Case Series

Staphyloccus intermedius group infections in humans: report of four cases and a literature review

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Introduction: Staphyloccus intermedius group (SIG) comprises coagulase-positive staphylococci isolated from veterinary wounds, with anecdotal association of this pathogen and disease in humans. To date, 28 human cases have been described in the literature. Here, we described four cases of human infection caused by SIG members and, through a literature review, identified potential common characteristics and risk factors for this infection.

Case presentations: Cases were obtained via electronic query of existing microbiology records for S. intermedius isolates at three teaching hospitals in Denver, CO, USA, between 2003 and 2008. Four cases were identified. Three cases were soft tissue and/or bone infection and one case was a urinary tract infection.

Conclusion: Staphyloccus intermedius infections in humans are rarely identified. Dog ownership as well as diabetes or other causes of immunosuppression may place patients at higher risk. Misidentifying SIG infections could lead to delays in treatment as well as undertreatment of this zoonosis.

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Introduction

The Staphyloccus intermedius group (SIG) comprises Staphyloccus intermedius, Staphyloccus pseudintermedius and Staphyloccus delphini groups A and B, coagulase-positive organisms that are frequently misclassified as coagulase negative (Pottumarthy et al., 2004). SIG members have been identified as a cause of disease in humans, and there is a rising number of methicillin-resistant cases in dogs, with a reported frequency in the USA reaching 17 % of all canine cases in 2004 (Morris et al., 2006). There is evidence of horizontal transmission of this pathogen between pet dogs and their owners. Given the above, SIG isolates are important pathogens of canines and humans, and warrant further study.

SIG isolates cause a unique spectrum of human zoonotic infections that may be significantly under-recognized due to their frequent misclassification as coagulase-negative staphylococci (CNS). While this pathogen is a coagulase-positive organism, the characteristics of its coagulase differ slightly from Staphyloccus aureus coagulase (Raus & Love, 1983; Harvey et al., 1994; Komori, et al.; 2001). This difference may lead to misidentification of S. intermedius as a coagulase-negative organism, and consequently to classification as a contaminant. Most medical microbiology laboratories use rapid coagulase tests (slide coagulase) as a screening method. These tests detect the presence of cell-bound protein A, which is absent in the cell wall of over 95 % SIG isolates (Cox et al., 1986; Cox et al., 1985; Lachica et al., 1979), and clumping factor, which is rarely (14 %) present in S. intermedius isolates. Results of the slide coagulase test in SIG isolates are variable, being reported as negative in up to 90 % of cases (Bond & Loeffler, 2012). Tube coagulase tests are typically positive in SIG isolates because they detect the presence of free coagulase (Bond & Loeffler, 2012). Thus, laboratory protocols that identify staphylococ-
cal isolates that are coagulase negative on a slide test may misidentify SIG isolates. Accurate identification is provided by automated methods such as Microscan, but only if the isolates are tested in that system and not discarded based on a negative slide coagulase test. Newer test methods may also provide accurate identification. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has been proved to be a useful, rapid, inexpensive and reliable method to identify bacterial isolates belonging to SIG (Decristophoris et al., 2011).

The primary objective of this review was to describe four cases of patients diagnosed with SIG infections in our hospitals. By performing a literature review, we also addressed our secondary objective, which was to identify common characteristics and thus provide our cases with a historical and clinical context.

**Case series**

This study was performed at three teaching hospitals in Denver, CO, USA. Denver Health Medical Center (DHMC) is a 470-bed urban academic safety net, level 1 trauma centre and teaching institution with 12 community health centres and cares for approximately one-third of Denver’s population. The Department of Veterans Affairs Medical Center – Denver (DVAMC-Denver) is a teaching hospital with 137 acute-care beds and 60 long-term care beds at the Denver campus. The University of Colorado Hospital (UCH) is a 440-bed academic institution with six community health centres.

Cases were obtained via electronic query of existing microbiology records at all three institutions. All isolates obtained on site from January 2003 to October 2008 were reviewed to identify patients with a positive culture for SIG isolates.

Isolates identified as catalase-positive Gram-positive cocci were subjected to a slide coagulase test. When the slide coagulase test was positive, colony morphology was assessed for its consistency with *S. aureus*. Coagulase-positive isolates with a colony morphology inconsistent with *S. aureus* were subjected to an automated identification using a Microscan (Siemens Healthcare Diagnostics) at UCH, a Microscan at DVAMC-Denver or a Microscan Walkaway 96Plus System (Siemens Healthcare Diagnostics) at DHMC. These techniques are used routinely in all three hospitals. If the slide coagulase test result is negative, DHMC will identify the isolate as CNS, while both UCH and DVAMC will perform a colony morphology assessment followed by a tube coagulase test (UCH) or a pyrrolidonyl arylamidase activity and ornithine decarboxylase test (DVAMC) if deemed appropriate by the microbiology technician. Both UCH and DVAMC follow up results with automated identification using the Microscans specified above for further identification.

For patients with a positive culture for *S. intermedius*, the medical record was reviewed for site of infection or colonization, demographic characteristics, predisposing conditions [diabetes mellitus (DM), immunosuppression other than DM and dog ownership], treatment and outcome.

The study protocol was reviewed and approved by the Colorado Multiple Institutional Review Board and the Veterans Affairs Eastern Colorado Health Care System Research Review Group.

A total of three SIG cases were identified at DVAMC-Denver (cases 1, 2 and 3), one case at the UCH (case 4) and no cases at DHMC in the 5-year period. Two of the cases at DVAMC and the UCH case were diagnosed in 2006. The third case at DVAMC was identified in 2008. In the same time period, 2175 cases of *S. aureus* infection were identified at DVAMC, more than 8000 cases at UCH and 7308 cases at DHMC. The case demographic characteristics are summarized in Table 1.

**Case 1**

Case 1 was a 61-year-old male with a history of diabetes and multiple foot infections who initially presented to the Emergency Department for evaluation of ongoing foot infection. He had undergone treatment with amoxicillin/clavulanate followed by outpatient treatment with cephalixin. His initial wound culture grew an SIG isolate, which was susceptible to commonly used antimicrobials, including cefazolin and oxacillin. On physical examination, he was noted to have multiple amputated toes as well as a 0.4 cm superficial ulceration with surrounding erythema on his right foot. One month later, the patient was readmitted with cellulitis and oedema of his right lower extremity. Physical examination revealed multiple ulcerations on this extremity. He received treatment with intravenous vancomycin and was discharged home to

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**Table 1. Demographics of the four cases in this study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>53</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>Site of infection</td>
<td>Soft tissue, right foot</td>
<td>Soft tissue, right leg</td>
<td>UTI</td>
<td>Soft tissue and bone, left heel</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dog owner</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
complete a 10-day treatment with doxycycline. The patient died at a later hospital admission, outside the Veterans Affairs system, due to traumatic head injury.

Case 2

Case 2 was a 53-year-old male with a history of diabetes who suffered a traumatic injury on his right lower extremity. He was initially seen by an outside physician who performed wound care and initiated antibiotic treatment (not specified in chart). Wound healing was complicated by dehiscence, and local wound care was attempted. Four months later, he presented to the podiatry clinic for a non-healing ulcer requiring surgical debridement. On physical examination, a posterior right calf lesion measuring 5 mm in diameter and 8 mm in depth was noted. The wound was incised and drained and subsequent cultures grew pan-susceptible SIG. The patient had died at the time of chart review and no further documentation on the cause of death was found.

Case 3

Case 3 was an 81-year-old male with a history of diabetes and a chronic indwelling urinary catheter who presented to the Emergency Department after failing outpatient treatment for a urinary tract infection (UTI). He had completed 15 days of oral levofloxacin. A repeat urine culture was obtained and he was discharged home on trimethoprim/sulfamethoxazole. After discharge, his urine culture was reported to be positive for SIG. He was readmitted to the hospital 3 days later for altered mental status, fever and abnormal urinalysis (20-50 white blood cells per High Power Field or HPF and >50 red blood cells per HPF, proteinuria, positive nitrite and high leukocyte esterase) thought to be secondary to a complicated UTI. Repeat cultures showed an SIG isolate that was resistant to oxacillin and ciprofloxacin. The patient was started on vancomycin, which resulted in a marked clinical improvement and resolution of fever. The patient was discharged home after completing 15 days of intravenous antibiotic treatment.

Case 4

Case 4 was a 50-year-old female with a history of diabetes who was admitted for surgical debridement of a left heel ulcer. Cultures were obtained during the procedure. Soft tissue and bone cultures were positive for multiple organisms including SIG (initially reported as CNS) resistant only to tetracycline and erythromycin, Candida albicans, mixed anaerobes and two different strains of CNS. The patient was treated initially with intravenous clindamycin, which was subsequently switched to moxifloxacin, fluconazole and rifampicin. She completed 6 weeks with this regimen. One year later, she underwent calcaneal resection for a chronic ulcer complicated by osteomyelitis. The following year, she sustained a traumatic right ankle fracture complicated by osteomyelitis requiring a below-the-knee amputation. All subsequent cultures, after the initial SIG isolate, grew mixed flora with many CNS. She has since had multiple prolonged hospital admissions due to soft tissue and bone infection.

Discussion

SIG isolates commonly colonize dog owners, and have been isolated from canine-inflicted wounds in humans and as a pathogen in systemic infections in immunocompromised patients (Talan et al., 1989a; Goldstein, 1992; Lee, 1994). Since their first description by Hajek (1976), SIG isolates have been recognized as commensal organisms of oral, nasal and skin flora in dogs, foxes, minks and horses, among other animals, and can cause invasive disease in these animals. In dogs, SIG infection is the dominant cause of skin disease and otitis. In 2009, it was reported that most isolates from canines that are identified as S. intermedius proved to be S. pseudintermedius by molecular analysis (Devriese et al., 2009; Sasaki et al., 2007). Although the clinical significance of this distinction is unclear, for the sake of accuracy, the term SIG is used in this report (Talan et al., 1989b).

We identified four cases of SIG infections in humans via electronic query of existing microbiology records at three teaching hospitals in Denver between 2003 and 2008. Three cases were soft tissue and/or bone infections and one case was a UTI. We compared our cases with those described previously in the literature.

Previously published reports on SIG were identified via a PubMed search for articles in English and Spanish from January 1976 to October 2014 using the medical subject heading terms and keywords ‘Staphylococcus intermedius’, ‘staphylocoagulases’ and ‘dog bite infections’, alone or in combination. Similar search parameters were used in Google Scholar. A total of 72 articles were identified.

Several case reports describe human colonization with SIG. In a series of 56 healthy subjects aged 22–43 years from Iwate, Japan, SIG isolates were found in 8.9 % of the subjects’ saliva and dental plaque samples (Ohara-Nemoto et al., 2008). A study from Denmark in 2004 investigated the incidence of SIG infection in 13 dog owners with pyoderma compared with a control group of subjects with pyoderma who did not own a dog (Guardabassi et al., 2004). S. intermedius was isolated in 48 % of the dog owners compared with only 8 % of non-dog owners tested. Another series from France showed that out of 3397 consecutive isolates of coagulase-positive staphylococci cultured from hospitalized patients, only two were confirmed to be SIG; however, it was unclear from the publication which coagulase test (slide or tube test) was performed as the screening method for detecting the presence of coagulases or whether SIG was linked to disease (Mahoudeau et al., 1997). While it has not yet been reported as a pathogen in food-borne illnesses, there is evidence that S. intermedius isolates from both veterinary and human samples have a 9 % prevalence of the staphylococcal enterotoxin C gene, and of these isolates, 93 % produced enterotoxin in vitro (Becker et al., 2001).

http://fmmcr.sgmjournals.org
Table 2. SIG case reports from January 1976 to October 2014

CABG, coronary artery bypass graft; F, female; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD, implantable cardioverter-defibrillator; IVDU, intravenous drug use; M, male; NSCLC, non-small-cell lung cancer; ND, not documented in publication.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Site of infection</th>
<th>DM</th>
<th>Dog owners</th>
<th>MRSIG</th>
<th>Age (years) and sex of patient where known</th>
<th>Predisposing factors other than DM</th>
<th>Recent surgery</th>
</tr>
</thead>
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<tr>
<td>Talan et al. (1989)</td>
<td>Dog bite</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>45/M</td>
<td>ND</td>
<td>No</td>
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<td>Talan et al. (1989)</td>
<td>Dog bite</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>20/M</td>
<td>ND</td>
<td>No</td>
</tr>
<tr>
<td>Talan et al. (1989)</td>
<td>Dog bite</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>34/F</td>
<td>ND</td>
<td>No</td>
</tr>
<tr>
<td>Barnham &amp; Holmes (1992)</td>
<td>Dog bite</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>78/M</td>
<td>ND</td>
<td>No</td>
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<tr>
<td>Lee (1994)</td>
<td>Skin infection</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>Elderly</td>
<td>Varicose ulcer</td>
<td>No</td>
</tr>
<tr>
<td>Lee (1994)</td>
<td>Skin infection</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>Elderly</td>
<td>Varicose ulcer</td>
<td>No</td>
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<tr>
<td>Lee (1994)</td>
<td>Skin infection (suture line)</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>13</td>
<td>Recent suture</td>
<td>Yes</td>
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<td>Llorca et al. (1992)</td>
<td>Infective endocarditis</td>
<td>No</td>
<td>ND</td>
<td>ND</td>
<td>M</td>
<td>HIV</td>
<td>No</td>
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<td>Vandenesch et al. (1995)</td>
<td>Venous catheter-related bacteraemia</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>63/M</td>
<td>NSCLC</td>
<td>ND</td>
</tr>
<tr>
<td>Gerstads et al. (1999)</td>
<td>Healthcare-associated pneumonia</td>
<td>Yes ND</td>
<td>Yes</td>
<td>ND</td>
<td>73/M</td>
<td>Status post-CABG</td>
<td>Yes</td>
</tr>
<tr>
<td>Talan et al. (1999)</td>
<td>Dog bite</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Talan et al. (1999)</td>
<td>Cat bite</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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</tr>
<tr>
<td>Tanner et al. (2000)</td>
<td>Otitis</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>38/F</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Kikuchi et al. (2004)</td>
<td>Mastoiditis</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>51/F</td>
<td>ND</td>
<td>Yes</td>
</tr>
<tr>
<td>Pottumarthy et al. (2004)</td>
<td>Cellulitis/nail bed infection</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
<td>60/F</td>
<td>Chemotherapy/breast cancer</td>
<td>No</td>
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<tr>
<td>Pottumarthy et al. (2004)</td>
<td>Cellulitis</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
<td>37/M</td>
<td>Laceration on affected extremity</td>
<td>No</td>
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<td>Atalay et al. (2005)</td>
<td>Brain abscess</td>
<td>No</td>
<td>ND</td>
<td>Yes</td>
<td>4/M</td>
<td>ND</td>
<td>ND</td>
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<td>Van Hoovels et al. (2006)*</td>
<td>ICD pocket infection</td>
<td>No</td>
<td>ND</td>
<td>No</td>
<td>60/M</td>
<td>Prostate cancer (cardiomyopathy)</td>
<td>ND</td>
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<td>Campanile et al. (2007)</td>
<td>Catheter-related bacteraemia</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>Gastric adenocarcinoma</td>
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<td>Kempker et al. (2009)</td>
<td>Sinusitis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
</tr>
<tr>
<td>Kelesidis &amp; Tsiodras (2010)</td>
<td>Skin abscesses</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>43/M</td>
<td>IVDU/HCV + licking needles</td>
<td>No</td>
</tr>
<tr>
<td>Erne et al. (2010)</td>
<td>Brain abscess/CAP</td>
<td>ND</td>
<td>ND</td>
<td>No</td>
<td>61/M</td>
<td>ND</td>
<td>No</td>
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<td>Durdik et al. (2010)</td>
<td>Meningitis</td>
<td>No</td>
<td>ND</td>
<td>No</td>
<td>11 months</td>
<td>ND</td>
<td>No</td>
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<td>Stegmann et al. (2010)*</td>
<td>Surgical wound infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>ND/M</td>
<td>Recurrent sinusitis</td>
<td>Yes</td>
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<tr>
<td>Chuang et al. (2010)*</td>
<td>Catheter-related bacteraemia</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>6/M</td>
<td>Haemophilia B</td>
<td>No</td>
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<td>Riegel et al. (2011)*</td>
<td>ICD-related endocarditis</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>70/F</td>
<td>Cardiomyopathy</td>
<td>ND</td>
</tr>
<tr>
<td>Hatch et al. (2012)</td>
<td>Bacteraemia (septic arthritis)</td>
<td>Yes ND</td>
<td>Yes</td>
<td>ND</td>
<td>76/M</td>
<td>Myelodysplastic syndrome</td>
<td>No</td>
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<tr>
<td>Wang et al. (2013)</td>
<td>Surgical wound on elbow</td>
<td>ND</td>
<td>Yes</td>
<td>No</td>
<td>73/F</td>
<td>ND</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Staphylococcus pseudintermedius.
CAP, community acquired pneumonia
To date, a total of 28 cases of documented human infection caused by SIG isolates have been reported in the English literature (Raus & Love, 1983; Talan et al., 1989a; Barnham & Holmes, 1992; Goldstein, 1992; Llorca et al., 1992; Lee, 1994; Imamura et al., 1995; Vandenesch et al., 1995; Gerstadt et al., 1999; Talan et al., 1999; Tanner et al., 2000; Kikuchi et al., 2004; Pottumarthy et al., 2004; Atalay et al., 2005; Van Hoovels et al., 2006; Campanile et al., 2007; Kempker et al., 2009; Chuang et al., 2010; Durdik et al., 2010; Erne et al., 2010; Kelesidis & Tsiodras, 2010; Stegmann et al., 2010; Riegel et al., 2011; Hatch et al., 2012; Wang et al., 2013) as presented in Table 2. Seventeen patients of the 28 cases documented were known to be dog owners (dog ownership was not documented in eight cases) and seven had meticillin-resistant SIG (MRSIG). The causes of immunosuppression or predisposing factors other than DM were documented for 15 cases, and seven had undergone recent surgery or laceration repair. Four of the cases were documented as S. pseudintermedius.

Our data adds one case of catheter-related UTI, an infection site that has not been reported previously, one case of osteomyelitis and two cases of skin and soft tissue infection.

Only a few of the reports of SIG infection found in the literature discriminated between the type of coagulase test used. Two publications reported a negative slide coagulase test with a positive tube coagulase test (Gerstadt et al., 1999; Kempker et al., 2009), one case had both tests positive (Talan et al., 1989a), one reported the use of a tube coagulase test (Vandenesch et al., 1995) and Talan et al. (1989a) only analysed cases that were slide coagulase positive. None of our four cases had tube coagulase testing performed; they were either positive in a slide test or identified via an automated method. Three of our four cases involved soft tissue and/or bone, and two of these patients were known to own dogs. We also reported a case of UTI secondary to SIG infection in a human; although this does not appear to be novel in animals (Ling et al., 1984), to the best of our knowledge, this is the first reported case of SIG UTI in humans. Based on our findings, diabetic patients (4/4) seem to be at higher risk; however, of the 28 cases reported in literature, 15 had no remarks on the presence of DM as co-morbidity.

We have presented the largest case series of SIG infections published thus far and confirmed human infection with MRSIG. In our series, we noted a low frequency of isolation of SIG isolates. All patients were diabetic, two patients were known to own dogs and one patient was found to have a MRSIG infection. The ratio of males to females was 3:1, probably associated with the inclusion of the Veterans Affairs population. This was a retrospective case analysis based on laboratory records and it is unknown to us how many cases may have been missed in our hospitals. Routine identification procedures in microbiology laboratories are likely to lead to misidentification of this organism as CNS.

There have been numerous publications describing differences in staphylococcal enzymes among staphylococci (S. aureus, SIG, Staphylococcus schleiferi and Staphylococcus hyicus) (Morris et al., 2006; Epstein et al., 2009; Sasaki et al., 2010); however only two reports of misidentification of SIG as coagulase negative in humans have been reported (Gerstadt et al., 1999; Kempker et al., 2009). Mahoudeau et al. (1997) described a very low rate (2/3397) of SIG among coagulase-positive staphylococci, but they did not specify which coagulase test was used when performing the initial coagulase screening of the staphylococci.

Interestingly, MRSIG has been described as being carried by humans as well as animals, and horizontal transmission has been proven (Guardabassi et al., 2004; van Duijkeren et al., 2008; Rutland et al., 2009). Meticillin-resistant Staphylococcus intermedius has been mistakenly called meticillin-resistant S. aureus (MRSA) in more than a few human cases (Pottumarthy et al., 2004), when a PBP2a latex agglutination test was performed on the isolate. In our series, case 3, who had MRSIG in his urine culture, tested positive for nasal MRSA colonization by Cepheid PCR, which was later confirmed by nasal culture. To date, there are no reports of PCR misidentification between S. intermedius and S. aureus, as the Cepheid PCR detects the mecA gene and the insertion site within S. aureus.

The most important limitation to our study was the small sample size. This could be secondary to a very low incidence of SIG infections in humans as currently believed, versus its misclassification as CNS, as the test used for screening is not designed to identify SIG. Furthermore, it should be pointed out that DHMC had no identified SIG cases. Notably, DHMC’s microbiology laboratory methods differ from those used at the DVAMC and UCH.

The true incidence of SIG isolates as human pathogens remains to be determined. We speculate that MRSIG/metincillin-sensitive SIG infections are underreported, being misidentified as meticillin-sensitive S. aureus/MRSA or CNS. Further epidemiological surveillance, determination of predisposing factors and efforts towards proper identification of staphylococci are needed as both meticillin-sensitive S. aureus and MRSIG have the potential to become an emergent public health problem. The similarity of SIG isolates to S. aureus, which includes its virulence, resistance pattern and even enterotoxigenic potential, as well as the fact that it is carried by ‘man’s best friend’, make appropriate microbiological identification imperative.

References


Kelesidis, T. & Tsiodras, S. (2010). *Staphylococcus intermedius* is not only a zoonotic pathogen, but may cause skin abscesses in humans after exposure to saliva. *Int J Inf Dis* 14, e838–e841.


