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Staphylococcus pseudintermedius: Is it a real threat to human health?

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Abstract

Staphylococcus Intermedius Group (SIG) staphylococci, especially *Staphylococcus pseudintermedius* (*S. pseudintermedius),* share many features with the common human *Staphylococcus aureus.* The similarities concern both the phenotypic characteristics and virulence of the bacteria. It is a cause of difficulties in identifying the species of isolated staphylococci. Until now, *S. pseudintermedius* was considered a typically animal species, of marginal importance for humans. However, it is likely that the incidence of this staphylococcus in humans is underestimated due to the misidentification of *S. pseudintermedius* strains as *S. aureus.* The cases of infections caused by *S. pseudintermedius* both in humans and animals described so far in the literature show that these bacteria have a similar pathogenic potential. *S. pseudintermedius* also produces virulence factors that favor colonization of various body regions and infections, and may affect the species composition of the natural microbiota and the host's immune response mechanisms. Also, *S. pseudintermedius* may show the ability to grow in the form of a biofilm, which significantly impedes effective antibiotic therapy in clinical practice. Due to its zoonotic potential, *S. pseudintermedius* deserves the attention of physicians and animal owners.

Keywords S. pseudintermedius • *SIG* • *zoonotic infections* • *Staphylococcus* • *biofilm* • *dogs* • *cats* • *multidrug resistance* • *virulence factors*

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Introduction

Staphylococci are ubiquitous, Gram-positive bacteria. Most of them are classified as opportunistic bacteria which inhabit the skin and the mucous membranes of various mammalian species. The composition of the natural microbiota differs between species and even between individuals, but several species of staphylococci colonize humans and animals more frequently. These include *S. aureus*, *S. epidermidis*, *S. haemolyticus*, *S. lugdunensis*, *S. saprophyticus*, and *S. warneri* in humans [1]; *S. felis*, *S. epidermidis*, *S. haemolyticus*, *S. xylosus,* and *S. aureus* in cats [2, 3]; and *S. pseudintermedius*, *S. aureus*, *S. haemolyticus* and *S. lentus* in dogs [4, 5, 6, 7]. Carriage of coagulase-positive *Staphylococcus aureus* is thought to present the greatest risk to humans. However, in dogs, and less so in cats, a similar risk is associated with colonization by *S. pseudintermedius* [5, 8]. Although it is primarily a *Staphylococcus* isolated from animals, cases of colonization and infections caused by *S. pseudintermedius* in humans have been increasingly reported in recent years, especially in people who have close contact with their animals. This is especially true for people who own dogs, which are natural carriers of *S. pseudintermedius* [8, 9, 10, 11, 12, 13].

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Description of the species

In taxonomic terms, this species falls into the Staphylococcus Intermedius Group (SIG), which includes three other coagulase-positive species: *S. delphini* and *S. intermedius* and the recently described *S. cornubiensis* [14, 15]. All staphylococci that belong to the SIG share many common features, such as the appearance of colonies (depending on the culture medium, they are usually round, smooth, shiny, opaque, white or grey colonies up to 1-2 mm in diameter after 24 hours of incubation), the ability to induce hemolysis on blood agar (presence of α- and β- hemolysins), rapid growth on nonselective media (e.g., nutrient agar – incubation at 37°C in 18–24 hours) and selective media (e.g., Chapman's medium – growth at 37°C in 24–48 hours) and are virtually indistinguishable in standard bacteriological examination [8, 9, 14, 16]. Therefore, for many years only one species, *S. intermedius*, was identified. Only in 2005, after analysis of genetic differences between individual isolates, separate species, including *S. pseudintermedius*, were distinguished [17]. Biochemical properties that differentiate *S. intermedius* strains from other SIG species include the ability to produce arginine dihydrolase and acid from β-gentiobiose under aerobic conditions and from D-mannitol under anaerobic conditions [9, 18]. Unfortunately, biochemical reactions do not unambiguously distinguish between *S. pseudintermedius* and *S. delphini* strains [9, 18, 19]. Therefore, molecular biology methods such as polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) using the restriction enzyme MboI [20] or multiplex-PCR detecting the gene encoding the thermonuclease (*nuc*) of coagulase-positive staphylococci [21] are necessary to identify SIG species. The use of mass spectrophotometry (matrix-assisted laser desorption ionization – time of flight mass spectrometry, MALDI-TOF MS) for assaying *S. pseudintermedius* from animals is also described, although some authors have demonstrated that the sensitivity of this method is still low [22].

Virulence factors

The species in question produce various virulence factors, some of which are similar to those produced by *S. aureus*. These factors favor the colonization of different body regions and promote infections [8, 23]. The determinants of *S. pseudintermedius* pathogenicity include adhesion factors - surface proteins involved in adhesion to host cells, as well as binding proteins (protein A, clumping factor - CF) - exoenzymes, exotoxins and superantigens. The following superantigens deserve special attention: TSST-1 (toxic shock syndrome toxine), exfoliative toxins, coagulase, staphylokinase, hyaluronidase, haemolysins, proteases and nucleases. The leukotoxin (Luk-I) produced by *S. pseudintermedius*, which resembles the Panton-Valentine leukocidin (PVL) produced by *S. aureus*, shows toxicity against multinucleated cells and macrophages, as well as CXCR2 receptor-presenting myeloid cells [8, 23, 24, 25]. Luk-I consists of the proteins LukS-I and LukF-I, which induce cell lysis [25]. Maali et al. [25] also indicate the production of δ-toxin and PSM, which exhibit potent cytotoxic activity against "non-professional phagocytic cells" (NPPc), e.g. dog keratinocytes, human epithelial cells and osteoblasts.

S. pseudintermedius can grow as a biofilm. Initial adhesion to the surface is mediated by MSCRAMM (microbial surface components recognizing adhesive matrix molecules) components such as *spsE*, *ebpS* and *atl*. Once adhered to the surface, an extracellular matrix is formed [26] [polysaccharide intercellular adhesion molecule – PIA (polysaccharide intercellular adhesin) or PNAG (polymeric N-acetyl-glucosamine)], which is encoded by the ica operon containing 4 distinct genes (A, B, C and D) [27, 28]. This is currently the best-known mechanism of biofilm formation in staphylococci.

A significant phenomenon that occurs in the bacterial biofilm is the ability of microorganisms to communicate using a "quorum-sensing" mechanism. This system is associated with the activity of the *agr* gene (accessory gene regulator) - *agrA*, *agrB* - involved in the regulation of biofilm structure and subsequent detachment of biofilm fragments [26]. However, the influence of the *agr* gene on the expression of *ica* and production of PIA/PNAG has not been demonstrated [28]. In staphylococci, cases of *ica*-independent biofilm production have also been reported, which are associated with the presence of the biofilm-associated protein (*bap*) and the transcription regulator *rbf* (regulator of biofilm formation) [28]. Staphylococcal biofilm is particularly difficult to control because it has increased resistance to antimicrobials and host immune response mechanisms, thus making antibiotic therapy difficult [8, 10, 23, 29]. In addition, as biofilm forms, strains permanently colonize abiotic surfaces, and this complicates the use of materials such as catheters, stents, and implants in human and veterinary medicine [29]. Biofilm formation by *S. pseudintermedius* has been studied by various authors, but it is still not fully understood and described. It has been shown that the percentage of *S. pseudintermedius* strains that were capable of forming a biofilm was up to 100% among the bacteria isolated, for example, from skin infections, wounds, hospital infections and surgical wounds [10, 30, 31]. Strains of *S. pseudintermedius* belonging to the dominant European ST71 type show a high ability for biofilm production and are often resistant to all types of antimicrobial drugs used in veterinary medicine [32, 33].

Drug resistance

As in the case of *S. aureus*, increasing resistance to commonly used chemotherapeutics has been observed among *S. pseudintermedius* strains in recent years. Methicillin-resistant *S. pseudintermedius* (MRSP) strains are isolated both from humans and animals [8, 13, 31, 34, 35, 36, 37]. Resistance to β-lactam antibiotics is most often associated with the presence of the *mecA* gene within the staphylococcal chromosomal cassette *mec* (SCC *mec*). As a mobile genetic element (MEG), it can be transferred horizontally between strains of the same or different *Staphylococcal* species [8, 9, 24, 36]. The SCC*mec* cassette is composed of the methicillin resistance determinant (*mecA*, *mecB*, or *mecC*) contained in the *mec* gene complex and includes site-specific *ccr* recombinase genes that are responsible for insertion of the cassette into the genome. It can also include a wide range of additional genes [38, 39, 40, 41]. SCC*mec* types were initially defined due to their combination of the *mec* gene complex class and the *ccr* recombinase gene. However, the classification of SCC*mec* elements and the use of the terminology have been complicated by the existence of composite cassettes and pseudo-SCC*mec* elements that do not contain *ccr* genes [41]. Currently, there are eleven SCC*mec* cassettes of MRSA strains in the International Working Group on the Staphylococcal Cassette Chromosome (IWG-SCC) database. They are numbered I to XI, according to the order in which they are described [41]; 13 major types of SCC*mec* cassette elements have been identified so far [40]. Although chromosome cassette sequences from strains other than *S. aureus* often vary from those identified in *Staphylococcus aureus*, all are classified as *ccrA*, *ccrB*, or *ccrC* [39]. In staphylococci other than *Staphylococcus aureus*, several additional *ccr* allotypes have been reported. For example, in *S. pseudintermedius* KM241, *ccrA*5 was identified as a counterpart to the *ccrA* gene [39]. Several SCC*mec* MRSP cassettes have been described, including SCC*mec* III (previously known as II-III), which is found in the globally dominant type ST71 as well as ST316 and ST25, variants of SCC*mec*VT, (ST496, ST64 and ST751) and the newly reported SCC*mec*NA45, which contains the *mec* class C1 gene and the *ccr*C recombinase gene.

Other SCC*mec* elements that are not recorded by IWG-SCC have also been described in *S. pseudintermedius*, for example SCC*mec*57395, which does not contain *ccr* genes, and SCC*mec*KM241 and SCC*mec*AI16 [38, 41]. As reported by Krapf et al. [40] in Central Europe, most MRSP isolates contain SCC*mec* III elements, followed by SCC*mec* IV and least frequently by SCC*mec* V/VT. Furthermore, SCC*mec* elements found in *S. pseudintermedius* have been shown to have significant similarity to those identified in MRSA strains, which suggests that interspecies transfer of mobile genetic elements is involved [8, 41].

Incidence in companion animals

Up to 92% of healthy dogs are carriers of *S. pseudintermedius* [25, 32]. This *Staphylococcus* can be isolated from many anatomical sites in healthy animals, including the ears, conjunctival sacs, nostrils, oral cavity, skin of the groin, and perineum [8, 11, 12, 13]. MRSP strains were most commonly isolated from dogs from the nose and anus, but these were also the most common sampling sites [8]. Carriage of *S. pseudintermedius* can be permanent, intermittent, or short-term [42], though the types of carriage have not been specified and are only defined by researchers for specific studies. Hartman et al. [42] looked at the number of isolations of *S. pseudintermedius* strains over a 12-month period and the relatedness of the bacteria when assessing carriage in dogs. They concluded that a single isolation of *S. pseudintermedius* within a given time period indicates short-term carriage, that at least two isolations of the bacteria (but not in consecutive swabs) are defined as intermittent carriage, and that two or more isolations in consecutive swabs from the same body region are interpreted as permanent carriage. Importantly, these studies also show that animals colonized by *S. pseudintermedius* permanently or intermittently are colonized with higher numbers of *S. pseudintermedius* cells than those colonized on a short-term basis, which increases the risk of *S. pseudintermedius* infections in these dogs and the potential for transmission to other animals and humans [43].

Depending on the study and the pattern of specimen collection, the isolation rate of *S. pseudintermedius* in healthy dogs ranges from 24.4-92%, while the percentage of MRSP strains ranges from 0-36.84 [44, 45, 46, 47, 48]. This *Staphylococcus* is considered to be the most common cause of purulent dermatitis in dogs [8, 49], and is also isolated from clinical specimens in wound infections, surgical wounds, external ear, upper respiratory tract, urinary and reproductive tract, and bone and bone marrow [9, 23, 40, 50, 51, 52]. Studies show that certain conditions, such as atopic dermatitis in dogs, promote more frequent colonization by *S. pseudintermedius* not only of the skin but also of the external auditory canal and conjunctival sacs [9, 53, 54]. There have also been reported cases of puppy death due to sepsis from *S. pseudintermedius* infection in the first two weeks of life. It has also been proven that colostrum and milk from female dogs can be a potential source of these bacteria for puppies [55, 56].

Carriage of *S. pseudintermedius* in cats is described less frequently than in dogs [3, 46]. According to some authors,

felids are not natural hosts of *S. pseudintermedius* [9]. Data on the frequency of isolation of this staphylococcal species in cats are still fragmentary. Hanselman et al. [46] described the isolation of *S. pseudintermedius* in 6.8% of cats studied, of which the percentage of animals carrying MRSP strains was 1.2%. In the study carried out by Bierowiec et al. [2], this *Staphylococcus* was isolated more frequently from cats with bacterial infections of the skin and mucous membranes than from clinically healthy cats. According to previous reports, *S. pseudintermedius* has been isolated in cats from infections of the upper respiratory tract, conjunctiva, urinary tract, external auditory canal, skin, and wounds [2, 46, 57, 58]. Isolation of this species from lung tissue has also been documented [25].

In both dogs and cats, certain risk factors for *S. pseudintermedius* infection have been reported, including infection with MRSP strains. In particular, a strong correlation between animal infection and previous hospitalizations (including for surgical procedures), frequent veterinary office visits, administration of glucocorticoids, and treatment with antimicrobial chemotherapeutics has been demonstrated [18, 40, 59]. There are also reports of possible staphylococcal contamination of veterinary facilities and their medical equipment. This suggests the need for special attention to hygiene and disinfection of surfaces and equipment in veterinary facilities to reduce the risk of pathogen transmission to patients and clinicians [32, 60, 61, 62].

Incidence in humans

There are increasing reports of *S. pseudintermedius* being isolated in humans; however, human infections caused by *S. pseudintermedius* are rarely reported [13, 63]. Colonization of people in contact with dogs or cats is more commonly described and affects 0.4-8.9% of owners or professional animal handlers [12, 35, 64, 65]. The prevailing opinion is that human colonization with this *Staphylococcus* is temporary [64] and affects mainly immunosuppressed or elderly people [11, 35, 66]. There are, however, some reports that stress the possibility of long-term colonization of human skin and mucous membranes by MRSP strains [65] and of infections appearing in people without immune deficits [64]. Most likely, though, the prevalence of this *Staphylococcus* in humans is underestimated due to the misidentification of *S. pseudintermedius* strains as *S. aureus* [11, 65, 66, 67].

The most commonly identified site of *S. pseudintermedius* isolation in humans has been the nasal cavity and soft tissues [11, 64, 66]. This may be because a significant proportion of infections caused by this pathogen presented with acute or chronic rhinosinusitis [11, 64, 65]. The bacteria were also isolated from cases of endocarditis, sepsis, deep abscesses, infection of wounds resulting from dog bites, pneumonia, arthritis, skin and soft tissue infections with ulceration and necrosis [11, 12, 13, 63, 64, 67, 68, 69, 70, 71]. Researchers point to the high pathogenic potential of *S. pseudintermedius* in humans, comparable to that described in *S. aureus* [69]. In addition to its ability to colonize human tissues, this species may also limit the growth of other bacteria that are components of the natural microbiota of the skin and mucous membranes [10]. There has also been a suggestion that MRSP may colonize humans more frequently than MSSP [65]. The significant resistance to antimicrobial chemotherapeutics and the ability to produce biofilm of *S. pseudintermedius* strains isolated from humans is also alarming [64]. It is also associated with the rapid spread of the dominant clone ST71 among humans in Europe [65, 66, 72].

Many authors note that people in contact with animals, especially dogs, are much more likely to be colonized [12, 32, 40, 64, 66, 70]. Nevertheless, cases of *S. pseudintermedius* infection have also been described in individuals with no previous contact with animals [67, 71]. An increased risk of colonization among veterinarians and veterinary assistants has also been cited [22, 35, 65]. It has also been shown that animal dust and dander may be involved in the transmission of MRSP to humans within the household [64].

Conclusion

The cases of infections caused by *S. pseudintermedius*, both in humans and animals, reported so far indicate that this *Staphylococcus* has a similar pathogenic potential to *Staphylococcus aureus*. Therefore, proper and judicious use of antimicrobial chemotherapeutics and adherence to hygienic standards seem essential to limit the spread of these bacteria between humans and animals. Because for years *S. pseudintermedius* (previously classified as *S. intermedius*) was considered a typically animal species of coagulase-positive staphylococci, laboratory procedures that favored identification of the more common human *Staphylococcus aureus* over *S. pseudintermedius* were widely used. Thus, it is now believed that the percentage of humans colonized by *S. pseudintermedius*, as well as the incidence of infection, may be higher than reported in the literature.

Authors' Contribution

M.M.: literature review, research concept and design, acquisition of data, data analysis and interpretation, writing-original draft preparation, writing – review and editing, final proofreading and approval of the version for publication, funding acquisition; **S.L.:** literature review; **K.B.:** research

concept and design, supervising the project, acquisition of data, data analysis and interpretation, writing – review and editing, final proofreading and approval of the version for publication.

Conflict of Interest

The authors have no potential conflicts of interest to declare.

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