EDITORIAL

For reprint orders, please contact: reprints@futuremedicine.com

Exploring *Staphylococcus pseudintermedius*: an emerging zoonotic pathogen?

“Use of highly discriminatory microbiological methods has allowed us to identify *S. pseudintermedius* as an emerging potential pathogen of zoonotic origin.”

Ranjani Somayaji¹, Joseph E Rubin^{*2}, Madalagama AR Priyantha²
& Deirdre Church^{3,4}

First draft submitted: 4 July 2016; Accepted for publication: 28 July 2016;
Published online: 18 October 2016

Staphylococcus pseudintermedius is a coagulase-positive bacterium within the *Staphylococcus intermedius* group (SIG) that was identified as a distinct species in 2005 [1]. Although considerable literature exists on the role and pathogenicity of *S. pseudintermedius* in animals, much remains to be learned on its role in human infections. *Staphylococcus pseudintermedius* is a common colonizer of companion animals and particularly dogs, and is most frequently associated with skin and soft tissue infections (SSTI) in animals [2]. Similarly, SSTIs occur most commonly with human *S. pseudintermedius* infections likely through zoonotic transmission, though invasive infections can also occur as demonstrated in case reports and more recently in a larger case series [3]. As *S. pseudintermedius* has virulence and antimicrobial resistance characteristics in

animal and human isolates comparable to *S. aureus*, this pathogen may be a potentially important emerging zoonotic pathogen [4,5]. We propose that companion animal-derived human infections with *S. pseudintermedius* are under recognized and may represent an important gap in our understanding of the epidemiology of methicillin-resistant staphylococci.

S. pseudintermedius is a normal inhabitant and common opportunistic pathogen of canines and other companion animals including cats and horses [6]. In dogs, colonization with *S. pseudintermedius* is ubiquitous, occurring in up to 90% of healthy dogs [2]. Like *S. aureus* colonization in humans, *S. pseudintermedius* can be recovered from multiple body sites in dogs with the pharynx and rectum being most frequently positive [2,6]. Otitis externa and pyoderma secondary

KEYWORDS

• canine • companion animal
• epidemiology • *Staphylococcus pseudintermedius* • zoonotic

“Up until recently, few data were available for human *S. pseudintermedius* isolates.”

¹Department of Medicine, University of Calgary, Calgary, AB, Canada

²Department of Veterinary Microbiology, University of Saskatchewan, Saskatoon, SK, Canada

³Department of Pathology & Laboratory Medicine & Medicine, University of Calgary, Calgary, AB, Canada

⁴Calgary Laboratory Services, Calgary, AB, Canada

*Author for correspondence: Tel.: +1 306 966 7246; jer298@mail.usask.ca

“Encouragingly, no resistance to drugs active against methicillin-resistant *S. pseudintermedius* strains such as vancomycin, daptomycin or linezolid have yet been identified in animal or human isolates.”

to food allergy, endocrine disease or other immuno-suppressive conditions are very common in dogs, and are most often associated with *S. pseudintermedius* [7]. *Staphylococcus pseudintermedius* is also a common cause of canine urinary tract infections and a frequent cause of opportunistic infections at any site where normal host defenses are disrupted.

The first reported case of human infection with *S. pseudintermedius* was a cardiac device pocket infection initially misidentified as *S. aureus* [8]. Notably, case reports have reported human *S. intermedius* infections prior to its reclassification as *S. pseudintermedius*. Despite emerging literature on *S. pseudintermedius* epidemiology in humans primarily attributable to improved microbiological technologies, much remains to be learned. Largely restricted to case reports, *S. pseudintermedius* is most commonly associated with SSTIs and device-associated infections though invasive infections have also been reported. More recently, a case series of patients with dog bite-associated wounds was examined, and 13 of 101 isolates (12.9%) were determined to be *S. pseudintermedius* having initially been identified as *S. aureus* [9].

In the largest case series to date of 24 patients, SSTIs occurred in 18 patients (75.0%), and two invasive infections (8.3%) including a bloodstream infection, and prosthetic joint infection occurred [3]. Cultures revealed that *S. pseudintermedius* was a component of a polymicrobial milieu in 91.7% of these cases [3]. The majority of these infections were mild to moderate in nature, and were managed as outpatients primarily with oral antibiotics. In the series, four patients with isolation of *S. pseudintermedius* were deemed to be colonized and not infected based on the clinical presentation [3]. Notably, 95.4% of patients had a pet dog in temporal association with their *S. pseudintermedius* infections [3]. When incidence was examined in relation to *S. aureus*, it remained relatively low with bloodstream infection incidence of $3.48 \times 10^{-4}\%$ per year compared with *S. aureus* at 0.006% per year [3]. Similarly, for SSTI and wound culture positivity, *S. pseudintermedius* annual rates were 0.025% compared with *S. aureus* rates of 30.0% [3].

Antimicrobial resistance, and specifically methicillin-resistant *S. pseudintermedius* (MRSP), may be a concern similar to

that noted in veterinary medicine in recent years [10]. In the case series by Borjesson *et al.* of 13 *S. pseudintermedius* dog bite-associated wound infections, one isolate (7.7%) was an MRSP [9]. Somayaji *et al.* found the six isolates of 27 (22.2%) corresponding to three patients (12.5%) had an MRSP isolate [3]. Additionally, these isolates also demonstrated multidrug resistance to other antibiotic classes including sulfonamides, macrolides, and fluoroquinolones [3]. When multi-locus sequence typing was performed on these isolates, sequence types corresponded to those identified in Europe (ST71 and ST181), both of which have been widely associated with multidrug resistance [3,11]. Encouragingly, no resistance to drugs active against MRSP strains such as vancomycin, daptomycin or linezolid have yet been identified in animal or human isolates.

As previously stated, *S. pseudintermedius* is a coagulase-positive *Staphylococcus* that is part of the SIG group comprised of *S. intermedius*, *S. pseudintermedius*, and *S. delphini*. These Gram-positive cocci may be misidentified as *S. aureus* in the as all of them with the exception of *S. intermedius* are typically positive for tube coagulase and negative for slide coagulase [9]. *S. pseudintermedius* is increasingly being accurately identified from human clinical specimens due to widespread implementation of matrix-assisted laser desorption/ionization time of flight mass spectrometry technology as the primary identification method for a wide variety of clinically relevant organisms [9]. Prior to matrix-assisted laser desorption/ionization time of flight mass spectrometry, coagulase-negative staphylococci were not identified to the species level, as high throughput phenotypic methods do not provide sufficient resolution.

As *S. pseudintermedius* can possess *mecA*-mediated methicillin resistance, these isolates should therefore be identified to the species-level to prevent their spurious classification as methicillin-resistant *S. aureus* (MRSA). The emergence of MRSP in dogs in recent years has presented substantial challenges for veterinarians, with prevalence proportions of up to 47% in some regions [11,12]. In Europe, the emergence of MRSP has been associated with the ST71 lineage while ST68 predominates in North America [5]. MRSP strains are commonly multidrug resistant to one or more classes of antimicrobials including

tetracyclines, chloramphenicol, trimethoprim-sulfamethoxazole, aminoglycosides, lincosamides, macrolides and fluoroquinolones [6,12].

Up until recently, few data were available for human *S. pseudintermedius* isolates. Wu *et al.* conducted a study to evaluate oxacillin and cefoxitin disk and MIC results as predictors of methicillin resistance (encoded by *mecA*) in a collection of 115 SIG isolates from human and veterinary specimens associated with clinical infections [13]. Cefoxitin testing as used for other species of *Staphylococcus* was a poor predictor, but oxacillin disk and MIC tests accurately detected *mecA* resistance in SIG. In the 26th edition of the Clinical Laboratory Standards Institute M100S (2016) [14] specific oxacillin breakpoints have been published for *S. pseudintermedius*. Immunochromatographic detection of PBP2a is also a reliable alternate method for identifying methicillin-resistance in *S. pseudintermedius* as well as MRSA. The antimicrobial susceptibility profiles for other classes of drugs tested for the same collection of 115 SIG isolates was recently published [15]. A total of 33% were methicillin resistant, among which 51.4% were susceptible to doxycycline, 29.7% to clindamycin, and 21.6% to trimethoprim-sulfamethoxazole. All of the 115 isolates however were susceptible to ceftaroline, daptomycin, linezolid, nitrofurantoin, quinupristin-dalfopristin, rifampin, tigecycline and vancomycin. Isolates were also variably susceptible to ciprofloxacin (82.6%), erythromycin (67.8%) and penicillin (23/5%).

Transmission of *S. pseudintermedius* from dogs into humans is an understudied and likely under-recognized epidemiological phenomenon; the ubiquity of canine colonization and the frequency of dog ownership provides ample opportunity for transmission. Although inadequately studied, putative within-household transmission between people and dogs has been reported; one study found 5.6% of dog owners carried *S. pseudintermedius* [16,17]. The propensity of *S. pseudintermedius* to colonize the pharynx and rectum may facilitate transmission through the fecal–oral routes [2]. Study of other organisms such as *Escherichia coli* have demonstrated that transmission between dogs and humans within households is highly frequent, and thus it is plausible that staphylococci may similarly be transmitted [18]. Notably, transmission of *S. pseudintermedius* may also occur from other companion animals to humans, and

potentially between humans in nosocomial settings [19].

The populations at risk of infection with *S. pseudintermedius* have not been defined, although our research group recently described a patient cohort with a median age of 61 suggesting that older adults may be at higher risk [3]. Working in the veterinary field is another plausible risk factor, and in a study of veterinarians, 5/128 (3.9%) sampled were MRSP colonized [20]. Individuals with open wounds or medical devices, who are in close contact with dogs, may also be at increased risk for *S. pseudintermedius* colonization and infection. Decolonization therapy in dogs is not currently recommended, nasal mupirocin is difficult to administer effectively and does not address enteral colonization. Similarly, the efficacy of systemic decolonization therapies has not been evaluated. It may be advisable for physicians to consider routine questions about animal contact in patients who have infections such that zoonotic transmission can be recognized.

Future perspective

Use of highly discriminatory microbiological methods has allowed us to identify *S. pseudintermedius* as an emerging potential pathogen of zoonotic origin. The ability of this organism to cause human infections highlights its lack of host specificity, and the importance of considering inter-species transmission. The close contact between people and their pets ostensibly presents unique opportunities for the transmission of bacteria including staphylococci, in similar fashion to well recognized food-borne zoonoses. Larger prospective laboratory-based and clinical studies of human *S. pseudintermedius* infections are required to better understand the epidemiology, risk factors and transmission characteristics of this organism.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- Devriese L, Vancanneyt M, Baele M *et al.* *Staphylococcus pseudintermedius* sp. nov., a coagulase-positive species from animals. *Int. J. Syst. Evol. Microbiol.* 55, 169–173 (2005).
- Rubin J, Chirino-Trejo M. Prevalence, sites of colonization, and antimicrobial resistance among *Staphylococcus pseudintermedius* isolated from healthy dogs in Saskatoon, Canada. *J. Vet. Diagn. Invest.* 23, 351–354 (2011).
- Somayaji R, Madalagama R, Rubin J *et al.* Human infections due to *Staphylococcus pseudintermedius*, an emerging zoonoses of canine origin: a report of 24 cases. *Diagn. Microbiol. Infect. Dis.* 85(4), 471–476 (2016).
- Fitzgerald J. The *Staphylococcus intermedius* group of bacterial pathogens: species re-classification, pathogenesis and the emergence of methicillin resistance. *Vet. Dermatol.* 20(5–6), 490–495 (2009).
- Perreten V, Kadlec K, Schwarz S *et al.* Clonal spread of methicillin-resistant *Staphylococcus pseudintermedius* in Europe and North America: an international multicentre study. *J. Antimicrob. Chemother.* 65(6), 1145–1154 (2010).
- Van Duijkeren E, Catry B, Greko C *et al.* Review on methicillin-resistant *Staphylococcus pseudintermedius*. *J. Antimicrob. Chemother.* 66(12), 2705–2714. (2011).
- Bannoehr J, Guardabassi L. *Staphylococcus pseudintermedius* in the dog: taxonomy, diagnostics, ecology, epidemiology and pathogenicity. *Vet. Dermatol.* 23(4), 253–266 (2012).
- Van Hoovels L, Vankeerberghen A, Boel A *et al.* First case of *Staphylococcus pseudintermedius* infection in a human. *J. Clin. Microbiol.* 44(12), 4609–4612 (2006).
- Borjesson S, Gomez-Sanz E, Ekstrom K *et al.* *Staphylococcus pseudintermedius* can be misdiagnosed as *Staphylococcus aureus* in humans with dog bite wounds. *Eur. J. Clin. Microbiol. Infect. Dis.* 34(4), 839–844 (2015).
- Weese JS, Van Duijkeren E. Methicillin-resistant *Staphylococcus aureus* and *Staphylococcus pseudintermedius* in veterinary medicine. *Vet. Microbiol.* 140(3–4), 418–429 (2010).
- Moodley A, Damborg P, Nielsen SS. Antimicrobial resistance in methicillin susceptible and methicillin resistant *Staphylococcus pseudintermedius* of canine origin: literature review from 1980 to 2013. *Vet. Microbiol.* 171(3–4), 337–341 (2014).
- Priyantha R, Gaunt MC, Rubin JE. Antimicrobial susceptibility of *Staphylococcus pseudintermedius* colonizing healthy dogs in Saskatoon, Canada. *Can. Vet. J.* 57(1), 65–69 (2016).
- Wu MT, Burnham CA, Westblade LF *et al.* Evaluation of oxacillin and cefoxitin disk and MIC breakpoints for prediction of methicillin resistance in human and veterinary isolates of *Staphylococcus intermedius* group. *J. Clin. Microbiol.* 54(3), 535–542 (2016).
- Institute CLS. Performance standards for antimicrobial susceptibility testing. M100S (2016). <http://shop.clsi.org/c.1253739/site/>
- Humphries RM, Wu MT, Westblade LF *et al.* *In vitro* antimicrobial susceptibility of *Staphylococcus pseudintermedius* isolates of human and animal origin. *J. Clin. Microbiol.* 54(5), 1391–1394 (2016).
- Gomez-Sanz E, Torres C, Ceballos S *et al.* Clonal dynamics of nasal *Staphylococcus aureus* and *Staphylococcus pseudintermedius* in dog-owning household members. Detection of MSSA ST(398). *PLoS ONE* 8(7), e69337 (2013).
- Walther B, Hermes J, Cuny C *et al.* Sharing more than friendship-nasal colonization with coagulase-positive staphylococci (CPS) and co-habitation aspects of dogs and their owners. *PLoS ONE* 7(4), e35197 (2012).
- Johnson JR, Owens K, Gajewski A *et al.* *Escherichia coli* colonization patterns among human household members and pets, with attention to acute urinary tract infection. *J. Infect. Dis.* 197(2), 218–224 (2008).
- Starlander G, Borjesson S, Gronlund-Andersson U *et al.* Cluster of infections caused by methicillin-resistant *Staphylococcus pseudintermedius* in humans in a tertiary hospital. *J. Clin. Microbiol.* 52(8), 3118–3120 (2014).
- Paul NC, Moodley A, Ghibaud G *et al.* Carriage of methicillin-resistant *Staphylococcus pseudintermedius* in small animal veterinarians: indirect evidence of zoonotic transmission. *Zoonoses Public Health* 58(5), 533–539 (2011).