Review

An overview of human infections caused by *Staphylococcus pseudintermedius*: A zoonotic risk of the oldest friend

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Abstract

Staphylococcus pseudintermedius is colonized in 90% of healthy dogs and the infection has also been reported in humans who have close contact with dogs. *S. pseudintermedius* is a Gram positive coagulase positive coccus which is an opportunistic pathogen. Human infection has been reported less frequently either due to misidentification or misdiagnosis or to underreporting. The objective of this overview is to highlight the epidemiology, clinical presentation, importance of laboratory tests and antimicrobial resistance of *S. pseudintermedius* in humans.

Human infections of *S. pseudintermedius* have been reported as case studies or clusters of infections in the literature. Several cases have been reported among the adult population, and in patients with metabolic diseases such as diabetes mellitus, immunocompromised states such as AIDS, cancers, and autoimmune diseases. The organism had been isolated and identified both in healthy people and individuals with adverse clinical outcomes. *S. pseudintermedius* causes skin and soft tissue infections, catheter associated infections and surgical site infections in humans. The incidence of skin and soft tissue infection by *S. pseudintermedius* in humans was 0.025% in Canada. Methicillin resistance *S. pseudintermedius* (MRSP) has been isolated both in healthy people and associated with clinical infections. MRSP is often multidrug resistant and therapeutic options are limited. Multidrug resistance has been detected in methicillin susceptible *S. pseudintermedius* (MSSP). Close association of a canine host is the major risk factor in humans and vulnerable individuals need to be persuaded to practice hygienic practices to minimize the risk of zoonotic infection.

In conclusion, differentiation of *S. pseudintermedius* from *S. aureus* is required to understand the epidemiology of the disease, diagnosis, clinical presentation, and further interpretation of antimicrobial resistance in the human clinical context. Suitable hygienic practices post handling of dogs and improvement of laboratory facilities would help minimize the incidence of *S. pseudintermedius* infections in humans.

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Introduction

The nomenclature of *S. pseudintermedius* is quite complicated, *S. pseudintermedius, S. intermedius* and *S. delphini* are collectively called *S. intermedius* group.[1] *S. pseudintermedius* is a coagulase positive Gram positive coccus which colonizes 90% of healthy dogs.[2] It is an opportunistic pathogen, and the most common cause of canine pyoderma, otitis externa and the second commonest cause of urinary tract infection in dogs.[3] Zoonotic infections have been reported worldwide with a range of clinical presentations.[4] However, reporting of this organism from human samples is rare.[5] The organism is often misidentified as *S. aureus* due to cultural, morphological and biochemical similarity.[6,7,8] Importantly, since *S. aureus* is the dominant pathogen in humans and both *S. aureus* and *S. pseudintermedius* are coagulase positive, laboratory misidentification is a possible reason for the low number of reports.[6] Differentiation of *S. pseudintermedius* from *S. aureus* is therefore required for further identification. The objective of this overview is to highlight the epidemiology, clinical presentation, importance of laboratory tests and antimicrobial resistance of *S. pseudintermedius* in humans.

Normal habitat

The canine family is the primary reservoir of *S. pseudintermedius.*[5] Although *S. pseudintermedius* is also found in cats and equines, it is primarily found in dogs, and has also been isolated in humans as either a coloniser or pathogen. Nasal colonization in methicillin resistant *S. pseudintermedius* (MRSP) has been reported in healthy people.[9] The organism colonizes 90% of healthy dogs and their saliva contains *S. pseudintermedius.*[6]

Epidemiology

Importantly, *S. pseudintermedius* was isolated from healthy pet owners and other household members with no clinical disease.[10,11] *S. pseudintermedius* had been detected in veterinary surgeons who medicate dogs and cats, both as a coloniser or a pathogen.[12,13] The bacterium had been isolated in veterinary health care providers, workers in vet hospitals, and also in dog owners.[14,15] Therefore, isolation of the organism is not an indicator of an infection either in dogs or humans. However, detection of the organism with an associated clinical infection is evidence of an infection in dogs and humans. The history of the patient is important to find the source of this bacterial infection in human.

In addition, economic significance or outcome of *S. pseudintermedius* has not been evaluated in humans. We searched Pubmed with keywords of "*Staphylococcus pseudintermedius*", "dogs", and "Sri Lanka". Only one publication was found from Sri Lanka as a collaborative project with a laboratory in the Netherlands.[2] Human infections caused by *S. pseudintermedius* have not been reported from Sri Lanka.

Pathogenesis of *Staphylococcus pseudintermedius* infection in humans

The pathogenesis of human *S. pseudintermedius* infection has not been fully understood. It is assumed that similar virulence mechanisms are found in *S. pseudintermedius* and *S. aureus.*[11] Panton valentine leukocidin (pvl), exfoliative toxins and other virulence factors such as coagulase, lipases, protein A and beta hemolysin may play a major role in the process of pathogenicity.[16] *S. pseudintermedius* sequence type (ST) 71 which was the world epidemic clone has been observed to have high affinity and a high degree of adherence to human corneocytes.[17] It is possible therefore that ST 71 may adhere to human skin more than any other ST type of *S. pseudintermedius*.

Being an opportunistic pathogen, *S. pseudintermedius* causes secondary infection in humans.[17] The majority of clinical cases were shown among the adult population, and in patients with metabolic disease such as diabetes mellitus, or with an immunocompromised disease, and in patients with AIDS, cancers and autoimmune diseases.[6,17-19] In addition, surgical interventions have been recognized as a potential risk factor in infection of a healthy human, while the clinical condition may be aggravated and worse in immunosuppressed people.[6] Although human to human transmission has not been reported in *S. pseudintermedius*, acquiring human infection through dogs have been investigated using different molecular techniques.[15,16] People who have close association with dogs have been grouped into vulnerable populations such as animal handlers, veterinarians, and veterinary technicians.[2] Therefore, close friendship with dogs by immune suppressed owners or senior citizens with canine companions require extra precautions including maintaining good personal hygiene (personal observation). Similar guidelines need to be followed after surgical intervention; limited contact with companion animals is advisable.

Clinical presentation of infection caused by *Staphylococcus pseudintermedius*

Reporting of zoonotic infection caused by *S. pseudintermedius* as case studies and collection of clusters of infections has increased in the literature.[6,7] A couple of papers highlighted that dog bite wounds were the commonest cause of human infection by *S. pseudintermedius.*[19,20] Therefore, looking for *S. pseudintermedius* in dog bite wounds is required since the organism is common in the oral cavity, pharynx and saliva of dogs.[1]

S. pseudintermedius had been observed with skin and soft tissue infection in humans.[6] A study by Somayaji R et al (2016) has discussed and reported the incidence of human *S. pseudintermedius* infection in Calgary, Canada, during the period 2013-15.[6] The bacterium had been isolated in 18 patients who reported with skin and soft tissue infections.[6,7] Most of the skin and soft tissue infections by *S. pseudintermedius* in humans were found on the lower limb.[6] The annual rate in culture positivity of *S. pseudintermedius* in skin and soft tissue infections was reported as 0.025%.[6] The patients were mostly managed as outpatients as admission to hospital was not required.[6] Importantly, most cases were reported as polymicrobial infection.[6] Moreover, skin infections of *S. pseudintermedius* were observed as common in adults or senior citizens who have close contact with a canine host.[4,6]

Bacteremia caused by *S. pseudintermedius* had been reported less frequently.[6,18] The incidence of blood stream infection was as low as 3.48/1000 in humans.[6] In the same study, the incidence of

blood stream infection caused by *S. aureus* was 0.006/1000 in humans.[6] *S. pseudintermedius* bacteremia had been diagnosed in a 4-month-old paediatric oncology patient and a bone marrow transplanted leukaemia patient who suffered an invasive spinal infection.[21] Catheter related blood stream infection has also been reported in *S. pseudintermedius.*[22] Cleanliness and catheter care are vitally important in patients who have close contact with dogs.[23] Handling of dogs needs to be avoided or extra care taken by patients who have a vascular catheter.

The first human case of *S. pseudintermedius* was reported in a patient who had a cardioverter-defibrillator implant.[24] Secondary infections have been detected after an application of bone implant and surgical implant as spinal fixation devices.[25,26] In addition, *S. pseudintermedius* had been isolated in patients who developed peritoneal dialysis-associated peritonitis.[27] The organism had also been isolated in a graft-versus-host disease-related wound infection caused by a multidrug-resistant strain.[25] Furthermore, *S. pseudintermedius* had been isolated in a 50-year-old female patient who has a history of bilateral lung transplantation.[28] This patient also showed signs of sepsis, and had pneumonia, rheumatoid arthritis and severe osteoporosis.[29] *S. pseudintermedius* had been isolated from totally implantable venous access ports (TIVAP), and post-surgery purulent rhinosinusitis.[30,31]

Rhinosinusitis, endocarditis, prosthetic joint infection, external ear infection, urinary tract infection, catheter associated bacteremia and surgical site infections caused by *S. pseudintermedius* in humans have been reported.[4,6,8,19,32-35] The organism had been isolated in a patient who had chronic sinusitis and was in close association with dogs.[8] *S. pseudintermedius* has been isolated from patients with sarcoidosis, Crohn's disease, or a history of lymphoma.[36] *S. pseudintermedius* was isolated from a patient with hepatocellular carcinoma with a urinary tract infection.[31] *S. pseudintermedius* was also isolated and identified in complicated urinary tract infections in senior citizens.[33]

Table 1: Biochemical tests of *S. aureus* and *S. pseudintermedius*

Biochemical test	***S. aureus***	***S. pseudintermedius***
Colony morphology	*Yellow/golden colonies*	*Greyish-white opaque colonies*
Hemolysis	*Alpha or Beta hemolysis*	*Beta hemolysis*
Catalase test	Positive	Positive
Tube coagulase test	Positive	Positive
Slide coagulase test	Positive	**Varied**
Hyaluronidase test	Positive	**Negative**
DNase	Positive	Positive
VP test	Positive	Positive
D Mannitol	Positive	Positive
Moltose	Positive	Positive
Trehalose	Positive	Positive
Lactose	Positive	Positive
Pyrrodinyl acryl amidase	Positive	**Negative**
Beta galactosidase	Negative	**Positive**

Laboratory diagnosis

S. pseudintermedius is a Gram positive coccus which is readily grown on 5% sheep blood agar.[1,17] It produces 1-2 mm greyish white colonies on 5% sheep blood agar with a double zone of hemolysis.[35] The colonies of *S. aureus* are yellow on 5% sheep blood agar, with either complete or partial hemolysis.[3] The differentiation of these two species on overnight blood agar plates under refrigerator conditions is challenging due to cold induced hemolysis of both species of staphylococci. Although both organisms are coagulase positive, only tube agglutination test has been recommended in *S. pseudintermedius,* while slide agglutination often shown false negative results.[1] Further differentiation is

done by a series of biochemical tests as shown in Table 1. In addition, species specific PCR (both conventional and qPCR) molecular techniques are being used to differentiate the two organisms.[1]

It is believed that *S. pseudintermedius* is misdiagnosed in human diagnostic laboratories due to the similar colony morphology and lack of awareness of the fairly new and canine dominant coagulase positive staphylococci.[20] Consequently, underreporting of the organism and misidentification of this species is possible in diagnostic laboratories.[6,20] Characteristics of this species as described above are when the organism is grown on 5% sheep blood agar. However, diagnostic laboratories in Sri Lanka often use human blood (personal communication) and there is no available information on colony characteristics on human blood agar. A study of dog bite wounds and wounds in patients having a close association with canines with particular emphasis on *S. pseudintermedius* would be timely.

Antimicrobial resistance is a serious challenge both in human and animal medicine.[6] MRSP has been isolated both in healthy and clinical patients.[6,7] Importantly, MRSP and methicillin resistant *S. aureus* (MRSA) are resistant to all the beta lactam antibiotics, and resistance to other classes of antimicrobials is often found.[3,6] As in MRSA, MRSP is caused by the presence of the *mec*A gene in SCC_{mec} element which is usually found in a transposon.[6,37] In addition, multidrug resistance has been reported both in MRSP and methicillin susceptible *S. pseudintermedius* (MSSP) in humans.[6,38] Two major epidemic clones have been reported in MRSP as sequence type (ST) 71 and ST 68, both of which have also been reported in human clinical infections.[6] The antimicrobial susceptibility testing clinical break point against methicillin is different in *S. aureus* (Minimum inhibitory concentration of resistance in methicillin is >2mg/l) and *S. pseudintermedius* (Minimum inhibitory concentration of resistance in methicillin is >0.5mg/l).[39,40] Therefore, when the bacterium is misidentified, interpretation of methicillin resistance may be incorrect (Table 2). In addition, oxacillin with NaCl has been recommended in *S. pseudintermedius* instead of cefoxitin to detect methicillin resistance in the disk diffusion method.[40,41] These differences in testing and interpretation of antibiotic susceptibility are a strong reason for pursuing identification of *S. pseudintermedius* in both medical and veterinary clinical microbiology laboratories.

Table: 2, Interpretation of Clinical breakpoint in *S. aureus* and *S. pseudintermedius*
(Source from EUCAST clinical breakpoint 2022/01/01. CSLI[39,40,42])

The organism	Description	Resistant breakpoint	Reference
S. pseudintermedius	No clinical BP cefoxitin	For oxacillin ≥0.5 µg/ml (≤17 mm for the disk diffusion test)	CLSI VET 01 S3, 2015 and CLSI news update 2020
S. pseudintermedius	No BP for cefoxitin of MIC determination either by cefoxitin or oxacillin	Oxacillin: 20 mm (1µg disk)	EUCAST
S. aureus	(No zone diameter for the disk diffusion test)	>2 µg/ml for oxacillin and >8 µg/ml for cefoxitin (≤21 mm for disk diffusion test)	CLSI news update 2020
S. aureus	No BP for oxacillin. BP for cefoxitin for the disk diffusion test and no breakpoint for MIC has been described.	Cefoxitin: 22 mm	EUCAST

Although no extensive studies have been published, *S. pseudintermedius* is a biofilm producer which encourages the emergence of antimicrobial resistance in an atypical environment.[24]

Conclusion

Differentiation of *S. pseudintermedius* from *S. aureus* is important both for laboratory interpretation and clinical decision making. *S. pseudintermedius* can be the cause of a risky bacterial infection when the normal immune system is not functioning and with wounds following dog bites. Multidrug resistant isolates can be a threat with severe clinical infection. Awareness of this species with improvement of laboratory diagnostic capability is required for rapid diagnosis and optimum intervention in both animals and humans.

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