Veterinary Microbiology 168 (2014) 154–160

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Case–control risk factor study of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) infection in dogs and cats in Germany

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ARTICLE INFO

Article history:
Received 6 August 2013
Received in revised form 25 October 2013
Accepted 31 October 2013

Keywords:
Pyoderma
Otitis
Veterinary
MRSP
Antimicrobial resistance
Infection control

ABSTRACT

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) has emerged as a highly drug-resistant small animal veterinary pathogen. Although often isolated from outpatients in veterinary clinics, there is concern that MRSP follows a veterinary-hospital-associated epidemiology. This study's objective was to identify risk factors for MRSP infections in dogs and cats in Germany. Clinical isolates of MRSP cases ($n = 150$) and methicillin-susceptible *S. pseudintermedius* (MSSP) controls ($n = 133$) and their corresponding host signalment and medical data covering the six months prior to staphylococcal isolation were analysed by multivariable logistic regression. The identity of all MRSP isolates was confirmed through demonstration of *S. intermedius*-group specific *nuc* and *mecA*. In the final model, cats (compared to dogs, OR 18.5, 95% CI 1.8–188.0, $P = 0.01$), animals that had been hospitalised (OR 104.4, 95% CI 21.3–511.6, $P < 0.001$), or visited veterinary clinics more frequently (>10 visits OR 7.3, 95% CI 1.0–52.6, $P = 0.049$) and those that had received topical ear medication (OR 5.1, 95% CI 1.8–14.9, $P = 0.003$) or glucocorticoids (OR 22.5, 95% CI 7.0–72.6, $P < 0.001$) were at higher risk of MRSP infection, whereas *S. pseudintermedius* isolates from ears were more likely to belong to the MSSP-group (OR 0.09, 95% CI 0.03–0.34, $P < 0.001$). These results indicate an association of MRSP infection with veterinary clinic/hospital settings and possibly with chronic skin disease. There was an unexpected lack of association between MRSP and antimicrobial therapy; this requires further investigation but may indicate that MRSP is well adapted to canine skin with little need for selective pressure.

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http://dx.doi.org/10.1016/j.vetmic.2013.10.023

1. Introduction

Staphylococcus pseudintermedius, belonging to the *Staphylococcus intermedius* group is a frequent opportunistic commensal and the most important staphylococcal pathogen in dogs and cats and frequently affects the skin, ears and wounds (Devriese et al., 2005; Holm et al., 2002; White et al., 2005). Until recently, treatment of the great majority of *S. pseudintermedius* infections caused few problems in small animal veterinary practice as a wide range of authorised antimicrobial drugs showed good efficacy both *in vitro* and *in vivo* (Beco et al., 2013; Lloyd et al., 1996; Pellerin et al., 1998; Rantala et al., 2004). However, the emergence of methicillin-resistant *S. pseudintermedius* (MRSP) over the past 10 years and its continuing spread worldwide (Gortel et al., 1999; Jones et al., 2007; Morris et al., 2006; Loeffler et al., 2007; Ruscher et al., 2009), present significant clinical challenges to veterinary surgeons. In addition, MRSP has implications for public health as it can spread between people and pets *via* direct and indirect contact and rarely MRSP infections in humans have been described (Campanile et al., 2007; Gerstadt et al., 1999; Stegmann et al., 2010; van Duijkeren et al., 2011a,b).

Resistance to methicillin in staphylococci is encoded by the gene *mecA* which confers resistance to all β-lactam antibiotics (Chambers, 1997). Epidemiologically, the significance of *mecA*-positive staphylococci is greatest in the context of nosocomial infections. Such isolates are likely to emerge as a consequence of antimicrobial selection pressure in hospitals and are typically multidrug-resistant. In MRSP, several other resistance genes have been identified which often render all clinically relevant pet-authorised systemic antimicrobial drugs ineffective (Kadlec and Schwarz, 2012). For canine pyoderma, it has been shown that most MRSP infections can still be resolved with topical antibacterial therapy and/or with the help of more 'exotic' or less frequently used antimicrobials but that treatment may be prolonged and may be more frequently associated with adverse effects (Bryan et al., 2012; Loeffler et al., 2007). Knowledge of risk factors that contribute to MRSP infection becomes highly relevant since early identification of predisposed patients should facilitate implementation of infection control and prevention strategies.

Risk factors such as antimicrobial therapy, surgical interventions and chronic disease have been suspected for MRSP infection in pets based on the initially observed clinical presentations in chronic skin and wound infections in hospitalised animals. Antimicrobial therapy during the 30 days prior to sampling was recently identified as a risk factor for MRSP infection in 56 hospitalised dogs in a North American case–control study while other medication (topical antibacterial therapy, glucocorticoids), animal signalment, clinical characteristics and veterinary interventions (such as concurrent disease, type of infection, surgery, hospitalisation) were not associated with outcome (Weese et al., 2012). For MRSP carriage in dogs and cats admitted to a veterinary hospital, previous hospitalisation and antimicrobial therapy in the six months before sampling have been proposed as risk factors (Nienhoff et al., 2011a,b). Studies on risk factors for MRSP infection in cats have not been published to the authors' knowledge.

This study aimed to identify risk factors for MRSP infection in dogs and cats in two regions in Germany with a particular focus on exploring a possible veterinary care-associated epidemiology.

2. Materials and methods

2.1. Study groups

Privately owned dogs and cats with *S. pseudintermedius* infection were eligible for inclusion in a prospective unmatched 1:1 case–control study. Cases with MRSP infection and controls with methicillin-susceptible *S. pseudintermedius* (MSSP) infection were identified based on bacterial isolation from clinical samples. Samples had been submitted for bacterial culture and antimicrobial susceptibility testing to one of the two laboratories in Germany (SynlabVet, Geestacht, Germany and Institute for Hygiene and Infectious Diseases, Justus-Liebig University, Giessen, Germany). SynlabVet Laboratory received submissions directly from general veterinary practices in the surrounding area and from a dermatology referral centre (Tierärztliche Spezialisten, Hamburg, Germany). The Giessen University laboratory received submissions from general veterinary practices in the surrounding area as well as samples from dermatology, surgery and internal medicine referral services within the university teaching hospital. Samples had been taken by veterinary surgeons as part of their diagnostic investigations into suspected canine and feline bacterial infection. All MRSP isolates identified between October 2010 and October 2011 inclusive were considered. MSSP isolates were selected throughout the study period using simple randomisation on www.randomizer.org.

2.2. Enrolment criteria

Animals were enrolled with their *S. pseudintermedius* isolate if their original bacterial isolate had been preserved (lyophilised or frozen in tryptone soya broth with 20% glycerol) by the diagnostic laboratory, when its identity had been confirmed by the phenotypic methods described below and when the corresponding questionnaire had been returned by the submitting veterinary surgeon for analysis; they were excluded if no or insufficiently completed questionnaires had been returned after two weekly reminder follow-up phone calls.

2.3. Questionnaires

When reporting *S. pseudintermedius* isolation, the laboratories invited the submitting veterinary surgeons to participate in the study and to complete a questionnaire. Questionnaires were returned by the participants *via* the laboratories to the lead investigator (GL) by fax, email or post. Cases and controls were coded and pet and owner details were deleted on receipt by the lead investigator (GL) to ensure confidentiality. Where the Hamburg dermatology referral centre or a referral service at Giessen