamination with staphylococci between humans and animals plays an important role not only during the close contact between pets and their owners but also in the veterinary setting.

When to suspect MRSA infection?

MRSA infections cannot be recognised from their clinical presentations alone. They resemble those of infections with methicillin-susceptible *S. aureus* and *S. intermedius* and helpful MRSA specific features have not been identified for dogs and cats (Loeffler, data presented at the 1st International Conference on MRSA in Animals, Liverpool, 20th June 2006, [51]). In general though, MRSA should be suspected 1) in post-operative and traumatic wound infections, 2) in skin and soft-tissue infections unresponsive to antimicrobial therapy and 3) in cases with a previous history of MRSA infection or where a zoonotic risk of MRSA infection has been identified. See Table 1.

Thus, diagnosis of MRSA infection is based on clinical signs consistent with bacterial infection, ideally supported by cytological evidence of cocci and inflammatory cells from material collected from the site of infection, together with isolation of MRSA by microbiological tests on submitted clinical material.

Sampling and laboratory submission

Sample collection for bacterial isolation will be aimed at collecting material most likely to yield the relevant pathogen. The sampling methods will depend on the site of infection but will not differ from those performed to investigate other bacterial infections. For example, a swab submitted in bacterial transport medium can be taken from a pustule or an ulcerated skin lesion while biopsy specimens in plain sample pots with a few drops of sterile saline or blood collected in blood culture vials may be required for deep tissue infections or in cases of suspected bacteraemia, respectively. Antimicrobial therapy should be discontinued prior to sampling to improve recovery of bacterial organisms. In such cases, cytological examination of material from infection sites may indicate whether bacteria are likely to be grown from samples. In addition, the clinician must assess whether discontinuation of therapy would be appropriate for the individual patient in the face of possible bacterial co-infections.

Occasionally, sampling for MRSA carriage at mucosal sites is indicated, for example to assess the risk for re-infection with this organism in animals susceptible to recurrent infections. Examples would be those suffering from allergic skin disease or those receiving immunosuppressive therapy, where surgical implants need to be kept in place or when owners raise concern about zoonotic transfer [35, 36]. Mucosal sites such as the distal part of the nares, the buccal mucosae and the perineum have been shown to yield staphylococci readily in carrier animals, and moistening the swab with sterile saline prior to sampling may aid recovery of bacteria [20, 52].

Sampling of environmental sites may sometimes be performed for example to monitor implementation of infection control measures or to identify problem areas in the clinic. To improve the bacterial yield, swabs can again be moistened with sterile saline prior to sampling [20].

Swabs, tissue or fluids are typically submitted to diagnostic veterinary laboratories together with the signalment of the animal, a brief summary of the suspected bacterial infection, sampling site and a request for bacterial culture and antimicrobial susceptibility testing. In an animal with known or suspected MRSA infection or when specifically investigating MRSA carriage or environmental contamination with MRSA, this should be indicated on the submission form. It will enable the laboratory to choose enrichment methods to increase the yield of staphylococci and it may accelerate the bacteriological diagnosis as MRSA-selective media can be used at an early stage.

Laboratory identification of MRSA

Staphylococci are initially identified by colony morphology as white or yellow, round, shiny and smooth colonies on blood agar. Additional criteria such as haemolysis, the ability to clot plasma (coagulase tests) and a number of other biochemical tests help to categorise them broadly into coagulase-negative staphylococci and the more commonly pathogenic coagulase-positive staphylococci, and to distinguish staphylococcal species. However, as morphological and biochemical characteristics vary even within a species, no single test exists to differentiate for example, *S. intermedius* and *S. aureus*, and a combination of several test results is required for reliable identification. While various molecular techniques are available to distinguish staphylococcal species based on species-specific sequences in highly preserved genomic regions [53-56], speciation in busy diagnostic laboratories with a high throughput of clinical samples is often based on results from automated bacterial speciation systems (e.g. Vitek or Microscan Walkway). These can perform a battery of biochemical tests in a short time [57]. Owing to such difficulties in bacterial speciation, MRSA may occasionally be misidentified as multi-resistant *S. intermedius* or the latter may mimic MRSA [58]. For example, an isolate reported as *S. intermedius* resistant to cefalexin is more likely to be *S. aureus* and perhaps an MRSA as resistance to cephalosporins has been extremely rare in *S. intermedius* so far [59-62]. In such cases, a critical evaluation of the report by the clinician together with the patient's history should prompt liaison with the laboratory to discuss unusual or unexpected results.

In vitro susceptibility testing for antimicrobials for clinical purposes is based either on disc diffusion tests with fixed cut off values designed to predict resistance *in vivo* or by estimation of minimum inhibitory concentrations of the antimicrobials by manual or automated methods. Phenotypic methicillin resistance can either be determined by disc diffusion tests using methicillin or its representatives oxacillin and ceftiofur [63]. Alternatively, the use of selective agar plates containing oxacillin and a colour-indicator can shorten the time to identification of MRSA but at additional expense. In a small proportion of *S. aureus* isolates with phenotypic resistance to methicillin and other β -lactam antibiotics, resistance has been due to an excessive production of penicillinase, rather than an altered penicillin-binding protein as in the epidemic MRSA isolates.

In addition to species identification, the definition of *S. aureus* isolates with phenotypic methicillin resistance as MRSA requires demonstration of the *mecA* gene, most commonly by PCR based methods. If expressed, this gene confers resistance to all penicillins and cephalosporins [64].

S. aureus has been shown to be highly clonal and typing of isolates of interest can provide valuable epidemiological data, such as for example identification of related isolates within an outbreak [65, 66]. Typing of clinical isolates, however, is unlikely to be of benefit for the management of the individual case.

Treatment of infection

The clinical manifestations of MRSA infection in animals are very variable; hence there is no treatment protocol which will be suitable for all patients. In human medicine, MRSA infections range from relatively benign superficial skin or wound infections through to life threatening bacteraemia with the development of septic shock [67]. Although the majority of reports in the veterinary literature describe patients with skin or post-operative infections [21, 25, 68], more serious systemic infections can occur. As with all infections, the treatment must be tailored to the individual patient.

When deciding on a treatment plan, consideration should be given to:

- the antibiotic sensitivity profile of the MRSA isolated from that patient
- the severity of the infection and, particularly, whether the patient exhibits any systemic signs (fever, leucocytosis)
- the patient's underlying disease or any co-morbid conditions.

In some cases of superficial wound infection in systemically well animals, diligent local wound management according to basic principles will result in resolution of infection without the need for systemic antibiotics. If the infection is associated with an implant (e.g. external skeletal fixator pin), removal of the implant, at the earliest possible opportunity, will also aid resolution.

However, in many patients antibiotic therapy is required. This includes patients with systemic evidence of infection and patients

where MRSA infection has occurred secondary to a predisposing condition (e.g. chronic urinary retention, chronic atopy). The antibiotic used should be chosen based on culture and sensitivity results; knowledge of the sensitivity pattern of the strain(s) of MRSA that are prevalent in the geographical area can help with empirical antibiotic choice whilst awaiting microbiological results. Although MRSA generally shows resistance to commonly used agents, most are sensitive to some classes of antimicrobial. In the UK, most infections in companion animals have been with MRSA sensitive to tetracycline and co-trimoxazole, with some showing sensitivity to the fluoroquinolones. Sensitivity to the topical antimicrobials, fusidic acid and mupirocin, is also commonly demonstrated. Recent guidelines for treatment of MRSA in the human population in the UK suggest that tetracyclines should be considered for the treatment of human patients with skin, soft tissue and urinary tract infections where there is a low risk of bacteraemia [69]. Similar guidelines do not exist for veterinary species but both tetracyclines and sulphonamides are licensed for use in veterinary species and are often a first line choice. Exposure to fluoroquinolones has been identified as a risk factor for infection with multi drug resistant bacteria of several species and they should be used with caution.

Rarely patients may develop MRSA sepsis. These critically ill patients require intensive management with monitoring and support of all vital organ systems. Antimicrobial therapy for these patients is challenging as MRSA is generally not sensitive to any of the intravenous bactericidal agents (e.g. aminoglycosides, β -lactam derivatives, cephalosporins) that would usually be chosen. Vancomycin is the current drug of choice in the human field [69] and has been used experimentally in dogs [70]. Clinical experience with vancomycin in small animal patients is however scarce. The expense of the drug and the recognition in human medicine of MRSA isolates with poor sensitivity to vancomycin may limit its application in the field of companion animal medicine.

Other than patients with sepsis, the prognosis for animals with MRSA infection is generally good with appropriate treatment. Dependent on the underlying condition, decolonisation may also be considered as part of the treatment regime.

Decolonisation

Decolonisation involves the use of antimicrobials to remove MRSA from colonisation sites. In man, this generally involves treatment of the nasal mucosa with a topical antimicrobial agent to which the colonising strains are sensitive, such as mupirocin ointment, together with the use of antimicrobial washes and, in some cases, systemic antimicrobials [71] and environmental cleansing. Higher success rates are achieved with patients in a hospital setting when all these methods are combined [72]. Topical treatment of healthy healthcare workers with intranasal mupirocin ointment twice daily for five days was associated with a 91% reduction in the prevalence of *S. aureus* carriage. However, recolonisation occurred in 26% of decolonized healthcare workers within four weeks [73]. The feasibility of routine MRSA decolonisation in humans is still in question [74] but in a major review of interventions for the prevention and control of methicillin-resistant *Staphylococcus aureus*, Loveday

et al. (2006) conclude that there is sufficient evidence to support the continuing use of such procedures although more experimental evidence is required [71].

No published data on decolonisation of MRSA carriers is available for pets but studies on decolonisation of dogs with *S. intermedius* was reported by Saijonmaa-Koulumies, Parsons and Lloyd in 1998 [52]. In this study normal laboratory beagles were treated at the nares, conjunctivae, anus and vulva with topical 1% fusidic acid twice daily for seven days; skin and the environment remained untreated. The frequency and populations of pathogenic staphylococci decreased significantly after therapy and were still reduced after three weeks. However populations returned to their original levels after three weeks. The authors concluded that the effect of mucosal treatment on cutaneous populations of *S. intermedius* indicated the importance of the mucosae as the carriage sites for these organisms. It might be expected that such treatment would have a similar effect on MRSA colonisation of dogs. In addition, as *S. intermedius* adheres to canine keratinocytes more readily than *S. aureus* [75] it is possible that, following decolonisation with *S. aureus*, recolonisation with *S. intermedius* may occur.

Limited clinical experience with decolonisation (Lloyd, personal observations) suggests that treatment of canine mucosal sites with 1% fucidic acid for two weeks coupled with the use of antimicrobial shampoos and systemic antimicrobial therapy is effective in removing MRSA but duration of decolonisation is not known. In principal, treatment of carrier animals should be started as soon as the chance of re-infection has reduced, e.g. once a wound has healed, skin lesions have resolved and implants, e.g. catheters, have been removed. Decolonisation can also be applied to carriers that have not been infected but present a risk to other animals or to humans in contact with them.

Prevention of spread

Although the prevalence of MRSA carriage and infection appear to be increasing in small animal patients, the level of infection is much lower than that seen in the human healthcare system in many European countries. The veterinary profession can learn from experience in the human field with action at this early stage to prevent MRSA becoming endemic within our clinics and patient populations. Each practice should develop a policy for dealing with MRSA positive patients. Rational control measures should be based on the available evidence from the human infection control field coupled with knowledge of MRSA epidemiology as it relates specifically to veterinary patients. Further information and up-to-date guidelines may be found on the BSAVA website at www.bsava.com/resources/mrsa/mrsaguidelines/mrsaguidelines.htm

Debate still exists within the human medical literature as to the most appropriate control measures [72, 76]. Transmission between patients on the hands of health care workers seems to be the major mode of spread but the role of the environment should not be overlooked [77]. In humans, prior colonisation with MRSA is also recognised as a significant risk factor for

