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Review on methicillin-resistant *Staphylococcus pseudintermedius*

Engeline van Duijkeren[1]*, Boudewijn Catry[2], Christina Greko[3], Miguel A. Moreno[4], M. Constança Pomba[5], Satu Pyörälä[6], Modestas Ružauskas[7], Pascal Sanders[8], E. John Threlfall[9], Jordi Torren-Edo[10] and Karolina Törneke[11] [Scientific Advisory Group on Antimicrobials (SAGAM)]

[1]Faculty of Veterinary Medicine, Department of Infectious Diseases and Immunology, Utrecht University, Utrecht, The Netherlands; [2]Scientific Institute of Public Health, Healthcare Associated Infections and Antimicrobial Resistance, Brussels, Belgium; [3]Department of Animal Health and Antimicrobial Strategies, National Veterinary Institute, Uppsala, Sweden; [4]Department of Animal Health, Faculty of Veterinary Medicine, Complutense University, Madrid, Spain; [5]Faculty of Veterinary Medicine, Technical University of Lisbon, Portugal; [6]Faculty of Veterinary Medicine, Department of Production Animal Medicine, University of Helsinki, Helsinki, Finland; [7]Veterinary Institute, Lithuanian University of Health Sciences, Kaunas, Lithuania; [8]Agence Nationale de Sécurité Sanitaire (ANSES), Laboratoire de Fougères, Fougères, France; [9]Health Protection Agency, Centre for Infections, London, UK; [10]European Medicines Agency, Animal and Public Health, London, UK; [11]Läkemedelsverket, Uppsala, Sweden

*Corresponding author. Tel: +31-30-2533603; Fax: +31-30-253199; E-mail: e.vanduijkeren@uu.nl

Staphylococcus pseudintermedius is an important opportunistic pathogen of companion animals, especially dogs. Since 2006 there has been a significant emergence of methicillin-resistant *S. pseudintermedius* (MRSP) mainly due to clonal spread. This article reviews research on MRSP with a focus on occurrence, methods used for identification, risk factors for colonization and infection, zoonotic potential and control options. Potential areas for future research are also discussed.

Keywords: MRSP, resistance, dogs, cats, *S. pseudintermedius*

Evolution of the taxonomy of *Staphylococcus pseudintermedius*

Staphylococcus intermedius was first described in 1976,[1] but during the past few years there has been confusion about its classification. In 2005 a novel staphylococcal species, *S. pseudintermedius*, was described.[2] Isolates formerly identified as *S. intermedius* by phenotypic characteristics were then reclassified based on molecular techniques. Following this, isolates belonging to the *S. intermedius* group were divided into three clusters: *S. intermedius*, *S. pseudintermedius* and *Staphylococcus delphini*.[3] This grouping has clarified that *S. pseudintermedius*, and not *S. intermedius*, is the species of the *S. intermedius* group (SIG) that colonizes and causes infections in dogs and cats.[4] It is difficult to differentiate *S. intermedius* from *S. pseudintermedius* during routine diagnostic procedures, but the vast majority of canine isolates are *S. pseudintermedius*. It has therefore been proposed to report all strains belonging to the SIG from dogs as *S. pseudintermedius*, unless genomic investigations prove that the strain belongs to a related species.[5] It must be noted that, when reviewing the literature, older reports on *S. intermedius* can in fact be reports on *S. pseudintermedius*. In this review we use the term *S. (pseud)intermedius* when the isolates previously identified as *S. intermedius* are probably *S. pseudintermedius*.

S. pseudintermedius: commensal and pathogen

S. (pseud)intermedius is a normal inhabitant of the skin and mucosa and can be isolated from the nares, mouth, pharynx, forehead, groin and anus of healthy dogs and cats.[6–10] The anal region and the nose are colonized more frequently than other areas in healthy dogs, the anal mucosa being colonized most heavily (more colonies/surface area).[11] *S. (pseud)intermedius* is an opportunistic pathogen and a leading cause of skin and ear infections, infections of other body tissues and cavities, and post-operative wound infections in dogs and cats.[12–14]

Virulence factors of *S. pseudintermedius*

The pathogenesis of *S. pseudintermedius* has recently been reviewed.[15] In general, knowledge of the pathogenesis of *S. pseudintermedius* is limited.[15] In *Staphylococcus aureus*, enzymes and toxins are thought to be involved in the conversion of host tissues into nutrients for bacterial growth in addition to having numerous modulatory effects on the host immune response. *S. pseudintermedius* has various virulence factors, including some that are closely related to virulence factors of *S. aureus*.[15,16] These virulence factors are involved in almost all processes from colonization of the host to bacterial nutrition and dissemination. *S. pseudintermedius* produces enzymes

such as coagulase, protease, thermonuclease and toxins, including haemolysins, exfoliative toxins and enterotoxins.[15,17] Exfoliative toxin is a virulence factor involved in canine pyoderma, because the exfoliative toxin gene can mainly be found among *S. (pseud)intermedius* isolated from skin infections.[18,19] Dogs injected with purified exfoliative toxin develop clinical signs such as erythema, exfoliation and crusting, which are signs of canine pyoderma.[20] *S. (pseud)intermedius* also produces a leucotoxin known as Luk-I, which is very similar to Panton–Valentine leucocidin (PVL) from *S. aureus*.[21,22] Luk-I shows strong leucotoxicity towards various polymorphonuclear cells.[21] *S. pseudintermedius* expresses surface proteins that resemble those from *S. aureus*. *S. pseudintermedius* has the capacity to bind to fibrinogen, fibronectin and cytokeratin, which could explain how *S. pseudintermedius* adheres to canine corneocytes.[23] *S. pseudintermedius* produces an immunoglobulin-binding protein called staphylococcal protein A (*spa*), similar to that of *S. aureus*.[24] Like most staphylococci, some *S. (pseud)intermedius* strains have the capacity to form biofilms.[25] Accessory gene regulator (*agr*) homologues were found in *S. (pseud)intermedius*.[26] The *agr* quorum-sensing and signal transduction system was first described in *S. aureus* and plays a key role in the regulation of virulence during infection.[26] Recently the first complete genome sequence of *S. pseudintermedius* was published, and this will hopefully contribute to a better understanding of the pathogenesis of *S. pseudintermedius*.[17]

Emergence of methicillin-resistant *S. pseudintermedius* (MRSP)

In the past, *S. (pseud)intermedius* isolates were generally susceptible to penicillinase-stable β-lactam antibiotics,[27–30] but, since 2006, MRSP has emerged as a significant animal health problem in veterinary medicine.[14] As in methicillin-resistant *S. aureus* (MRSA), the methicillin resistance of *S. pseudintermedius* is mediated by the *mecA* gene that encodes production of a modified penicillin binding protein (PBP). Normally, β-lactam antibiotics bind to PBP of *S. pseudintermedius* to prevent cell wall construction by the bacterium. The modified PBP of MRSP has a low affinity for β-lactams and therefore cell wall construction is not prevented by these antimicrobials. The *mecA* gene is located on the chromosome of the bacterium on a mobile element called the 'staphylococcal chromosomal cassette' (SCC*mec*).[14] The SCC*mec* element can be transferred between different staphylococcal species.[31]

As with susceptible *S. pseudintermedius*, infections with MRSP are (surgical) wound infections and infections of the skin, urinary tract, ear, respiratory tract and other body sites.[4,14] Infections with MRSP are more common in dogs than in cats.[32,33] MRSP isolates are often not only resistant to β-lactam antibiotics, but also to several other classes of antimicrobial drugs. The treatment of infections with MRSP is a new challenge in veterinary medicine because of the very limited therapeutic options.[34] Several reports on isolates not susceptible to any antimicrobials authorized for use in veterinary medicine have been published.[4,14,34–37] This has resulted in potential pressure for veterinarians to use antimicrobials authorized for human medicine.[14]

Identification of *S. pseudintermedius* and MRSP

In the first section, current knowledge on the differentiation between the members of the SIG group will be reviewed briefly, because proper identification of *S. pseudintermedius* is a prerequisite to detect MRSP. The interpretative criteria to determine methicillin resistance in staphylococci differ according to species, and species identification within the SIG is difficult.[38] In the second section, the methods used for confirming *S. pseudintermedius* as MRSP are summarized. *Staphylococcus schleiferi* subspecies *coagulans* does not belong to the SIG, but can be confused with *S. pseudintermedius*.

Methods used for identification and typing of S. pseudintermedius

Differentiation between the members of the SIG by phenotypic tests is very difficult. *S. intermedius* can be differentiated from *S. pseudintermedius* by a combination of biochemical tests (arginine dihydrolase test, β-gentiobiose test and D-mannitol test). In contrast, there are no differences in the biochemical reactions between *S. pseudintermedius* and *S. delphini*.[3] Commercial identification systems for fast and correct identification of *S. pseudintermedius* are not available to date. *S. pseudintermedius* is a relatively new species and remains to be included in the databases of most systems. In many cases, isolates will be erroneously identified as *S. intermedius* or *S. aureus*.[39,40] The occurrence of *S. (pseud)intermedius* in human infections is probably underestimated, because in many laboratories all coagulase-positive staphylococci are grouped together as *S. aureus*.[41] Talan *et al.*[10] reported 14 isolates from human dog-bite wounds that were originally identified as *S. aureus* and of these 3 were found to be *S. (pseud)intermedius*. In a case study reporting a post-operative sinusitis, a methicillin-resistant *S. (pseud)intermedius* was initially misidentified as MRSA because the identification as *S. aureus* was only based on a positive tube coagulase test.[42] The isolate was re-identified as *S. intermedius*, but this isolate was most likely *S. pseudintermedius* because the source of the isolate was a dog. A *Listeria*–CAMP test strain originally designated as *S. aureus* ATCC 49444 was recently reclassified as *S. pseudintermedius*.[43] Rapid, easy-to-use tests could enhance the correct differentiation between coagulase-positive staphylococci in veterinary and human laboratories. Correct differentiation between all members of the SIG is only possible by using molecular methods. Phylogenetic analysis based on partial *sodA* gene sequences and *hsp60* gene sequences was the first molecular method described that was sufficiently discriminative for *S. intermedius* and *S. pseudintermedius*.[3] Various DNA-based techniques have been developed for typing and epidemiological surveillance of *S. (pseud)intermedius*, including ribotyping[44] and PFGE.[45–47] More recently, techniques such as PCR restriction fragment length polymorphism (PCR-RFLP),[48,49] *spa* typing[24] and multilocus sequence typing (MLST)[48] have been adapted for this purpose.

PFGE is time consuming and often difficult to standardize for inter-laboratory comparison, and therefore is not suitable for long-term epidemiological surveillance. It cannot be used for

discrimination between the members of the SIG group. Nevertheless, this method has been used successfully to analyse and compare isolates from outbreaks.[50] A species-specific *spa* typing method can be used for rapid typing of methicillin-susceptible *S. pseudintermedius* (MSSP) and MRSP.[24] This single-locus sequence-based approach is less time consuming than PFGE, and results of *spa* typing can be better compared between laboratories. Sasaki *et al*.[38] developed a multiplex PCR method for species identification of coagulase-positive staphylococci targeting the *nuc* gene locus. MLST is time consuming and expensive, but inter-laboratory comparability of the results is good. PCR-RFLP also seems an effective approach for *S. pseudintermedius* identification, allowing discrimination from the other SIG species and *S. aureus*.[48,49] The results of identification of the SIG by the very fast matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry identification system are promising, although the sensitivity and specificity of the method were better for *S. intermedius* than for *S. pseudintermedius*.[51]

Methods used for detection of methicillin resistance in S. pseudintermedius

Most veterinary diagnostic laboratories use phenotypic methods for the detection of methicillin resistance in staphylococci. Commonly oxacillin or cefoxitin is used as a surrogate for methicillin because it is sensitive and more stable. Broth microdilution and disc diffusion tests are most commonly used.

As a screening test for methicillin resistance of *S. pseudintermedius*, cefoxitin disc diffusion testing using the interpretative criteria for *S. aureus* leads to an unacceptably high percentage of false-negative results and has been reported to be inappropriate.[52–54] In 2008 the CLSI published document M31-A3, with new interpretive criteria for the determination of *in vitro* antimicrobial susceptibility of MRSP for isolates from animals to replace those from 2004. This guideline advises that oxacillin susceptibility of veterinary coagulase-positive staphylococci, like *S. (pseud) intermedius*, should be determined using clinical breakpoints equivalent to those recommended for human and veterinary isolates of *S. aureus* (i.e. $\geq$4 mg/L for agar and broth dilution and $\leq$10 mm for disc diffusion). It must be noted that these interpretive criteria fail to detect methicillin resistance in some *mecA*-positive isolates of *S. pseudintermedius*.[52]

An oxacillin MIC of $\geq$0.5 mg/L (agar and broth dilution) and a zone diameter of $\leq$17 mm around a 1 μg oxacillin disc (disc diffusion) used for coagulase-negative staphylococci (CNS) are highly correlated with the detection of *mecA* in *S. pseudintermedius*.[53] In 2009 the CLSI Veterinary Antimicrobial Susceptibility Testing (VAST) subcommittee re-evaluated the interpretative criteria stated in document M31-A3 and decided to change them.[55] The new interpretive criteria (oxacillin MIC breakpoint $R \geq 0.5$ mg/L; disc diffusion $R \leq 17$ mm) will be included in the forthcoming document M31-A4.

The most reliable test for the detection of methicillin resistance is *mecA* PCR. However, few laboratories perform PCR for *mecA* in routine diagnostics.[52] PBP2a latex agglutination testing developed for MRSA can result in false-positive reactions when applied to *S. pseudintermedius* isolates, and is therefore not recommended as the sole test for confirmation of methicillin resistance in *S. pseudintermedius*.[41] As in MRSA, SCC*mec* typing can also be used in MRSP.[4,45,56]

Epidemiology and ecology

Contamination, colonization and infection

Both animals and humans can be contaminated, colonized or infected with MRSP. Colonization is the presence, growth and multiplication of MRSP in one or more body sites without observable clinical signs or immune reaction. The term 'carrier' in animals or humans refers to an individual colonized with MRSP. The most commonly reported site of MRSP colonization in dogs is the nose and the anus, but these are also the most commonly tested sites. Other sites, such as the pharynx, might also be important, but this has not been thoroughly investigated. Infection is a condition whereby MRSP has invaded a body site, is multiplying in tissue, and is causing clinical manifestations of disease. Contamination of the coat, skin and nose can occur. When an individual is contaminated, the bacteria can be easily washed off, and often only one culture is MRSP positive, while subsequent cultures are negative. As most studies on MRSP are one-point prevalence studies and only one sample per individual is investigated, it is often unclear whether individuals are colonized or merely contaminated with MRSP. Longitudinal studies involving repeated cultures of the same individuals could help to clarify if animals or humans are colonized or contaminated by MRSP.

Occurrence

MRSP colonization and infection has been described in dogs, cats, horses, birds and humans.[14,56] Colonization with MRSP is more common in dogs than in cats.[57] Dogs can carry the same or similar MRSP strains for months without active infection.[58] In dogs with pyoderma, indistinguishable strains as the one isolated from the lesions can be found at other sites, most frequently the anus. These sites can thus be reservoirs for MRSP infections.[59] The prevalence of MRSP colonization or contamination has been studied in various dog populations in different countries, with rates of 0%–4.5% in dogs in the community and upon admission to veterinary hospitals,[13,57,60–62] and 0%–7% in dogs with skin disease.[13,27,63] An unexpectedly high prevalence of 30% was found in dogs at a veterinary clinic in Japan.[64] Another Japanese study reported that 66% of the *S. pseudintermedius* isolates cultured from dogs with pyoderma visiting two referral hospitals were methicillin resistant based on the detection of *mecA*.[65] The prevalence of MRSP in cats was 4% in healthy cats, whereas no MRSP was found in cats with inflammatory skin disease.[12] In Canada, the prevalence of MRSP colonization in healthy cats was 1.2%.[57] No MRSP was found among 300 horses in different farms in Slovenia.[62] In Germany, the prevalence of MRSP in 16103 clinical specimens of small animal and equine origin was 0.8% in dogs (61/7490), 0.1% in cats (6/3903) and 0.1% in horses and donkeys (5/4710). MRSP prevalence in dogs was significantly higher than in cats and equines.[66] The skin and the ears are the most common MRSP infection sites.[66]

Clonal distribution

Black *et al*.[45] compared MRSP and MSSP isolates from Tennessee by PFGE and MLST and found that MSSP isolates were more genetically diverse than MRSP isolates. MRSP isolates were predominantly MLST sequence type (ST) 68 and fell within the same PFGE cluster. These findings are in agreement with those of Bannoehr *et al*.,[67] who investigated 89 MRSP and MSSP isolates from different animal species originating from different countries in Europe and the USA. They found 61 different STs among the isolates revealing considerable clonal diversity, but the 16 MRSP isolates belonged to only 5 distinct STs. Together these data show that although MSSP isolates are genetically diverse, a limited number of MRSP clones are disseminated worldwide, with a distinct geographical distribution. One major clonal lineage seems to dominate in Europe (MLST ST71-*spa* t02-SCC*mec* II-III), whereas in North America another clonal linage is predominant (MLST ST68-*spa* t06-SCC*mec* V).[4,56] MRSP isolates of ST71 carrying SCC*mec* II-III have also been found in dogs with pyoderma in Hong Kong[59] and in dogs in Canada and the USA,[4] suggesting worldwide dissemination of certain clones. The reason why certain MRSP clones are so successful remains unclear. The situation resembles that of MRSA, in which the worldwide dissemination is also mainly due to a few successful clones with a rather specific geographical pattern.[68]

Outbreaks and nosocomial transmission

Zubeir *et al*.[69] investigated 10 MRSP isolates in eight dogs and one cat at one veterinary clinic during a 6 month period and found the same PFGE pattern for all isolates, indicating cross-infection at the clinic or the distribution of a single clone in the pet population. Methicillin-resistant *S. (pseud)intermedius* isolates that were indistinguishable by PFGE were cultured from several dogs and a cat, the environment and personnel at a veterinary practice in the Netherlands. This suggests that veterinary hospitals and practices play a role in the dissemination of MRSP.[50]

Additional resistances

Besides *mecA*, MRSP also contains a wide range of different antibiotic resistance genes, making them resistant to almost all classes of commonly used antimicrobial agents.[4] The multidrug resistance profile of MRSP in Europe and North America includes resistance to all oral antimicrobials routinely used for the treatment of infections in pets, and the drugs to which they remain susceptible are not authorized for use in animals.[4] In addition to β-lactam resistance, resistance to 11 other antimicrobials was observed in a study of 103 epidemiologically unrelated MRSP isolates from dogs from Canada, the USA, Denmark, Germany, France, Italy, Sweden, Switzerland and the Netherlands (Table 1).[4] Isolates originating from North America were often susceptible to chloramphenicol, whereas isolates from Europe were often resistant to chloramphenicol. Inducible clindamycin resistance was reported in 2% of the isolates.[4] Eighty percent of all isolates were resistant to seven or more antimicrobials and only 3% were susceptible to all antimicrobials except for β-lactams (Table 1). Similar resistances have been found by Ruscher *et al*.[56] The presence of different SCC*mec* elements among members of different genetic lineages suggests that the *mecA* gene has been acquired by different *S. pseudintermedius* strains on multiple occasions.[4] To date, several types of SCC*mec* elements (SCC*mec* II-III, SCC*mec* III, SCC*mec* IV, SCC*mec* V, SCC*mec* VII and non-typeable cassettes) have been characterized in MRSP.[4,45,70] SCC*mec* VII and SCC*mec* II-III, which consist of a combination of SCC*mec* II from *Staphylococcus epidermidis* and SCC*mec* III from *S. aureus*, are new elements, whereas SCC*mec* V is largely homologous to SCC*mec* type VT from *S. aureus*. The latter finding suggests recent transfer of the SCC*mec* element from *S. aureus* to *S. pseudintermedius*.[71]

Table 1. Resistance to antimicrobial agents for 103 MRSP isolates from Europe and North America[4]

	Resistance breakpoint (mg/L)	Percentage of resistant isolates	Resistance genes involved
Erythromycin	≥8	89	*erm*(B)
Clindamycin	≥4	89	*erm*(B); *Inu*(A)[a]
Trimethoprim	≥16	90	*dfr*G
Ciprofloxacin	≥4	87	ND
Gentamicin	≥16	70	*aac(6′)-Ie-aph(2′)-Ia*
Kanamycin	≥64	93	*aph(3′)-III*
Streptomycin	≥32	90	*ant(6′)-Ia*
Tetracycline	≥16	70	*tet*(M); *tet*(K)
Chloramphenicol	≥32	57	cat_{pC221}

[a]*Inu*(A) confers resistance to lincomycin and pirlimycin; MICs of clindamycin are increased, but still below the breakpoint of resistance.

Risk factors for colonization and infection

Studies on the risk factors for MRSP colonization or infection are scarce. Dogs with MRSP infections had likely been treated with antimicrobials within the 30 days prior to the onset of the infection compared with dogs with MSSP infections.[72] This and a study by Sasaki *et al*.[64] indicate that antimicrobial use is a risk factor for MRSP infections. A recent study by Nienhoff *et al*.[73] shows that prior hospitalization and antibiotic treatment was associated with MRSP colonization in dogs admitted to a small animal hospital.

Further studies are needed to confirm these findings. Because post-operative wound infections are often caused by MRSP, potential additional risk factors could be surgical interventions.

Human contact hazard

The zoonotic potential of MRSA and MRSP has recently been reviewed.[14] As the information on zoonotic transmission of MRSP is very limited, all information available on *S. (pseud)intermedius* will be discussed.

MSSP colonization

S. (pseud)intermedius colonization is uncommon in humans, even among people with frequent contact with animals.[74]

S. (pseud)intermedius isolates are also rare among coagulase-positive staphylococcal isolates from hospitalized humans.[75] The number of persons owning a pet is high and the contact between companion animals and their family members is often close, but humans are not natural hosts for MSSP, and this explains why human colonization is rare although exposure is considerable. The importance of *S. (pseud)intermedius* as a zoonotic pathogen is therefore much smaller than that of MRSA. However, several cases of zoonotic transmission of methicillin-susceptible *S. (pseud)intermedius* between companion animals and humans have been reported. In some cases humans were only colonized or contaminated, but in other cases transmission resulted in human infections.

Owners of dogs with deep pyoderma were more often culture positive for *S. (pseud)intermedius* than individuals without daily contact with dogs and they often carried the same *S. (pseud)intermedius* strain as their dogs. However, persons were sampled for a second time at the time the dogs no longer had purulent lesions and were found to be no longer culture positive, thus long-term colonization seems uncommon in humans.[76] Daily direct contact with lesions may be a risk factor for the transmission of the organism to humans. One recent study reported an unexpectedly high prevalence (4.1%) of *S. pseudintermedius* among humans living in a household with a cat or dog. However, the veterinary profession was over-represented, accounting for 42.5% of the participants.[57] The finding of indistinguishable strains of *S. pseudintermedius* in 44% of the households where both a dog and person were culture positive, together with the low prevalence of the organism in humans, may indicate a canine to human route of transmission.[57]

MSSP infection

S. (pseud)intermedius is a common and potentially invasive pathogen of dog-bite wounds in humans.[77] In addition, *S. (pseud)intermedius* has been associated with bacteraemia,[78] a brain abscess,[79] pneumonia,[80] ear infections,[81,82] varicose leg ulcers,[77] an infected suture line[77] and an infected implantable defibrillator.[38,83] In most cases the origin of the organism remained unknown and zoonotic transmission was not proven. Recently a case report on a catheter-related bacteraemia caused by *S. pseudintermedius* in a child with dog exposure was published, but no effort was made to isolate the organism from the dog.[84]

MRSP colonization

As reported for MSSP, colonization of humans with MRSP seems to be uncommon and transient. MRSP was identified in 1 of 242 (0.4%) humans living together with a dog or cat.[57] In a veterinary clinic in Japan, MRSP was cultured from 1 of 20 staff members, and this isolate showed susceptibility patterns and PFGE patterns similar to dog-derived isolates from the same hospital, indicating zoonotic transmission.[64] Transmission of methicillin-resistant *S. (pseud)intermedius* between humans and animals in a veterinary practice has also been reported in the Netherlands.[50] In Hong Kong, veterinary personnel ($n=150$) were sampled for nasal colonization/contamination with MRSP and only one person was found to be positive.[85] A similar study in Japan found 3/92 (3.3%) personnel at a veterinary academic hospital were MRSP positive in 2007 and 10/127 (7.9%) in 2008.[86] In a Dutch study investigating the prevalence of MRSP in people, pets and the environment in households with a pet with a clinical MRSP infection within the past year, transmission of MRSP between infected or colonized dogs and cats and healthy people occurred, but was relatively uncommon, while transmission to pets occurred frequently. In this study, transmission of MRSP between an infected cat and two owners within the same household was reported.[87] MRSP was isolated from 2 of 25 owners of dogs with pyoderma, 15 of which were MRSP positive. MRSP was no longer isolated from the owners after treating the dogs for 1 month.[88] A study investigating the prevalence of MRSP in veterinary dermatology practice staff ($n=171$) revealed that nine persons (5.3%) were MRSP positive.[89] Owners of infected pets and veterinarians in contact with infected animals seem to have a higher risk of being MRSP positive, although this risk seems to be smaller than with MRSA. All humans involved were asymptomatic.[87]

MRSP infection

Reports on infections in humans with MRSP are rare. One report describes isolation of methicillin-resistant *S. (pseud)intermedius* from a patient with gastric adenocarcinoma and developing bacteraemia.[90] Another case involved a patient with pneumonia.[80] In the first case, no information on contact with animals was available, and in the second case, the patient had no exposure to dogs. Recently a human case of post-operative sinus infection caused by methicillin-resistant *S. (pseud)intermedius* was described. The patient's pet dog carried a methicillin-resistant *S. (pseud)intermedius* strain with a PFGE pattern indistinguishable from the patient's strain, strongly suggesting zoonotic transmission. The dog had recent bouts of pyoderma that had been treated with antimicrobials.[42] A similar case of sinusitis caused by MRSP of MLST ST71, the predominant clone disseminating in dogs and cats throughout Europe, was reported from a patient in Switzerland. The patient owned a dog that had been treated with antimicrobials, but no samples were taken from the animal.[91]

Control options for colonized animals

Non-antimicrobial control options

Evidence of the effectiveness of routine application of measures such as disinfecting shampoos to decolonize animals is lacking. Expected effectiveness is particularly dubious for animals that have mucosa colonized with MRSP. To date, there is limited information on the indications for decolonization of animals. Although studies on risk factors for MRSP infections are rare, it can be hypothesized that animals colonized with MRSP are at greater risk of developing MRSP infections in case of surgical or non-surgical wounds and when exposed to antimicrobials. In certain cases, e.g. an animal needing invasive surgery, it might be desirable to decolonize the animal before surgery.

Non-antimicrobial management may include washing the animal with, e.g. chlorhexidine-containing products, which may help to decontaminate the coat. There are no studies on long-term colonization of animals with MRSP, thus it is unknown if MRSP carriage is transient or persistent, but it is likely that long-term

colonization with MRSP similar to *S. aureus*/MRSA colonization in humans occurs, since dogs are natural hosts for *S. pseudintermedius*. Cleaning and disinfection of the house will probably help to prevent re-colonization through the contaminated household environment.

Antimicrobial control options

There is no evidence of the effectiveness of antimicrobials to decolonize animals. The use of antimicrobials for this purpose is likely to increase the risk for selection of additional resistances. Decolonization with antimicrobial drugs might be considered in individual animals in certain cases. However, no antimicrobials have been studied or approved for local or systemic application to decolonize MRSP carrier animals. In some countries, veterinary use of last-resort antimicrobials, including mupirocin, is limited to exceptional conditions or prohibited by law (Regulation 847/2008, Ministry of Agriculture and Forestry, on prohibiting or limiting the use of certain medicinal substances for animal treatment, 12 December 2008, Finland).

Control options for infected animals

Non-antimicrobial control options

Many MRSP infections are (post-operative) wound infections, and the improvement of wound management without the use of antimicrobial drugs is likely to be adequate and the preferred option for treatment. This would include proper wound cleansing and debridement. Topical antiseptics currently used for wound management include chlorhexidine and products containing iodine (e.g. povidone-iodine).

A commercial ear antiseptic containing chlorhexidine and Tris-EDTA showed good *in vitro* bactericidal activity against MRSP.[92] Disinfectants might thus be used in the therapy of certain MRSP infections, but controlled studies are necessary to evaluate their clinical efficacy and side effects. To date, no such studies have been published. Topical therapy might be used for superficial infections, but is unlikely to cure deep infections.

Novel approaches for the prevention of canine pyoderma, like vaccines, could help to improve the control options.[15] Curtis *et al*.[93] demonstrated that an autogenous bacterin of MSSP could be used successfully for the control of idiopathic pyoderma.

Alternative therapeutic strategies for MRSP infections could include the use of bacteriophages with lytic activity towards MRSP. There is recent interest in phage therapy in human and veterinary medicine because of the emergence of multidrug-resistant bacteria. In addition to using phages themselves, their products, e.g. phage lysins, could potentially be used in the treatment or prophylaxis of MRSP. To date, there are no data on the efficacy of bacteriophages or lysins in the prevention or therapy of MRSP infections. At present, no authorized products containing phages or lysins are available for MRSP infections.

Antimicrobial control options

As the clinical manifestations of MRSP infections are variable, no single treatment protocol is suitable for all infections, and therefore the treatment must be tailored to the individual patient. When choosing a treatment plan, the risk for development of further resistance in the infecting strain needs to be considered. In addition, the susceptibility profile of the MRSP isolate from the animal, the severity and site of the infection, the presence of systemic disease, and the presence of an underlying disease or any co-morbidity should be taken into account. Local antimicrobial therapy may be an option in certain cases, e.g. wound and ear infections, while in other patients systemic antimicrobial therapy will be required. Close monitoring of progress of the localized disease or development of systemic disease is required.

Many infections with MRSP are (surgical) wound infections. The European Wound Management Association has written a position document on the management of human wound infections.[94] The principles underpinning this guidance are to provide an optimal environment to promote rapid healing, to restrict the use of antimicrobial agents to occasions when they are specifically indicated, and to use antimicrobial agents appropriately to reduce the selection of resistant strains.

Information on the efficacy of antimicrobial treatment of animals infected with MRSP is scarce. The only available information on the outcome of patients with MRSP infections is based on case studies with only a few patients included.[34,35] From these preliminary data it may be concluded that clinical and microbiological cure of patients with MRSP infections is possible with or without antimicrobials, but larger controlled studies with more patients are needed to define the best therapeutic strategies.

The potential use in pets of antimicrobials that are critical for MRSA treatment in humans is controversial, due to the risk for development of resistance against those agents.[14] In some European countries there are already legal restrictions on the use of certain antimicrobial drugs, e.g. mupirocin, in animals. Recently rifampicin-resistant MRSP isolates have been found in clinical infections in 10 Dutch dogs. Nine of the 10 dogs had been treated with rifampicin. Rifampicin-susceptible MRSP had been isolated from nine dogs prior to the use of the antimicrobial drug.[95] Limitation of veterinary use of last-resort antimicrobial agents for MRSA and other serious infections in humans needs to be considered because of the risk for development of resistance against these agents and subsequent spread of resistant bacteria to humans.

More information is needed on the efficacy of various therapeutic strategies in animals infected with MRSP. Research should focus on non-antimicrobial strategies to treat (surgical) wounds, skin diseases like pyoderma, and otitis externa, the most common conditions associated with MRSP.

Prevention of transmission

In veterinary clinics

Guidelines on the management of MRSA in veterinary practices have been developed by the British Small Animal Veterinary Association[96] and are generally also applicable to MRSP. Proper hand hygiene is essential. In line with standard infection control principles, patients diagnosed with or suspected of MRSP infections should be isolated in order to minimize the risk of nosocomial transmission. In veterinary clinics, this includes using barrier nursing precautions and limiting staff contact. This includes wearing protective aprons, overshoes and gloves. Widespread contamination of the environment of veterinary

hospitals has been reported and the environment remained MRSP-positive after cleaning and disinfection, indicating that current cleaning procedures were unable to eliminate MRSP or rapid re-contamination occurred.[87] Decolonization of personnel that test MRSP-positive repeatedly should be considered. MRSP-infected wounds should be covered with clean bandages if possible, in addition to isolation of the patient.

In households

Intra-household transmission from MRSP-infected or -colonized animals to healthy contact animals has been described.[87] Widespread contamination of the environments of households has also been reported, indicating that direct contact with a patient or colonized animal is not necessary, as indirect transmission through the environment can also occur. It is difficult or even impossible to clear the organism from the environment as long as the MRSP-infected animal still has clinical signs of MRSP infection and lives in the environment, especially when the infection site is the skin or the ears, because shedding of the organism will continue.[87] Proper cleaning and disinfection of the contaminated environment will reduce the number of organisms. Other possible interventions in households with MRSP-positive animals include removing the pet from the household (temporarily) in order to avoid transmission to other pets and washing the pet to reduce the contamination of the coat. Although the risk of zoonotic transmission of MRSP is small and colonization of humans seems to be transient, persons in close contact with infected animals seem to have a higher risk to be MRSP positive. Clearly, for all people having contact with companion animals, appropriate hygiene is the cornerstone in minimizing the spread of MRSP between animals and humans. One study indicates that routine hand hygiene may be effective in reducing transmission of *S. pseudintermedius* between humans and pets in the household.[57]

Conclusions

There has been a sudden emergence of MRSP in dogs and cats, mainly due to clonal spread. Due to the multiresistant characteristics of these bacteria, they constitute a new prominent risk to animal health. Veterinary education on the recent taxonomical and resistance evolutions with regard to MRSP is needed. While MRSA strains infecting companion animals are evolutionarily related to different typical human-associated MRSA clones and are thought to be of human origin, this is not the case for MRSP. MRSP seems to originate from an animal reservoir and is present in different hosts. The transfer of SCC*mec* elements between different staphylococcal species is a concern. Although colonization or infection with MRSP is rare in humans, the potential transfer of new SCC*mec* elements from MRSP to other staphylococcal species like *S. aureus* and the subsequent clonal spread of such a new MRSA clone might be a threat for human health in the future.

Better diagnostic tools are needed for the identification of *S. pseudintermedius*, and to avoid misidentification with *S. aureus* and *S. intermedius*. Rapid, easy-to-use tests would enhance the correct differentiation between coagulase-positive staphylococci in veterinary and human laboratories. Molecular methods are needed for the correct differentiation of *S. pseudintermedius*.

Studies need to document whether the long-term colonization of MRSP exists and find efficient ways to decolonize animals. More information is needed on the efficacy of various therapeutic strategies in animals infected with MRSP. Research should focus on non-antimicrobial strategies to treat (surgical) wounds, skin diseases like pyoderma, and otitis externa, the most common conditions associated with MRSP. Although most infections can probably be controlled without antimicrobials, there are severe cases that might be life threatening for which only a few, if any, effective veterinary-approved antimicrobials are available for treatment. Animals might be treated against MRSP with antimicrobial agents that are regarded as critically important in human medicine for use against MRSA. Treatment of dogs and cats with such antimicrobial agents could result in the development of additional resistances with subsequent spread to humans. If antimicrobial treatment of a severe infection is necessary, the risk of emergence of further resistance in the strain of MRSP infecting the animal should be managed to avoid subsequent spread of resistance to animals and humans. Appropriate hygiene in households and veterinary clinics is the cornerstone in minimizing the spread of MRSP between animals. Detailed guidelines for the appropriate use of antimicrobials in companion animal medicine are needed, as well as surveillance of consumption of antimicrobial agents in these animals.

Transparency declarations

None to declare.

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