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Coagulase-Negative Staphylococci

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SUMMARY

The definition of the heterogeneous group of coagulase-negative staphylococci (CoNS) is still based on diagnostic procedures that fulfill the clinical need to differentiate between *Staphylococcus aureus* and those staphylococci classified historically as being less or nonpathogenic. Due to patient- and procedure-related changes, CoNS now represent one of the major nosocomial pathogens, with *S. epidermidis* and *S. haemolyticus* being the most significant species. They account substantially for foreign body-related infections and infections in preterm newborns. While *S. saprophyticus* has been associated with acute urethritis, *S. lugdunensis* has a unique status, in some aspects resembling *S. aureus* in causing infectious endocarditis. In addition to CoNS found as food-associated saprophytes, many other CoNS species colonize the skin and mucous membranes of humans and animals and are less frequently involved in clinically manifested infections. This blurred

gradation in terms of pathogenicity is reflected by species- and strain-specific virulence factors and the development of different host-defending strategies. Clearly, CoNS possess fewer virulence properties than *S. aureus*, with a respectively different disease spectrum. In this regard, host susceptibility is much more important. Therapeutically, CoNS are challenging due to the large proportion of methicillin-resistant strains and increasing numbers of isolates with less susceptibility to glycopeptides.

INTRODUCTION

It was 20 years ago that Kloos and Bannerman (1) updated our knowledge on the clinical significance of coagulase-negative staphylococci (CoNS), following a review, 6 years previously, of their laboratory, clinical, and epidemiological aspects by Pfaller and Herwaldt (2), both in this journal. Although the pathogenic potential of CoNS had become accepted by the end of the 1980s, most of the underlying molecular mechanisms still awaited discovery. Presently, a PubMed search on CoNS results in more than 15,000 references, reflecting the increasing medical impact of these bacteria.

Over the past 2 decades, the research toolbox has greatly expanded, providing a large array of modern molecular and phenotypic methods, including the routine use of whole-genome sequencing and mass spectrometric approaches. Nevertheless, the problem of an increasing health burden due to CoNS infections is far from resolved. Demographic and medical developments creating more elderly, multimorbid, and immunocompromised patients and the increasing use of inserted or implanted foreign bodies have contributed to the progressively increasing importance of CoNS in health care. Furthermore, as for other nosocomial pathogens, increasing rates of antibiotic resistance are an even greater problem for CoNS than for *Staphylococcus aureus*, limiting our therapeutic options.

Today, CoNS, as typical opportunists, represent one of the major nosocomial pathogens, having a substantial impact on human life and health. They are particularly associated with the use of indwelling or implanted foreign bodies, which are indispensable in modern medicine. Colonization of different parts of the skin and mucous membranes of the host is the key source of endogenous infections by CoNS. However, they are transmitted mainly by medical and/or nursing procedures. Once inserted, foreign bodies can become colonized by CoNS and the success of the respective medical procedure is significantly impaired, resulting in enormous medical and economic burdens.

Describing CoNS is challenging because they represent a heterogeneous group within the genus *Staphylococcus* that is not based on phylogenetic relationships. They were defined by delimitation from coagulase-positive staphylococci (CoPS), i.e., *Staphylococcus aureus*, the only known coagulase-positive species at the time of the introduction of this concept. Superficially, this concept seemed to be solely a diagnostic procedure-based classification, but it became a clinical approach to differentiate between the pathogenic species *S. aureus* and a group of staphylococci initially classified as nonpathogenic. A deeper understanding of the nature of CoNS has now fundamentally changed our views.

In this review, human medical issues and the epidemiological, pathogenetic, clinical, diagnostic, and therapeutic aspects of CoNS and their infections in relation to the pathogens' biology are reviewed. For aspects of CoNS related to veterinary medicine and food production, please refer to specialized reviews (3, 4).

TABLE 1 Historic and valid designations within the *Staphylococcus* genus reflecting the early dualism concept of pathogenic versus nonpathogenic staphylococci

Yr	"Pathogenic" species	"Nonpathogenic" species	Author of description (reference)
1884	*Staphylococcus* (*pyogenes*) *aureus*[a]	*Staphylococcus* (*pyogenes*) *albus*[b]	Rosenbach (8)
1896	*Micrococcus pyogenes aureus*	*Micrococcus pyogenes albus*	Lehmann and Neumann (610)
1908	*Aurococcus aureus*[c]	*Albococcus epidermidis*[d]	Winslow and Winslow (11)
1916	*Staphylococcus aureus*	*Staphylococcus epidermidis*	Evans (611)
1940	*Staphylococcus pyogenes*[e]	*Staphylococcus saprophyticus*[e,f]	Fairbrother (12)
1980	*Staphylococcus aureus*	*Staphylococcus epidermidis*	Skerman et al.[g] (612)

[a] In 1885, a lemon-colored species, designated *Staphylococcus* (*pyogenes*) *citreus*, was described by J. Passet (613).
[b] The pus-derived "*albus*" variant was probably rather a less or nonpigmented *S. aureus* isolate, as its pathogenicity was proven by Rosenbach via animal experiments (8). Later on, "*S. epidermidis albus*" was described by U.S. pathologist W. H. Welch, in 1891, as a colonizer of the human epidermis found also in aseptic wounds (10).
[c] Described as a "parasitic coccus, living normally on the surface of the human or animal body, or in diseased tissues" (11).
[d] Described as a "parasitic coccus, living normally on the surfaces of the human or animal body" (11).
[e] After the introduction of coagulase production as the major principle to differentiate staphylococcal species by Fairbrother (12).
[f] *S. saprophyticus* was used in a broader sense to designate nonpathogenic coagulase-negative staphylococci.
[g] Still valid definitions of the taxa *S. aureus* and *S. epidermidis*, together with other staphylococcal species described until this point, by the Ad Hoc Committee of the Judicial Commission of the ICSB (612).

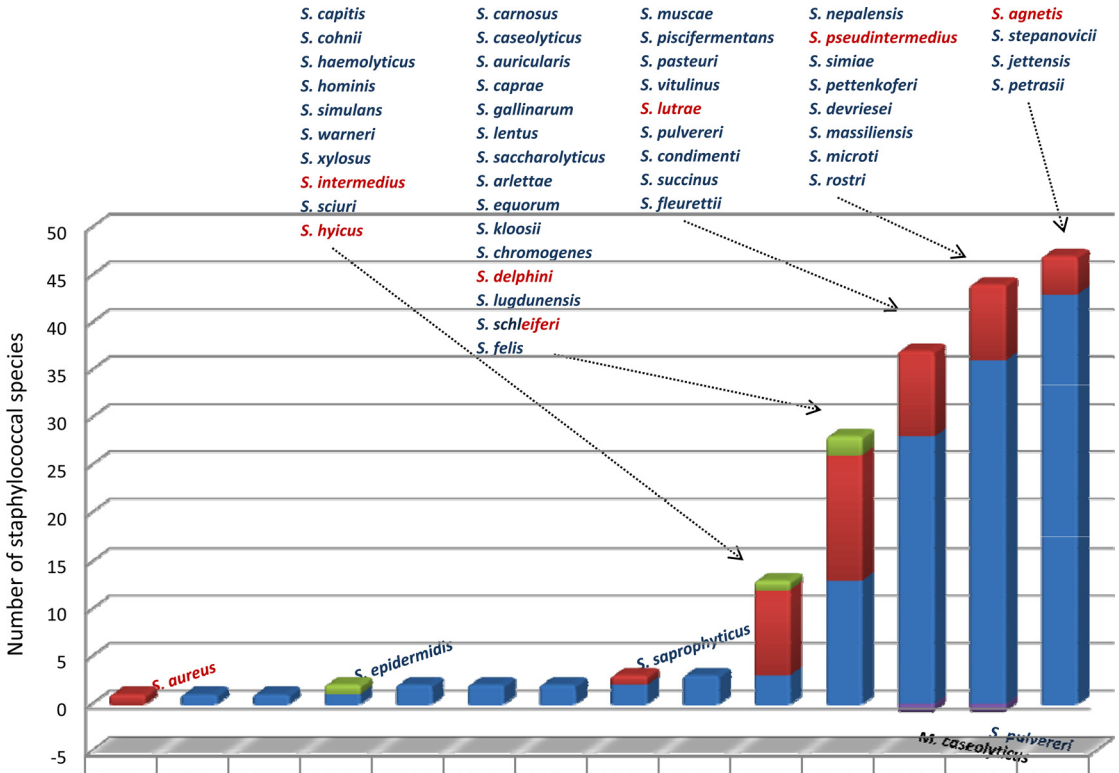
TAXONOMY AND CLASSIFICATION

Historic and Contemporary Clinical Concepts

Early concepts of separation within the *Staphylococcus* genus—the dualism story. As for other genera, the early history of the discovery of staphylococci was characterized by many taxonomic reclassifications and renaming of species (Table 1). The different concepts of species and limited tools for identification prevalent in the premolecular era should be taken into consideration in consulting older literature. Surgeons such as Billroth, reporting on "*Coccobacteria septica*" in 1874, and Ogston, who first proposed the term "*Staphylococcus*" in 1882, were the first to closely link *Staphylococcus*-like microorganisms with wound infections (5–7).

One of the earliest references to different species being named "*Micrococcus*" and, particularly, "*Staphylococcus*" in terms of pathogenicity was given in 1884 by Rosenbach, a German surgeon, who demonstrated in cultivation and animal experiments that different microorganisms could be recovered from abscesses; these were designated "*Staphylococcus pyogenes aureus*" and "*Staphylococcus pyogenes albus*" (8). However, the pus-derived "*albus*" variant was probably a less or nonpigmented *S. aureus* isolate, as its pathogenicity was subsequently demonstrated in animal experiments by Rosenbach (9). In contrast, in 1891, the U.S. pathologist Welch described "*Staphylococcus epidermidis albus*" as an almost constant colonizer of the human epidermidis which was also found in aseptic wounds (10).

Since the temporary division of staphylococci into two genera in the early 1900s (*Aurococcus* [including *Aurococcus aureus*, asso-



	1881-1890	1891-1900	1901-1910	1911-1920	1921-1930	1931-1940	1941-1950	1951-1960	1961-1970	1971-1980	1981-1990	1991-2000	2001-2010	2011-
Species eliminated/transferred												-1	-1	
Reclassified from other genera				1						1	2			
Valid description	1							1		9	13	9	8	4
Until then validly described species	0	1	1	1	2	2	2	2	3	3	13	28	36	43

FIG 1 Time line of the discovery of the species belonging to the genus *Staphylococcus*. Coagulase-negative species are shown in blue; coagulase-positive and coagulase-variable species are shown in red (note that only *S. schleiferi* subsp. *coagulans* is coagulase positive). Note that at the times of establishment of the first three species designations, *S. aureus*, *S. epidermidis*, and *S. saprophyticus*, these terms comprised a broader content than that accepted today. In particular, *S. epidermidis* and *S. saprophyticus* were used to describe nonpathogenic, saprophytic staphylococci (and other Gram-positive cocci occurring in clusters).

ciated with diseased tissues] and *Albococcus* [including the first valid taxonomic description of *S. epidermidis*, as *Albococcus epidermidis*]) (11), the challenge was to distinguish between both pathogenic staphylococcal "varieties." This was a common thread running through many old scientific papers. In the early decades of investigating staphylococcus-like bacteria, the classification of the genus *Staphylococcus* was based on the production of pigment, even though this method was eventually generally considered disappointing. In 1940, R. W. Fairbrother introduced coagulase production as a major differentiating principle for staphylococcal species (12). However, instead of using the term "*S. epidermidis*," Fairbrother proposed the taxon "*S. saprophyticus*" to distinguish between nonpathogenic CoNS and CoPS, designated "*S. pyogenes*" (12). Subsequently, in 1951, Shaw et al. used the "*S. saprophyticus*" term in a broader sense; however, the type strain originally defined by these authors still represents the type strain of *S. saprophyticus* subsp. *saprophyticus* (13). Staphylococci and micrococci were distinguishable by the ability to ferment glucose under anaerobic conditions. Since *S. saprophyticus* ferments glucose very slowly in an anaerobic environment, it was misclassified as "*Micrococcus*, subgroup 3" (14), until its reclassification in 1974, as noted in *Bergey's Manual of Determinative Bacteriology* (15).

The era of a limited number of staphylococcal species came to an end in the 1970s, with descriptions of 10 newly identified species (e.g., *S. haemolyticus*, *S. hominis*, and *S. intermedius*), followed by a progressive increase to more than 40 validly described species by the beginning of 2014 (16) (Fig. 1).

Contemporary clinical concepts. Apart from phylogenetic findings and classifications, a simplified but more useful and well-accepted scheme, mainly based on clinical and diagnostic aspects, is still used in human medicine: staphylococci are divided into CoPS, almost exclusively represented by *S. aureus*, and CoNS (Fig. 2).

In regard to other CoNS, the clinically defined "*S. epidermidis* group," comprising *S. epidermidis* and *S. haemolyticus* as the most prevalent species, along with other traditionally included species (e.g., *S. capitis*, *S. hominis*, *S. simulans*, and *S. warneri*), can be distinguished from *S. saprophyticus* by the latter being a specific cause of acute urethritis. However, *S. saprophyticus* may also be found as a pathogen causing infections like those known for members of the *S. epidermidis* group. Some of the recently discovered CoNS species, such as *S. pettenkoferi* and *S. massiliensis*, might belong to this group as well. Notably, gradations in pathogenic capacity within this heterogeneous group occur not only at the species level but also at the strain level. Recently, *S. lugdunensis* has

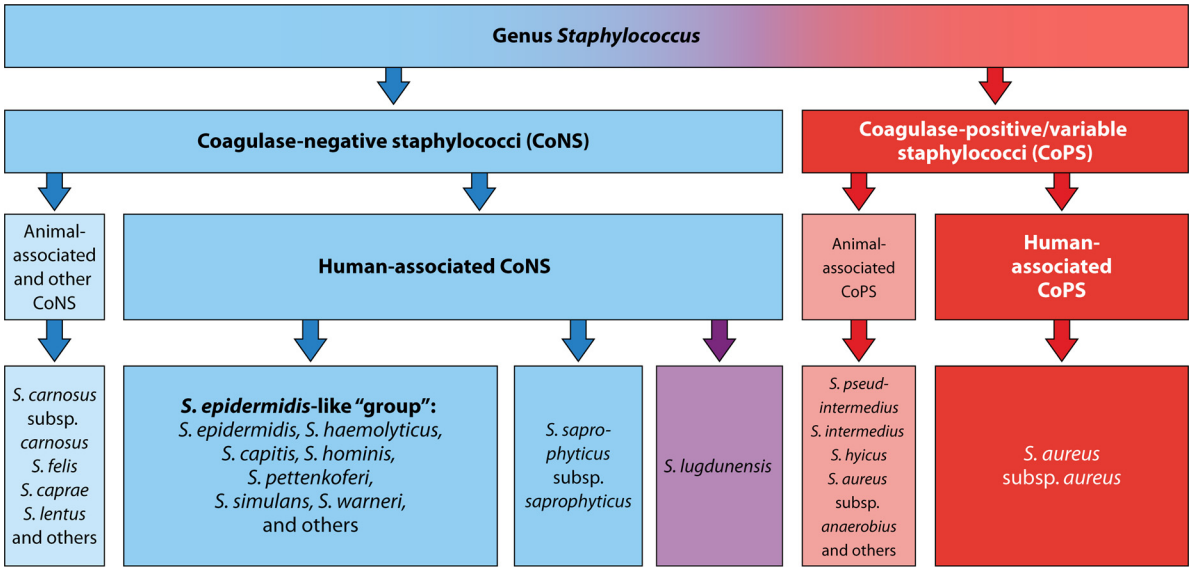


FIG 2 Clinical and epidemiological schema of staphylococcal species, based on the categorization of coagulase as a major virulence factor and its resulting impact on human health.

increasingly become known as a CoNS species in an "intermediate position" between *S. aureus* and the *S. epidermidis* group, displaying clinical features of both groups. In this review, the scheme outlined in Fig. 2 is applied unless phylogenetic and taxonomic aspects are discussed.

Taxonomy, Classification, and Phylogeny

Current status of staphylococcal species and subspecies. As of 2014, the genus *Staphylococcus* consists of 47 species and 23 subspecies that are validly described (Fig. 3). Of these, 38 fulfill the categorization of a coagulase-negative species, and one further species, *S. schleiferi*, includes both a coagulase-negative subspecies (*S. schleiferi* subsp. *schleiferi*) and a coagulase-positive subspecies (*S. schleiferi* subsp. *coagulans*). Most recently described CoNS species isolated from human clinical specimens comprise *S. jettensis*, *S. massiliensis*, *S. petrasii* (including *S. petrasii* subsp. *petrasii* and *S. petrasii* subsp. *croceilyticus*), and *S. pettenkoferi* (Fig. 1) (17–20). A further CoNS species, *S. pseudolugdunensis*, has been proposed (21).

Meanwhile, two species previously considered to be CoNS were removed from this genus. *S. pulvereri*, described in 1995, was found to be identical to the previously described species *S. vitulinus* (22). *S. caseolyticus* was transferred to the newly established genus *Macrococcus*, comprising Gram-positive, catalase-positive cocci characterized by a higher DNA G+C content, the absence of cell wall teichoic acids, and larger cells than those of the *Staphylococcus* species (23, 24).

The family *Staphylococcaceae*. The family *Staphylococcaceae* was first proposed by a taxonomic outline during the formulation of the 2nd edition of *Bergey's Manual of Systematic Bacteriology* (25, 26). In addition to the staphylococcal genus, the *Staphylococcaceae* family comprises the genera *Jeotgalicoccus*, *Macrococcus*, *Nosocomiicoccus*, and *Salinicoccus* (16). *Jeotgalicoccus* and *Salinicoccus* species have been recovered from diverse food and environmental samples. For *Nosocomiicoccus ampullae*, isolation from the surfaces of saline bottles used in wound cleansing has been reported (27). To date, the *Macrococcus* genus comprises seven species, adapted to hoofed animals (23).

Classification into suprafamiliar taxa. While the genera *Staphylococcus* and *Micrococcus* were historically placed together with the genera *Planococcus* and *Stomatococcus* in the same family, designated *Micrococcaceae*, molecular phylogenetic and chemotaxonomic analyses revealed that the various Gram-positive, catalase-positive cocci were not closely related (28). Now the family *Staphylococcaceae*, together with *Bacillaceae*, *Listeriaceae*, *Paenibacillaceae*, *Planococcaceae*, and other families, belongs to the order *Bacillales* of the class *Bacilli* (29). The *Bacilli* are part of the phylum *Firmicutes*, which comprises Gram-positive bacteria with a rather low DNA G+C content. In contrast, the phylum *Actinobacteria* now contains micrococcal species, which are characterized by a high DNA G+C content. Meanwhile, the "micrococci" have largely been reclassified and rearranged into two families: the redefined family *Micrococcaceae* and the newly established family *Dermacoccaceae*. Both belong to the suborder *Micrococcineae* (class *Actinobacteria*) (28, 30, 31).

Phylogenetic analysis of staphylococci. Based on four loci, i.e., the noncoding 16S rRNA gene and three protein-encoding genes (*dnaJ*, *rpoB*, and *tuf*), Lamers et al. (32) recently proposed a refined classification based on molecular data for the *Staphylococcus* genus, with species being classified into 15 cluster groups. These groups were shown to belong to six species groups (Auricularis, Hyicus-Intermedius, Epidermidis-Aureus, Saprophyticus, Simulans, and Sciuri species groups) according to phenotypic properties (Fig. 3).

EPIDEMIOLOGY AND TRANSMISSION

CoNS as Part of the Microbiota of the Skin and Mucous Membranes

The skin, as a physical barrier and interface with the outside environment, is physiologically colonized by a multitude of diverse microorganisms (33). CoNS represent a regular part of the micro-

Oxidase	Negative							
Novobiocin	Susceptible							
Coagulase	Negative	Positive[1] – variable[2] – negative[3]		Negative				
Species group	Hyicus-Intermedius			Epidermidis-Aureus				
Cluster group	Muscae	Hyicus	Intermedius	Aureus	Epidermidis	Warneri	Haemolyticus	Lugdunensis
Species	*S. muscae* *S. microti* *S. rostri*	*S. hyicus*[2] *S. agnetis*[2] *S. chromogenes*[3] *S. felis*[3]	*S. intermedius*[1] *S. delphini*[1] *S. lutrae*[1] *S. pseudintermedius*[1] *S. schleiferi* *ssp. schleiferi*[3] *ssp. coagulans*[1]	*S. aureus* *ssp. aureus*[1] *ssp. anaerobius*[1] *S. simiae*[1]	*S. epidermidis* *S. capitis* *ssp. capitis* *ssp. urealyticus* *S. caprae* *S. saccharolyticus*	*S. warneri* *S. pasteuri*	*S. haemolyticus* *S. devriesei* *S. hominis* *ssp. hominis* *ssp. novobiosepticus* *S. jettensis* *S. petrasii* *ssp. croceilyticus* *ssp. petrasii*	*S. lugdunensis*

Oxidase	Negative						Positive
Novobiocin	Susceptible		Resistant				
Coagulase	Negative						
Species group	Auricularis	Simulans	Saprophyticus				Sciuri
Cluster group	Auricularis	Simulans-Carnosus	Pettenkoferi-Massiliensis	Saprophyticus	Cohnii-Nepalensis	Arlettae-Kloosii	Sciuri
Species	*S. auricularis*	*S. simulans* *S. carnosus* *ssp. carnosus* *ssp. utilis* *S. condimenti* *S. piscifermentans*	*S. pettenkoferi* *S. massiliensis*	*S. saprophyticus* *ssp. saprophyticus* *ssp. bovis* *S. equorum* *ssp. equorum* *ssp. linens* *S. gallinarum* *S. succinus* *ssp. succinus* *ssp. casei* *S. xylosus*	*S. cohnii* *ssp. cohnii* *ssp. urealyticus* *S. nepalensis*	*S. arlettae* *S. kloosii*	*S. sciuri* *ssp. sciuri* *ssp. carnaticus* *ssp. rodentium* *S. fleurettii* *S. lentus* *S. stepanovicii* *S. vitulinus*

FIG 3 Phylogenetic separation of staphylococcal species and subspecies (ssp.), extended by key diagnostic characteristics as proposed by Lamers et al. (32).

biota of the skin and mucous membranes of humans and animals (Table 2). While the skin has been perceived as the human body's largest organ, differences in skin thickness and folds and the densities of hair follicles and glands define distinct habitats of differing microbiota, including CoNS. Age-related dynamics of CoNS colonization may occur and is discussed later [see "Other infections. (i) Infections in neonates," below].

In accordance with data from early studies that applied traditional culture approaches (34, 35), recent metagenomic analyses have revealed that staphylococci prefer areas of higher humidity (36, 37). Such moist sites include the axillae, the gluteal and inguinal regions, the umbilicus, the antecubital and popliteal spaces, and the plantar foot region. Additionally, the anterior nares not only are the major habitat of *S. aureus* but also are constantly colonized by CoNS (38). Likewise, the ocular surface, the conjunctiva, is usually colonized by CoNS (39, 40).

The question of the extent to which CoNS and other skin commensals provide a direct benefit to the host is still unresolved (41). Interestingly, a serine protease Esp-secreting subset of *S. epidermidis* strains was recently shown to inhibit and destroy *S. aureus* biofilm formation and to prevent nasal colonization (42).

Ecological Niches of Human-Associated CoNS

***S. epidermidis* group.** In humans, *S. epidermidis* is the most frequently recovered staphylococcal species (Table 3). This bacterium colonizes the body surface, where it is particularly prevalent on moist areas, such as the axillae, inguinal and perineal areas, anterior nares, conjunctiva, and toe webs (43). *S. haemolyticus* and *S. hominis* are preferentially isolated from axillae and pubic areas high in apocrine glands (43, 44). *S. capitis* is found surrounding the sebaceous glands on the forehead and scalp following puberty (45). With reference to the recently described species *S. pettenkoferi*, it may be assumed that it also colonizes the human skin. However, these species may occasionally be found on other body sites. *S. auricularis* is part of the human external ear microbiota, exclusively colonizing this region (46).

S. lugdunensis. *S. lugdunensis* is an integral part of the normal skin flora. *S. lugdunensis* is found particularly in the pelvic and perineum regions, in the groin area, on the lower extremities, and in the axillae (47, 48). Compared to *S. aureus*, it is less frequently found in the anterior nares (49). No data are available on whether *S. lugdunensis* colonizes these areas permanently or only intermittently.

S. saprophyticus* subsp. *saprophyticus. *S. saprophyticus* subsp. *saprophyticus* frequently colonizes the rectum and genitourinary tract, in an age- and season-dependent manner (preferentially in summer and fall) (43). In a study by Rupp et al. (50), the urogenital tract was colonized in 6.9% of healthy women (median age, 29 years) from an outpatient gynecology practice; however, in 40% of

TABLE 2 Main characteristics of CoNS species

Species or subspecies[a]	Diagnostic characteristics			Site or source of detection[b]			Clinical association (frequency)[c]	
	Colony appearance	Novobiocin resistance	Oxidase	Environment and/or food	Animals	Humans	FBRI	Other
S. arlettae	Yellow or beige	+	−	Textile and tannery industrial effluents	Cattle, goats, pigs, poultry, sheep	−	−	BSI (+)
S. auricularis	White	−	−	−	−	External auditory canal (principle habitat), seldom on other skin regions	−	BSI in preterm infant (?)
S. capitis subsp. *capitis*	Chalk white	−	−	−	Cats, dogs, horses	Predominantly on the scalp and arms, less frequently on other skin regions	CRBI (+), PVIE (+), CAPD (+), DRBJI (++)	BSI in neonates (+)
S. capitis subsp. *urealyticus*[d]	White, delayed yellow pigmentation in ~70% of isolates	−	−	−	−	Predominantly on skin (mostly from heads, primarily ears and foreheads)	CRBI (+), PVIE (+)	BSI in neonates (++)
S. caprae	Nonpigmented	−	−	−	Goats	Skin, anterior nares	CRBI (+), CAPD (+), CFDAI (+), DRBJI (+)	UTI (+)
S. carnosus subsp. *carnosus*	Gray-white	−	−	Fermented food (starter cultures, soy sauce mash)	Cattle	−	−	−
S. carnosus subsp. *utilis*	Cream colored after 48 h	−	−	Fermented food (soy sauce mash, fermented fish)		−	−	−
S. chromogenes	Butyrous, orange, or creamy	−	−	−	Cattle, pigs, horses, goats, sheep	−	−	−
S. cohnii subsp. *cohnii*	Unpigmented or, occasionally, tinted slightly yellowish	+	−	−	Dogs, goats, poultry	Skin	CRBI (++), DRBJI (++)	BSI in burn patient (+)
S. cohnii subsp. *urealyticus*[e]	Translucent with concentric ring patterns[c]	+	−	−	Apes, clams, monkeys, horses	Skin	−	BSI (+), infected pressure ulcer (?)
S. condimenti	Cream colored after 48 h	−	−	Fermented food and starter cultures	−	−	−	−
S. devriesei	Gray-yellow, yellow. or yellow-orange	−	−	−	Cattle	−	−	−
S. epidermidis	Gray or grayish white	−	−	Fermented sausages	Cats, cattle, dogs, goats, gorillas, horses, pigs, sheep	Skin (preferentially axillae and the head; also arms and legs) and mucous membranes of the nasopharynx	CAPD (!), CFDAI (!), DRBJI (!), PVIE (!), and virtually all other kinds of FBRIs	BSI in neonates (!)
S. equorum subsp. *equorum*	White	+	−	Fermented food (starter cultures)	Cattle, goats, horses, sheep	−	DRBJI (+)	−
S. equorum subsp. *linens*	White	+	−	Smear-ripened cheese (starter culture)	−	−	−	−
S. felis	Unpigmented	−	−	−	Cats, horses	−	−	−
S. fleurettii	Unpigmented or cream colored	+	+	Milk cheese	Goats, pigs, small mammals	−	−	−
S. gallinarum	Yellow, yellowish tint, or unpigmented	+	−		Chickens, pheasants	−	CRBI (+)	−

S. haemolyticus	Gray-white, white, or slight yellow tint	−	−	Milk, fermented food	Cats, cattle, dogs, horses, goats, pigs, sheep	Skin (preferentially legs and arms)	CAPD (+++), CFDAI (+++), DRBJI (++)	BSI in neonates (+++)
S. hominis subsp. *hominis*	Dull, gray-white to yellowish or yellow-orange	−	−	Goat milk, fermented food	Cats, dogs, goats, pigs, sheep	Skin (preferentially axillae, arms, legs, and pubic and inguinal regions)	CRBI (++), DRBJI (++)	BSI in neonates (+)
S. hominis subsp. *novobiosepticus*	Butyrous, gray-white	−	−	−	−	−	CRBI (++)	BSI in neonates (+)
S. jettensis	Yellow (after prolonged incubation)	−	−	−	−	−	CRBI (+)	−
S. kloosii	Opaque	+	−	−	Goats	−	CRBI (+)	BSI (+)
S. lentus	Gray-white to white or creamy	+	+	Soy bean oil meal, meat, milk	Clams, goats, horses, mink, pigs, poultry, sheep	−	CRBI (+)	BSI (+), splenic abscess (+)
S. lugdunensis	Cream-white to slightly yellow	−	−	−	Cats, chinchillas, dogs, goats, guinea pigs	Skin (preferentially lower abdomen and extremities)	PVIE (++), CFDAI (+), DRBJI (+)	Native valve endocarditis (++), wound infection (++), SSI (++)
S. massiliensis	White	−	−	−	−	Skin (?)	−	Brain abscess (+)
S. microti	Opalescent whitish	−	−	−	Mice	−	−	−
S. muscae	Butyrous, grayish white	−	−	−	Flies (trapped in cattle sheds)	−	−	−
S. nepalensis	White	+	−	Environment (not specified)	Goats, pigs, squirrel monkeys, bats (guano), dry-cured ham	−	−	Cystitis (?; recovered from human urine)
S. pasteuri	Mostly yellow, also white	−	−	Fermented sausages	Pigs	−	CAPD (+), DRBJI (+), CRBI (?)	BSI (+)
S. petrasii subsp. *croceilyticus*	Pale creamy yellow	−	−	−	−	Skin (?; so far only from acoustic meatus)	−	−
S. petrasii subsp. *petrasii*	Unpigmented	−	−	−	−	Skin (?)	−	BSI (?)
S. pettenkoferi	Mostly white, also yellow	−	−	−	−	Skin (?)	CRBI (++)	Wound infection (?), osteomyelitis (+)
S. piscifermentans	Unpigmented, white, yellowish orange	−	−	−	Dogs (feces), fermented food and starter cultures	−	−	−
S. rostri	White	−	−	−	Pigs, poultry, water buffalo	−	−	−
S. saccharolyticus[f]	Grayish white	−	−	−	Gorillas	Skin, particularly on the forehead and arm	PVIE (?)	Spondylo-discitis (+), joint infection (?), pneumonia (?)
S. saprophyticus subsp. *bovis*	Creamy to pale orange, also unpigmented	+	−	−	Cattle	−	−	−
S. saprophyticus subsp. *saprophyticus*	Unpigmented or slight yellow tint	+	−		Horses, goats, sheep, cats, fermented food	Skin	CRBI (+)	UTI (!), BSI (+), NVIE (+)
S. schleiferi subsp. *schleiferi*		−	−	−	Dogs, cats	Skin (particularly preaxillary)	CFDAI (+), CRBI (+), DRBJI (+), PVIE (+)	BSI (+), wound infection (+), UTI (?)
S. sciuri subsp. *carnaticus*		+	+	−	Cattle, dolphins	Skin	−	BSI (?)
S. sciuri subsp. *rodentium*		+	+	−	Rodents, whales	Skin	−	BSI (?)

(Continued on following page)

TABLE 2 (Continued)

Species or subspecies[a]	Diagnostic characteristics			Site or source of detection[b]			Clinical association (frequency)[c]	
	Colony appearance	Novobiocin resistance	Oxidase	Environment and/or food	Animals	Humans	FBRI	Other
S. sciuri subsp. *sciuri*	Gray-white with yellowish or cream-colored tint toward the center, yellowish (rare)	+	+	−	Cats, cattle, clams, dogs and other carnivores, dolphins, goats, horses, insectivores, marsupials, monkeys, pigs, rodents, whales	Skin	CAPD (+), CRBI (+), DRBJI (+)	BSI (?), diabetic food infection (?), wound infection (?)
S. simiae	White	−	−	−	Squirrel monkeys	−	−	−
S. simulans	Gray-white	−	−	−	Cattle, horses, sheep	Skin (legs, arms, and heads of children; occasionally in adults)	DRBJI (+)	−
S. stepanovicii	Unpigmented	+	+	−	Insectivores, rodents	−	−	−
S. succinus subsp. *casei*	White	+	−	Fermented food	Insectivores, rodents	−	−	−
S. succinus subsp. *succinus*	White	+	−	Amber, fermented food (starter cultures)	Cattle, insectivores, rodents, songbirds	Eye (single report)	−	BSI (?)
S. vitulinus	Cream to yellow, rarely unpigmented	+	+	Fermented food	Horses, poultry	−	−	Hip infection (?)
S. warneri	Gray-white (20%), slightly yellowish colonial center to bright yellow-orange	−	−	Fermented food	Dogs, cats, goats, horses, insectivores, monkeys, pigs, prosimians, rodents, sheep	Skin (preferentially nares, head, legs, and arms)	CAPD (+), DRBJI (++)	Septic arthritis (+)
S. xylosus	Orange-yellow, yellowish, or gray to gray-white	+	−	Fermented food (starter cultures)	Cats, clams, goats, horses, insectivores, lower primates, rodents, sheep	Skin (rare)	DRBJI (+)	−

[a] Assignment of characteristics, occurrence, and association with infections might be questionable between staphylococcal subspecies, particularly prior to their definition; in those cases, refraining from differentiation down to the subspecies level, the data were assigned to the subspecies bearing the species epithet.

[b] In particular for livestock and animal food products, as well as for companion animals, contamination by the human CoNS microbiota should be considered and, vice versa, observations of primarily animal-associated CoNS species on human skin could be caused by professional and domestic animal contacts.

[c] Abbreviations: BSI, bloodstream infection; CAPD, continuous ambulatory peritoneal dialysis-related infection; CFDAI, cerebrospinal fluid device-associated infection; CRBI, catheter-related bloodstream infection; FBRI, foreign body-related infection; DRBJI, device-related bone and joint infection; NVIE, native valve infectious endocarditis; PVIE, prosthetic valve infectious endocarditis; SSI, skin and soft tissue infection; UTI, urinary tract infection; −, unknown, not described; ?, questionable or unconfirmed; +, single cases; ++, occasional detection; +++, frequent detection; !, most common origin.

[d] For literature search, note that this subspecies was originally described in 1991 as *S. capitis* subsp. *ureolyticus*.

[e] For literature search, note that this subspecies was originally described in 1991 as *S. cohnii* subsp. *urealyticum*. While strains isolated from humans are usually unpigmented and their colonies have gray and gray-white rings, strains isolated from nonhuman primates are (i) usually pigmented with brilliantly colored colonies, with alternating yellow-orange, gray, gray-white, orange, and gray rings or bands; or (ii) show colonies with a yellow-green tint and only a subtle ring pattern.

[f] For literature search, note that this species, originally described in 1948 as belonging to the *Micrococcus* genus, was transferred from the *Peptococcus* genus into the *Staphylococcus* genus in 1984.

TABLE 3 Species distribution of CoNS in human clinical samples in recent studies (published since 2000)

Parameter	Value or description in study[b]							
	Petinaki et al., 2001 (614)	Cuevas et al., 2004[c] (615)	Sivadon et al., 2005[d] (616)	Arciola et al., 2006[e] (130)	Gatermann et al., 2007 (617)	Koksal et al., 2009 (618)	Jain et al., 2011[f] (619)	Shin et al., 2011 (91)
Study design parameters								
Country	Greece	Spain	France	Italy	Germany	Turkey	India	South Korea
No. of CoNS isolates	450	369	212	601	494	200	98	51
Underlying infection	Not specified[g]	Not specified[c]	BJI	PJI, surgical wound revision	BSI, CRBI	BSI	CRBI	CAPD peritonitis
Method of identification	API ID 32 Staph, BBL Crystal GP ID kit	SP	SP, *sodA*	API Staph, API ID 32 Staph	SP, *sodA*	API ID 32 Staph	SP	16S rRNA, *tuf*, *sodA*
% Identified staphylococci								
S. auricularis						1.0		
S. capitis	3.5	3	6.1	1.9	1.0	7.5	12.2	3.9
S. caprae			1.9	0.3	1.4			5.9
S. chromogenes	0.5				0.2	1.5		
S. cohnii	1.2	<1.0	0.5	1.2	1.0	1.0	8.2	
S. equorum				0.2				
S. epidermidis	50.0	56	71.2	36.1	67.4	43.5	23.5	66.7
S. haemolyticus	14.8	5	2.4	2.8	11.9	11.5	36.7	11.8
S. hominis[a]	11.1	18	4.2	3.2	7.5/1.0	9.5	3.0	
S. lentus						2.5		
S. lugdunensis	2.0		2.8	0.5	3.0	9.0		
S. pasteuri			1.9	0.1				2.0
S. saprophyticus	5.7	19		0.1	0.4	2.5		
S. schleiferi				0.1	0.6	1.0		
S. sciuri	1.2			0.1	0.6			
S. simulans	2.0	1	1.4	0.1	1.2	2.0	1.0	
S. warneri	4.0	4	7.1	2.1	1.8	4.0		7.8
S. xylosis	4.0	<1.0		0.1	0.8	5.0	13.3	

[a] If data for subspecies were provided, the percentages are separated by a slash, as follows: *S. hominis* subsp. *hominis*/*S. hominis* subsp. *novobiosepticus*. Differences from 100% are due to ambiguously and nonidentified isolates.
[b] Differences from 100% are due to ambiguously and nonidentified isolates or nongiven coagulase-positive isolates. Abbreviations: BJI, bone and joint infection; BSI, bloodstream infection; CAPD, continuous ambulatory peritoneal dialysis; CRBI, catheter-related bloodstream infection; IVD, intravenous device; PJI, (peri)prosthetic joint infection; SP, standard procedures (based on the work of Kloos and Schleifer [407] and subsequent modifications and supplementations).
[c] Data are from the fifth study period, carried out in 2002. The most frequent sources of isolation of CoNS were blood (32%), catheter tips (20%), wounds and abscesses (21%), and urine (12%); 8% were represented by other CoNS species.
[d] Data comprise about 60% BJIs related to revision arthroplasty surgery and 40% due to fracture nonunions, contiguous osteitis, and other entities.
[e] Data are percentages of overall prevalence among all 1,490 clinical isolates, including 530 (46.9%) *S. aureus* isolates.
[f] Data are given for IVD tip examination (see the respective publication for results of examination of blood samples and skin swabs from the site of IVD insertion).
[g] Comprising blood cultures (41.1%), wounds (22%), vascular catheters (11.1%), urine cultures (6.2%), and tissue culture foci (19.6%).

TABLE 4 Species distribution of CoNS[b] in animal- and food-derived samples in recent studies (published since 2000)

Parameter	Value or description in study[a]						
	Faria et al., 2009 (55)	Gillespie et al., 2009 (620)	Coton et al., 2010 (621)	Hauschild et al., 2010 (622)	Leroy et al., 2010 (623)	Huber et al., 2011 (624)	Waller et al., 2011 (625)
Study design parameters							
Country	Portugal	USA	France	Poland	France	Switzerland	Sweden
Animal or food source (no. of samples)	Drinking water (172)	Cow (618)	Food-related samples (431)	Free-living insectivores and rodents (NG)	Meat products (27)	Food-related samples (1,639)	Cow (NG)
Sample origin	Distribution network	Mammary quarter milk	French cheese, dry sausage types	NG	Processing units ($n = 9$)	Farms (>800)	Milk
No. of isolates	242	383	431	197	388	275 (only MR-CoNS)	154
Identification method	16S rRNA gene PCR	API Staph	Several PCR and hybridization strategies	*rpoB* and *dnaJ* PCR-RFLP analysis	*sodA* gene PCR	MALDI-TOF MS, *sodA* gene PCR	*tuf* gene PCR
% Identified staphylococci							
S. arlettae					0.3		1
(*S. aureus*)[b]				1.5			
S. auricularis			0.5				
S. capitis	1.7		0.2		0.0		
S. carnosus			1.9		3.6		
S. caprae							
S. chromogenes		48	0.5				24
S. cohnii					0.0	0.4	
S. epidermidis	28.5	10	4.4	4.1	2.1	1.4	22
S. equorum			28.5	2.0	58.2		
S. fleurettii			0.5	0.5	0.0	35.6	
S. gallinarum							1
S. haemolyticus		<1	4.4	1.0		2.2	14
S. hominis		2	1.2	1.0	0.0		
(*S. hyicus*)[b]		26					5
(*S. intermedius*)[b]		<1					
S. lentus			2.6	1.0		10.9	<1
S. lugdunensis	1.2						
S. microti				0.5			
S. pasteuri	65.7		0.2	2.0	2.3		
(*S. pseudintermedius*)[b]							<1
S. saprophyticus	2.3	1	12.5	0.5	11.9		5
S. sciuri	0.6	<1	1.4	7.6	0.3	48.7	
S. simulans		7	1.2				18
S. stepanovicii				18.3			
S. succinus			7.7	27.9[c]	7.7		
S. vitulinus			1.2	2.5	2.1		
S. warneri		2	2.8	5.6	0.3	0.7	
S. xylosus		1	28.3	20.8	11.3		4

[a] Differences from 100% are due to ambiguously and nonidentified isolates or nongiven coagulase-positive isolates. Abbreviations: NG, not given; SP, standard procedures (based on the work of Kloos and Schleifer [407] and subsequent modifications and supplementations).
[b] If part of the study, percentages of coagulase-positive or coagulase-variable species (species names in parentheses) are also given.
[c] Comprises *S. succinus* subsp. *succinus* (9%) and *S. succinus* subsp. *casei* (91%).

humans, the major reservoir is the gastrointestinal tract. These observations were supported by a study by Schneider and Riley (51) in which *S. saprophyticus* was recovered from 4.6% of Australian females of 13 to 40 years of age but not from older women or men. More recently, *S. saprophyticus* was isolated from 7% and 4% of general practice patients in the age categories 11 to 20 years and 21 to 50 years, respectively, and was isolated significantly less (0.5%) from patients aged 51 to 70 years (52). *S. saprophyticus* also seems to be part of the gastrointestinal flora of cattle and pigs and is a common contaminant of respective foods, such as raw beef and pork (53, 54).

Other CoNS. *S. pasteuri* was found in a large percentage (65.7%) of drinking water samples from a distribution network responsible for supplying water to consumers (Table 4) (55). *S. carnosus*, *S. condimenti*, *S. equorum*, *S. piscifermentans*, *S. succinus*, and *S. xylosus* represent staphylococcal species that are typically associated with fermented foods and their starter cultures (4) (Table 4).

Population Structure and Epidemiological Typing Systems

Clonal diversity among CoNS species varies and is much less studied than that of *S. aureus*. While *S. epidermidis* is characterized by pronounced genomic diversity, other CoNS species, such as *S. haemolyticus*, *S. lugdunensis*, and *S. schleiferi*, exhibit less diversity as shown by pulsed-field gel electrophoresis (PFGE) (56, 57). Later on, multilocus sequence typing (MLST) based on nucleotide sequencing of housekeeping genes revealed distinct related clones of methicillin-resistant (MR) *S. epidermidis* predominating among clinically significant isolates (58). Subsequently, *S. epidermidis* MLST type ST27 (corresponding to ST2 of an improved MLST scheme [59, 60]) was shown to differ from clones in the community and to be distributed widely in various hospital environments in the United States and Europe (61); this may have been facilitated by the presence of biofilm- and resistance-mediating genes. Further studies confirmed a high degree of genetic diversity within *S. epidermidis* at slowly evolving loci but, on the other hand, showed a worldwide predominance of only a few hospital-associated, epidemic clonal lineages (62–64). For U.S. cardiac centers, remarkably clonal health care-associated *S. epidermidis* infections were shown (65). In contrast, extreme genetic diversity was observed among community-related *S. epidermidis* isolates in healthy children and adults (63, 66). *S. epidermidis* studies have revealed a population with an epidemic structure of emerging, well-adapted clones evolving rapidly through genetic recombination by frequent transfer of genetic mobile elements, such as staphylococcal cassette chromosome *mec* (SCC*mec*) elements (61, 62). Thus, in contrast to *S. aureus*, which is evolving preferentially by point mutations, *S. epidermidis* cannot be considered a highly clonal organism (62).

For the short-term surveillance of *S. epidermidis* in outbreak situations, PFGE targeting the entire bacterial genome can be regarded as an appropriate and powerful tool. MLST and multilocus variant analysis (MLVA), which target distinct conserved loci of the chromosome, are more suitable for long-term evolutionary analyses or the surveillance of geographic dissemination (59, 67). Additionally, the *rpoB* gene has been used as an epidemiological target for CoNS typing (68).

In the case of methicillin-resistant CoNS (MR-CoNS), additional typing of the SCC*mec* element is highly recommended and shows a high genetic diversity in methicillin-resistant *S. epidermidis*, *S. haemolyticus*, *S. hominis*, and other CoNS (see "Resistance Mechanisms and Susceptibility Patterns," below) (62, 69–72).

Whole-genome sequencing will drastically enhance our knowledge by improving the resolution of the genetic organization of CoNS species and—as shown in initial applications for *S. aureus* (73)—their clonal distribution. For *S. haemolyticus*, an extreme plasticity of the genome was reported and a high abundance of insertion sequence elements was found, conferring the frequent genomic rearrangement characteristics found in this species (74).

Transmission in the Hospital Environment

Compared to methicillin-resistant *S. aureus* (MRSA) transmission, much less is known regarding the epidemiology of CoNS in health care facilities, as well as their potential to cause outbreaks. The predominance of CoNS isolates in exhibiting (multi)resistance to antibiotics and antiseptics (75–77), as well as their capacity for biofilm production (78, 79), is strongly indicative of selection processes facilitated by modern medicine, i.e., mainly from (over)use of antibiotics and insertion of foreign body devices. The number of unrecognized cases of transmission of clonal CoNS lineages may actually be higher, since CoNS outbreaks usually still remain unidentified. However, in patient groups which are highly vulnerable to CoNS infections, CoNS and their clonal spread have been acknowledged as substantial contributors to morbidity and mortality.

For neonatal intensive care units (ICUs), in particular, it has been shown that single clones of multiresistant *S. epidermidis* and *S. haemolyticus* strains that produce biofilms are associated with colonization and disease among preterm neonates (80). The clonal spread of endemic, multidrug-resistant CoNS within a hospital was also detected in nonneonatal ICUs and wards (81–83). Several outbreaks of antibiotic-resistant CoNS clones have been reported in ICUs (84–86). Within an 11-year period, one molecular cluster emerged as the predominant cause of CoNS sepsis in a Dutch neonatal ICU (87). Moreover, possible interhospital spread was also demonstrated (82). In contrast, a pronounced genetic diversity of *S. epidermidis* was found in healthy, nonhospitalized persons (66).

While nosocomial CoNS clones may have been selected primarily by respective antibiotic selection pressure, other putative, pathogen-related selective factors may also have contributed to successful intra- and interhospital spread, such as adhesion factors for the colonization of foreign body biomaterials, a capacity for biofilm production, and resistance to opsonophagocytosis. Known hygiene-related factors enhancing the distribution of MRSA in the hospital setting, such as insufficient hand hygiene and inadequate disinfection and/or sterilization of medical instruments and surfaces, may also be assumed to be causative of clonal CoNS spread.

CLINICAL SIGNIFICANCE AND INFECTIONS

Drastic changes in patient populations—increased numbers of premature newborns and of elderly, multimorbid, chronically ill, and, often, immunocompromised patients—as well as the increasing use of inserted foreign bodies, led to an acknowledgment of the large variety of infections caused by CoNS. This was confirmed by a multitude of clinical studies that considered certain entities and patient groups. However, most studies address CoNS as a whole and do not distinguish between different species. Thus, the real impact of less frequently occurring species might be underreported (Tables 2 and 3). Moreover, due to difficulties in the differentiation of CoNS in the premolecular/mass spectrometry era, species-related data should be interpreted with caution, in particular if less commonly encountered species are implicated.

Despite all being commensals that colonize host or natural food surfaces, the ability of various staphylococci to cause infection differs. Besides highly pathogenic *S. aureus*, one can differentiate between "medium"-pathogenic staphylococci—with the *S. epidermidis* group, *S. lugdunensis*, and *S. saprophyticus* as typical examples—and relatively nonpathogenic staphylococci, represented by saprophytic species associated with foods of plant and animal origin and/or those that are animal adapted (88). Strain-specific features at the subspecies level and host-specific capabilities of a given staphylococcal species also have to be considered. Thus, even less-virulent CoNS species may cause infections, particularly if cofactors are present that favor infections, such as foreign bodies and/or immunosuppression (88).

Overall, *S. epidermidis* is the most common species in CoNS

infections, followed by *S. hominis*, *S. haemolyticus*, and *S. capitis* (89–91). In contrast, in a global endocarditis study, *S. lugdunensis* was reported as the second most common CoNS pathogen (68).

The most important clinical entity associated with CoNS is foreign body-related infections (FBRIs), also designated device-associated health care-associated infections (DA-HAIs). These comprise local and bloodstream-related entities associated with inserted or implanted medical devices. FBRIs comprise a unique, complex constellation of many factors that have to be considered for their successful management (92).

While *S. aureus* is capable of causing superantigen- and exfoliative toxin-mediated diseases, such as toxic shock syndrome (TSS), staphylococcal scalded skin syndrome (SSSS [dermatitis exfoliativa neonatorum Ritter von Rittershain disease]), and staphylococcal food poisoning (SFP), confirmed clinical cases caused by CoNS are lacking. Early reports of CoNS also being causative agents of TSS and SFP (93) have not yet been confirmed. *S. epidermidis* strains recovered from patients with TSS symptoms produced no superantigens but were able to stimulate human monocytes to produce cytokines, which may have been responsible for clinical symptoms (94). After a bibliographic survey, it was found that CoNS species isolated from milk or dairy products have never been involved in any case of SFP following the ingestion of dairy products (4). However, CoNS may carry enterotoxin genes (see "PTSAgs and exfoliative toxins," below).

S. epidermidis Group

The *S. epidermidis* group comprises typical "medium"-pathogenic staphylococci, necessitating a decision, each time they are detected in clinical specimens, on whether they represent true infection or only colonization/contamination. Also, study data on the prevalence and distribution of *S. epidermidis*-group CoNS in various infection entities are often hampered by the fact that the causative significance of enrolled isolates is not adequately validated.

Nevertheless, infections due to *S. epidermidis* or *S. haemolyticus*, the most frequently isolated species, have the largest clinical impact. *S. epidermidis* has certainly become the most important model organism for studying DA-HAIs. With descriptions of many novel CoNS species in the past 2 decades and improvements in diagnostic differentiation approaches, further organisms of this group have become apparent. One example of these diagnostically emerging species is *S. pettenkoferi* as a causative agent of human bloodstream infections (BSIs) and osteomyelitis (18, 95). One might assume that difficult-to-detect CoNS species may be underdiagnosed, at least in infections of immunocompromised patients (96, 97). In an era where matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) as well as diagnostic and whole-genome sequencing is being established in routine procedures, these species may increasingly be identified.

While the vast majority of CoNS infections of this group are characterized by a subacute or even chronic course of infection, with a nonspecific, mild, and subtle clinical picture (98), aggressive, severe, and/or lethal infections have (rarely) been reported. However, data giving valid species identification are sometimes absent in these cases.

Infections associated with medical devices. No kind of inserted or implanted foreign body has ever failed to be colonized and infected by CoNS of the *S. epidermidis* group, with *S. epidermidis* as the leading causative organism (Table 2). CoNS account for the majority of FBRIs in both temporarily and permanently implanted devices (99). FBRIs comprise local (e.g., exit site) and systemic infections. Originating from bacteremia or other systemic spread of causative organisms and depending on the nature and localization of the foreign body, sepsis, endocarditis, meningitis, joint sepsis, vertebral abscesses, and other local manifestations due to metastatic seeding may result. Local inflammation signs include erythema, warmth, swelling, tenderness, and purulent drainage, which characterize exit-site infections.

(i) Foreign body-related bloodstream infections (FBR-BSIs). CoNS of the *S. epidermidis* group are a very common cause of health care-associated bacteremia (100). Most FBR-BSIs are catheter-related bloodstream infections (CRBSIs), i.e., those resulting from the insertion of intravascular catheters or totally implanted ports (e.g., Port-a-Cath, MediPort, and Infusaport varieties). Based on a study of 422 hospital ICUs in 36 countries that participated in the International Nosocomial Infection Control Consortium (INICC) between 2004 and 2009, the pooled rate of central line-associated BSIs was found to be 6.8 per 1,000 central line-days (101). While infection control programs focusing on DA-HAI surveillance were shown to reduce the incidence of DA-HAIs by as much as 30% (102), rates for CRBSIs still ranged from approximately 2 per 1,000 central line-days, in U.S. medical/surgical ICUs, to >30 per 1,000 central line-days, in burn units (101, 103, 104). At the end of a 7-year period, the most common isolates recovered from nosocomial bloodstream infections, as recorded within the U.S. nationwide Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) database, were CoNS (31%), followed by *S. aureus* (20%) (105).

There are several studies showing that patients with FBR-BSIs have significantly longer ICU and/or hospital stays and higher mortality rates and hospital costs than uninfected patients (106–108); in a nonteaching hospital, attributable ICU and hospital stays of 2.41 and 7.54 days, respectively, were found (107). The attributable mortality rate for CRBSIs was estimated to be 1.8% at a university hospital's general ICU (109). The attributable costs per infection were estimated to be $11,971 to $56,000 (106–108).

CoNS of the *S. epidermidis* group also act as main pathogens for other entities resulting in FBR-BSIs. These comprise infections associated with prosthetic vascular grafts, prosthetic heart valves, cardiac devices, and coronary stents. In contrast to an earlier assumption that CoNS are more frequent in late-onset prosthetic vascular graft infections, there is no relationship between the microbiological pattern of infection, the time of infection onset, and the graft location (110). CoNS of the *S. epidermidis* group are still considered the most frequent cause of early prosthetic valve infective endocarditis (PVIE)—being responsible for 37 to 47% of early cases and about 25% of late cases, followed by *S. aureus* (20% and 11 to 21%, respectively) (111–113). A fatal early PVIE secondary to *S. epidermidis*, with a very aggressive progression, has been published (114).

Past data have described clinical courses of PVIE caused by *S. epidermidis* group CoNS as being subacute or even chronic, usually subtle, and without fulminant signs of infection (115). However, even usual cases of PVIEs caused by CoNS may exhibit a more aggressive character than previously thought. Findings from the International Collaboration on Endocarditis merged database showed that heart failure was encountered significantly more frequently with CoNS (54%) than with either *S. aureus* (33%) or viridans group streptococci (32%) (116). Moreover, prosthetic

material-associated infective endocarditis (IE) due to CoNS is associated with a high rate of methicillin resistance and significant valvular complications, as evidenced by an observational study of prospectively collected data from a multinational cohort of patients (117, 118). CoNS of the *S. epidermidis* group are also common causative agents of infections of left ventricular assist devices and coronary stents (119–121).

Importantly, clinical symptoms of FBR-BSIs can be subtle and nonspecific at the beginning of the colonization process; however, persistent CoNS infection may lead to metastatic seeding, embolic complications, and septic thrombophlebitis, resulting in severe complications and a fatal outcome (92).

(ii) Local FBRIs. There are a multitude of medical devices without direct connection to the bloodstream that can be colonized by CoNS of the *S. epidermidis* group, leading subsequently to local infections.

In nosocomial drain-associated cases of meningitis/ventriculitis, CoNS of the *S. epidermidis* group were responsible for 73% of documented infections, with two-thirds of isolates found to be oxacillin resistant (122). In a retrospective study of cerebrospinal fluid shunt-associated infections in adults over an 11-year period, the most prevalent organisms were CoNS (55% oxacillin resistant), which were found in 37% of specimens (123). In a study enrolling culture-proven, adult bacterial meningitis caused by a single pathogen, 14/127 (11%) cases were caused by CoNS strains, comprising *S. epidermidis* (71%) and *S. haemolyticus* (29%) (90); however, the small sample size limited the study's power. All patients with CoNS infection in that study harbored medical devices, whereas only 55% of patients with non-CoNS bacterial meningitis were characterized as having inserted foreign bodies.

Another shunt-associated CoNS-caused entity is peritonitis in the context of ventriculo-peritoneal (VP) shunts or, more frequently, continuous ambulatory peritoneal dialysis (CAPD), including respective exit-site infections. In several studies, CoNS of the *S. epidermidis* group were shown to represent the most frequent cause of peritonitis, accounting for around 30% of all episodes, including recurrences (124–126). Of 51 nonduplicated CoNS isolates collected from CAPD peritonitis episodes within a 2-year period and differentiated by several sequencing approaches, *S. epidermidis* was the most common CoNS species isolated, accounting for 67% of cases, followed by *S. haemolyticus* (12%), *S. warneri* (8%), and other species (91). In a recent Canadian study, it was reported that obesity might be associated with a higher risk of CoNS peritonitis among peritoneal dialysis (PD) patients (127).

Even though prosthetic joint infections (PJIs) are relatively uncommon (1% to 3%), they remain one of the most devastating complications of prosthetic surgery and are associated with significant morbidity (128, 129). The most commonly cultured microorganisms are CoNS (primarily *S. epidermidis*), occurring in approximately 30% to 50% of cases, followed by *S. aureus* (about 10% to 45%) and mixed flora (about 10%) (128, 130–132). Non-*S. aureus* and non-*S. epidermidis* species, in particular *S. hominis* and *S. haemolyticus*, account for about 17% of cases (88, 130) (Table 3). PJIs have traditionally been divided into early infections, occurring within 4 weeks postoperatively (class I), those occurring between 4 weeks and 2 years postoperatively (class II), and late infections, occurring thereafter (class III) (133) (for current classification, see the website of the American Association of Orthopedic Surgeons). The last stage, showing more subtle signs of inflammation, chronic persistent postoperative pain, and implant loosening (low-grade PJIs), is more commonly associated with CoNS (134). In a retrospective cohort study conducted across 10 hospitals over a 3-year period, CoNS were isolated from 24% of culture-positive PJIs; 89% of these were methicillin-resistant strains (129).

CoNS of the *S. epidermidis* group can also be detected regularly in association with other implanted devices. In particular, these CoNS may be involved in the pathogenesis of fibrous capsular contracture—the leading long-term complication of augmentation mammoplasty (135). Species of the *S. epidermidis* group were predominantly found in, and the presence of CoNS was significantly associated with, capsular contracture (136). CoNS were also commonly isolated from cases of late-onset endophthalmitis. After implantation of artificial intraocular lenses following cataract surgery, they comprised about 60% of all pathogens recovered (of these, >90% of strains were *S. epidermidis*) (137, 138).

Other infections. (i) Native valve endocarditis. CoNS have emerged as being responsible for IE, not only PVIE but also native valve IE (NVIE) (139). CoNS causing both entities have been identified as *S. epidermidis* (71.4%), followed, with a considerable gap, by *S. lugdunensis* (8.8%), *S. hominis*, *S. capitis*, *S. haemolyticus*, and others (68). However, CoNS are still considered rather unusual causes of community-acquired native valve IE, accounting for only 1 to 5% of cases (140). In contrast, as shown in a French population-based study, CoNS are significantly more prevalent in health care-associated cases of IE (including NVIE), being the second most frequent causative agent (26.2%), after *S. aureus* (32.8%) (139). Based on the U.S. Agency for Healthcare Research and Quality's Nationwide Inpatient Sample for 1998 to 2009, examination of IE revealed that non-*S. aureus* staphylococci, in third place, accounted for 6.7% and 10.3% of all cases and cases with known microorganisms, respectively (141). Based on patient records for all operations for NVIE from 1985 to 2004, CoNS (8%) belonged to the four most commonly identified organisms linked to NVIE in a retrospective, monocenter study (142).

In intravenous drug (IVD) addicts, repeated episodes of *S. epidermidis* bacteremia as a result of nonsterile injections may have led to right-sided IE (143). Although tricuspid valve involvement is significantly more prevalent in IVD abuse (IVDA) patients, more frequent left heart involvement is emerging, with a severe clinical course and a need for surgery in the active phase (144). After *S. aureus* (51.3%) and streptococcal species (23.1%), *S. epidermidis* (15.4%) was the third most common pathogen in IVDA-related IE (144). NVIE cases due to *S. haemolyticus*, *S. hominis*, *S. warneri*, and other members of this group have rarely been reported (118, 145, 146).

In contrast to typical clinical courses of IE due to CoNS, studies have demonstrated that more aggressive *S. epidermidis*-caused NVIE courses may also exist, which can lead to valve destruction requiring valve replacement, heart failure, annular or myocardial abscesses, emboli, and mortality, comparable to the course observed with NVIE caused by *S. aureus* (147–150). Study results comparing *S. epidermidis* NVIE and PVIE isolates for virulence in a *Caenorhabditis elegans* model suggested that NVIE isolates might constitute a more virulent subset within this species (151). Unusually, a very rapidly destructive IE caused by *S. epidermidis*, with fast valve destruction, has been reported (152).

(ii) Infections in neonates. While in healthy term infants CoNS

of the *S. epidermidis* group habitually represent commensals with a rather low invasive capability, preterm newborns are predisposed to invasive CoNS infections. The reasons for this include the immature immune system as well as the impaired skin and mucosal barriers of preterm newborns. Moreover, extremely preterm infants or very-low-birth-weight (VLBW) infants are regularly exposed to invasive procedures, including the insertion of foreign bodies, during neonatal intensive care.

Colonization of the surface of the human body by CoNS is initiated in the first few days or weeks of life, with *S. epidermidis*, *S. warneri*, and *S. haemolyticus* as the most prevalent species (153, 154). During hospitalization, resistant skin isolates, especially multidrug-resistant, *mecA*-positive *S. haemolyticus*, become more prevalent (154). Moreover, CoNS are the first and most abundant gut colonizers, at least under the conditions of a modern Western lifestyle (155). Genotyping demonstrates that the gastrointestinal tract of newborns is colonized by those strains of *S. epidermidis* and *S. haemolyticus* responsible for subsequent, late-onset sepsis (LOS) in preterm neonates (156).

In terms of infectious disease management of neonates, early-onset (<72 h of life) and late-onset (between 72 h and 30 days of life) (90) infections can be distinguished. Furthermore, preterm infants, characterized by birth before 37 weeks of gestational age, can be differentiated from term infants. CoNS (as with *S. aureus*) were more frequently causes of late-onset, nosocomial sepsis in the neonatal period, especially in VLBW infants (157). These infants were at increased risk for neonatal morbidities, prolonged hospitalization, and mortality (158). In evaluating late-onset neonatal infections, a population-based prospective observational study showed that CoNS accounted for 13.6% (*Escherichia coli*, 55.5%; *S. aureus*, 12.7%; and group B beta-hemolytic streptococci [GBS], 7.3%) of all infections, with an incidence rate of 0.67 (*E. coli*, 2.72; *S. aureus*, 0.62; and GBS, 0.36) per 1,000 live births (159). Thus, besides *E. coli*-induced urinary tract infection (UTI) among term infants and GBS infections, CoNS septicemia affecting preterm infants was recognized as one of the three major types of late-onset neonatal infection (159).

Regarding neonatal blood culture-confirmed sepsis, the median incidence is 16 per 1,000 live births (early-onset sepsis, 2.2 to 9.8 per 1,000 live births) (160). For developed countries, the incidence of sepsis in neonates is usually estimated as 1 to 5 per 1,000 live births, with mortality rates as high as 15 to 20% (161). Studies in developing countries have demonstrated clinical sepsis rates ranging from 49 to 170 per 1,000 live births (162). In comparison with *S. aureus* infections, CoNS infections were more frequently associated with VLBW (<1,500 g at birth), lower gestational age, a history of intravascular catheters, and prolonged parenteral nutrition (159, 163). Until the 1970s, GBS and Gram-negative bacteria were most frequently recovered from symptomatic bacteremia of newborns in ICUs; CoNS subsequently became recognized as pathogens in critically ill, hospitalized, premature infants (164, 165). Among both early and later infections occurring in ICU neonates, Gram-positive organisms, with *S. epidermidis* as the predominant species, became the most prevalent pathogens (166). In a recent study of early-onset neonatal sepsis in term and preterm infants, CoNS (2.4/1,000 and 2.5/1,000 admissions, respectively) were the most common microorganisms (167).

Questions regarding CoNS infection-associated morbidity and, in particular, mortality in the case of CoNS-caused neonatal sepsis, have not been answered clearly. While in several studies CoNS-related mortality was rather rare (168, 169), other investigations indicated that the mortality rate attributable to CoNS was comparable to that of *S. aureus* and that persistent bacteremia—in the absence of central venous catheterization—and significant morbidity, despite aggressive antibiotic therapy, may still occur (78, 163, 170, 171). In neonates requiring intensive care, biofilm production, independently of the presence of the *ica* operon, was shown to be the most significant risk factor for persistent, late-onset CoNS bacteremia (78). Persistent CoNS sepsis in neonates was associated with severe thrombocytopenia (78, 170).

CoNS of the *S. epidermidis* group were the most frequent agents of central venous catheter (CVC)- and umbilical catheter-associated BSIs in neonatal ICUs (172). Besides BSIs, CoNS may cause further invasive infections in preterm infants, such as infective endocarditis, meningitis, and necrotizing fasciitis (171, 173, 174).

(iii) Bacteremia/septicemia in neutropenic patients. Especially with chemotherapy-induced neutropenia, CoNS of the *S. epidermidis* group are still the main cause of septicemia in febrile patients, accounting for approximately 20 to 40% of cases (175–178). In a multicenter study analyzing the etiology of 1,051 bacteremic episodes in 782 cancer patients, CoNS accounted for more than 40% of the pathogens isolated (179). Stratifying patients with hematological malignancy and with solid tumors in a prospective, multicenter study involving 54 hospitals, there was no significant difference in the distribution of CoNS involved in bacteremia (180); CoNS were the leading pathogens, comprising 50.6% and 44.9%, respectively, of the strains isolated (180). Notably, nosocomial spread of CoNS among hematological patients with neutropenia can occur, and oncology wards may for years harbor predominant clones of *S. epidermidis* as a cause of BSIs (181, 182).

S. lugdunensis

Given its specific pathogenic capacity and clinical significance, *S. lugdunensis* has a special position among all other CoNS (183) (Fig. 2). It is generally accepted to have a role as an infrequent but aggressive cause of IE. *S. lugdunensis* IE is characterized by an often destructive course of disease with a high mortality rate, which appears unusually fulminant for a CoNS species IE but which makes it rather similar to *S. aureus* IE. Starting with its discovery as a causative agent of IE in 1989, by Etienne et al. (184, 185), many case reports and case studies have confirmed this behavior, which is unusual for other CoNS species (186–188). In an analysis of clinical cases combined with a review of the literature, native valve IE by *S. lugdunensis* exhibited a mortality rate of 42% and was characterized by mitral valve involvement and frequent complications, including heart failure, abscess formation, and embolism (186). In comparison, prosthetic valve IE was characterized by aortic valve involvement, which was also typically aggravated by abscess formation, but with an even higher mortality (78%). Both IE entities required surgery in more than 50% of cases (186). Another literature search reported an overall mortality rate of 38.8% (189). In a case of a recurrent pacemaker-related bloodstream infection, recovered *S. lugdunensis* isolates exhibited several phenotypes, including small-colony variants (SCVs), which were shown to have the same genetic background (190).

Several reports highlight the ability of *S. lugdunensis* to cause various kinds of FBRIs, including catheter-related bacteremia, VP shunt infection, and prosthetic joint infection (185, 191–193). VP shunt infections or other central nervous system procedures may

be accompanied by severe complications, such as meningitis and brain abscesses (191, 194). Recurrent exit-site infection due to this species has also been described (195). Venous catheters or other foreign devices are the most common portals for *S. lugdunensis* bacteremia (196–198). Among patients with signs of bacteremia due to *S. lugdunensis*, 23.8% had clinically significant bacteremia, with an incidence of 1.3 cases per 100,000 admissions (197). In a rather high percentage of cases, i.e., up to 50% of cases, *S. lugdunensis* bacteremia was associated with IE (196).

In the past few years, there has been mounting evidence to show that *S. lugdunensis* is also a common cause of skin and soft tissue infections (SSTIs), with an incidence of 53 per 100,000 per year if optimized identification methods are applied (199). Recently, a case of *S. lugdunensis* involvement in necrotizing fasciitis was also reported (198). While several studies and many case reports corroborate its role in SSTIs (200, 201), further prospective studies are warranted to verify its position as a pathogen and/or a colonizing bacterium for skin-related entities (202). In accordance with its known main habitat, *S. lugdunensis*-induced abscesses have been reported to occur mostly in perineal and inguinal areas (199, 203). However, *S. lugdunensis* has also been isolated from breast exudates and pus, and an association with nonpuerperal mastitis has been postulated (204).

Further entities ascribed to *S. lugdunensis* comprise single cases of brain abscess, peritonitis, osteomyelitis, discitis, septic arthritis in native joints and as a complication of arthroscopy, endometritis with premature rupture of membranes, and pyomyoma after cesarean section (205–210).

S. saprophyticus subsp. *saprophyticus* as a Cause of Urinary Tract Infection

S. saprophyticus subsp. *saprophyticus* is the second most frequent causative microorganism of uncomplicated lower UTI in young, sexually active women (211). However, there are also case reports of this microorganism associated with UTIs in girls and males of all ages. Complications include acute pyelonephritis and nephrolithiasis and, in the case of male patients, urethritis, epididymitis, and prostatitis (212, 213). BSIs with *S. saprophyticus* subsp. *saprophyticus* that are not related to urinary tract infections, such as septicemia, which is commonly associated with tunneled central venous catheters, as well as endocarditis, have been reported anecdotally for both genders (214, 215).

Other CoNS

Staphylococci associated with foods of plant or animal origin (Table 4), and considered primarily nonpathogenic, have only very rarely been reported as putative causative agents of infections. However, doubts may remain in regard to the validity of species identification and/or association with the infectious process (Tables 2 and 4).

Infections Due to Small-Colony Variants

SCVs have been recognized since at least the beginning of the 20th century, often being described as dwarf, pleomorph, or "G" forms. Later on, they were associated with infections of a chronic nature, often characterized by a recurrent and relapsing course (216).

While most clinical studies and case reports of chronic infections caused by SCVs describe infections by *S. aureus*, cases are also associated with CoNS-SCVs. Notably, almost all published cases of infections due to CoNS-SCVs were foreign body related. Initial cases described prosthetic valve IE and osteosynthesis infections during the 1970s and -80s (217, 218). SCVs of *S. epidermidis* and *S. capitis* were detected in cases of pacemaker electrode infections (219, 220). A fatal case was reported for a catheter-associated BSI with a teicoplanin-resistant *S. epidermidis* SCV isolated from the blood culture of a patient with acute leukemia and therapy-induced neutropenia (221). For *S. lugdunensis*, SCVs were described in a case of recurrent pacemaker-related BSI (190).

The enhanced ability of *S. epidermidis* SCVs to colonize foreign bodies and to form biofilms and abscesses has been confirmed by *in vitro* and animal experiments (222, 223). Further details on SCV pathogenesis are given in the next section.

PATHOGENICITY

Staphylococci, with the capacity to colonize and infect human and animal hosts, own a species- and strain-specific arsenal of diverse strategies to enable adherence, aggression, invasion, persistence, and/or evasion of both innate and adaptive immunity. However, in comparison with *S. aureus*, clearly less is known about the virulence mechanisms in CoNS, except for aspects of biofilm formation by *S. epidermidis*. In general, CoNS isolates lack the virulence determinants responsible for aggression. Nevertheless, factors involved in colonization may successfully support the bacterium-host interaction, a phenomenon that may be based, at least partly, on the multifunctional character of various staphylococcal virulence factors known to exhibit redundant and overlapping functions.

Adherence to Surfaces and Phases of Biofilm Formation

The critical first event in establishing colonization and/or infection by staphylococci is adherence to host or—as a consequence of modern medicine—foreign body surfaces. The colonization of the polymer surface of a medical device by formation of a multilayered biofilm has been considered the critical factor in the pathogenesis of foreign body-associated infections caused by CoNS (224–226). Among the CoNS, *S. epidermidis* is by far the species recovered most often from biofilm-associated infections. The infection of the polymer surface likely occurs during insertion of the device, after the inoculation of a small number of bacteria from the patient's mucous membranes or skin. In the biofilm, huge bacterial cell agglomerates are encased in an amorphous extracellular material composed of bacterial products, such as teichoic acids, proteins, polysaccharides, and extracellular DNA (eDNA), and host products (227–232). Biofilms may be formed on the abiotic surfaces of medical devices or on biotic surfaces, such as host tissue. Biotic surfaces may also be medical devices, which become conditioned with plasma and host extracellular matrix (ECM) proteins after their insertion.

To mediate attachment to abiotic surfaces or host factors, such as plasma extracellular and matrix proteins or even host cells, as well as to facilitate intercellular adhesion, members of the genus *Staphylococcus* produce various proteinaceous and nonproteinaceous adhesins (233). Proteinaceous adhesins have been grouped into covalently surface-anchored proteins, also termed cell wall-anchored (CWA) proteins, noncovalently surface-associated proteins, including the autolysin/adhesin family, and membrane-spanning proteins (234–237). Nonproteinaceous adhesins include the polysaccharide intercellular adhesin (PIA) (also known as poly-*N*-acetylglucosamine [PNAG]) as well as wall teichoic and lipoteichoic acids.

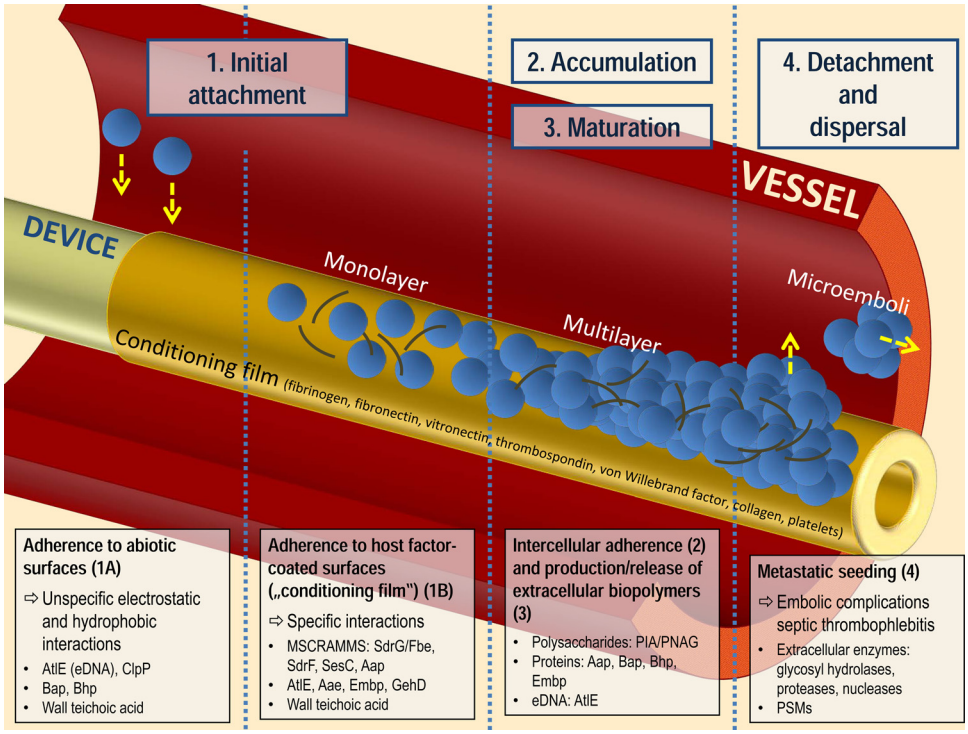


FIG 4 Pathogenesis of catheter-related infections and factors influencing biofilm genesis. The image shows the three-step process of biofilm formation on the surface of an intravascular catheter, with rapid initial adhesion and attachment of CoNS microorganisms to the polymer foreign body surface resulting in a monolayer (1), followed by a prolonged accumulation phase which involves cell proliferation, intercellular adhesion processes, and maturation (2 and 3). (4) Finally, microorganisms may disaggregate from the macrocolony and drift into the bloodstream, resulting in metastatic and embolic complications.

The distinct phases of biofilm formation by CoNS and the respective underlying molecular mechanisms have been analyzed thoroughly in past years. The formation of the biofilm may be divided into four steps (Fig. 4). First, bacteria rapidly attach to the biotic or abiotic surface. In the second step, after attachment, bacteria multiply and accumulate in multilayered cell aggregates, a process requiring intercellular adhesion. In the third phase, the biofilm grows and matures into a thick, structured layer. A mature biofilm contains channels that are fluid filled to ensure the delivery of oxygen and nutrients to the bacterial cells located in the deeper layers of the biofilm (238). Finally, single cells or cell agglomerates can dissociate from the biofilm and disseminate via the bloodstream to start colonization and biofilm formation at a different site.

Attachment to abiotic surfaces. The attachment of bacteria to various biomaterials is determined by the surface properties of the bacteria and the foreign bodies. It involves physicochemical forces, such as hydrophobic interactions, van der Waals forces, and charge. These interactions may be mediated by different surface components of CoNS, i.e., CWA proteins that are covalently linked to peptidoglycan; surface-associated proteins that are surface attached by different mechanisms, such as hydrophobic or ionic interactions; and nonproteinaceous surface molecules, such as teichoic acids.

(i) Noncovalently linked surface-associated proteins. Cell surface hydrophobicity and primary attachment have been ascribed to bacterial CWA and surface-associated proteins. The major 148-kDa surface-associated autolysin/adhesin, AtlE, from *S. epidermidis* mediates initial adherence of bacterial cells to the polymer surface and is highly similar to the *S. aureus* autolysin Atl (239). AtlE and Atl are organized in the same modular structure and are functionally interchangeable (239, 240). AtlE is proteolytically cleaved into two bacteriolytically active domains: a 60-kDa amidase (AM) and a 52-kDa glucosaminidase (GL). The central portion of the protein contains three repeats (R1, R2, and R3), which seem to mediate targeting to the bacterial cell surface via binding to peptidoglycan. They are possibly also involved in adhesion to polystyrene (239, 241). The targeting of Atl to the equatorial ring on the staphylococcal cell surface, which marks the cell's future division site, is based on an avoidance mechanism by wall teichoic acid (WTA) (242). WTA prevents binding of Atl, and because it is abundant in the former cell wall but not at the cross wall region, it directs Atl to the cross wall to carry out the last step of cell division, i.e., cell separation (242).

Recently, homologous Atl proteins with similar functions were also reported for other CoNS, such as *S. caprae* (AtlC), *S. saprophyticus* (Aas), *S. lugdunensis* (AtlL), and *S. warneri* M (Atl_{WM}) (243–246). Initial adhesion most probably is mediated not only directly, by the AtlE protein itself, but also indirectly, via its enzymatic function: the hydrolysis of the cell wall peptidoglycan leads to autolysis and thus to the release of eDNA, which has been shown to be an important component of staphylococcal biofilms. Treatment with DNase I is able to limit initial adherence of *S. epidermidis*, but it does not cause disintegration of mature biofilms, suggesting that eDNA may be most important as a matrix component during the early stages of *S. epidermidis* biofilm formation (247). Another study demonstrated that the presence of DNase I in culture medium is able to inhibit biofilm production

by both *S. aureus* and *S. epidermidis*. However, treatment of preformed biofilms with DNase I does not cause biofilm detachment in the case of *S. epidermidis*, while it does with *S. aureus*, suggesting different functional roles for eDNA in *S. aureus* and *S. epidermidis* biofilm production (232). Recently, it was demonstrated that point mutations in the active sites of the AM and GL domains of Atl result in the loss of enzymatic functions and also in the loss of biofilm formation, further supporting a role for the Atl-mediated release of eDNA in biofilm formation (248). Crystal structures are available for the catalytically active AM domain and the repeat R2 domain, unraveling their enzymatic mechanism and substrate- and ligand-binding properties, respectively (249, 250).

A role in biofilm development has also been identified for the *S. epidermidis* protease ClpP (251). ClpP proteases degrade misfolded proteins and may be involved in stress adaptation, virulence, and biofilm formation (251). An *S. epidermidis clpP* mutant revealed reduced biofilm production *in vitro* and decreased pathogenicity in a rat model of intravascular CVC-associated infection compared to those with the wild type (251). These defects could be restored by complementation with a functional copy of the *clpP* gene. Decreased biofilm formation of the *clpP* mutant resulted from both less initial attachment to a polystyrene surface and less PIA/PNAG production, although the expression of the *icaADBC* operon (see below) was comparable between both the *clpP* mutant and the wild-type strain (251). ClpP expression was also shown to be controlled by the quorum sensing (QS) *agr* system (see below), explaining one possible mechanism by which *agr* negatively regulates initial attachment for biofilm formation.

(ii) Covalently linked surface proteins. Some *S. aureus* isolates associated with bovine mastitis produce a 240-kDa surface protein, called biofilm-associated protein (Bap), which mediates attachment to polystyrene and the accumulation phase of biofilm production (see below) (252). The occurrence of *bap* significantly enhanced the capability of *S. aureus* to colonize the bovine mammary gland and to persist *in vivo*. Recently, *bap*-orthologous genes were also found in CoNS recovered from animal mastitis, such as *S. epidermidis*, *S. simulans*, *S. hyicus*, and *S. chromogenes* (253). In all these isolates, Bap orthologues were able to mediate biofilm formation when the PIA/PNAG exopolysaccharides were absent (see below). While the *bap* gene has been reported to be absent from *S. aureus* isolates of human origin, the genome of the human clinical isolate *S. epidermidis* RP62A harbors a gene encoding a protein homologous to Bap, namely, Bhp (253). Bhp shares 20%, 31%, and 53% identical amino acids in the N-terminal A-domain, B-repeat, and C-repeat regions, respectively, with the *S. epidermidis* Bap protein. Because of the structural similarity, the 258-kDa Bhp protein was assumed to promote biofilm formation, but experimental evidence is still lacking (253). The structural properties of Bhp and Bap correspond to those of other CWA proteins (see below). More recently, the presence of the *bap* gene was also demonstrated in nosocomial human isolates of *S. haemolyticus* and *S. cohnii* (254).

(iii) Teichoic acids. Surface charge also depends on teichoic acids. Wall teichoic acid (WTA) is covalently linked to the peptidoglycan, while lipoteichoic acid (LTA) is linked to the cytoplasmic membrane via a membrane-spanning lipid anchor. Teichoic acids are strongly charged cell wall polymers composed of alternating ribitol or glycerol and phosphate groups. *S. epidermidis* RP62A WTA is composed of poly(glycerol phosphate) units that are substituted at the 2 position of glycerol with alpha-glucosamine, alpha-glucose, alpha-6-D-alanyl-glucose, or D-alanine (255). DltA catalyzes the incorporation of D-alanine into WTA and thus renders the cell surface less negatively charged. A *dltA* mutant of *S. aureus* has a biofilm-negative phenotype, because primary adherence to a glass or polystyrene surface, which is negatively charged or hydrophobic, respectively, is abrogated (256). The genome of the human clinical isolate *S. epidermidis* RP62A harbors a *dltA* homolog, suggesting that the surface charge determined by teichoic acids may also contribute to *S. epidermidis* colonization of artificial surfaces. Moreover, it was recently demonstrated that the deletion of *S. epidermidis tagO*, whose gene product mediates the first step of WTA biosynthesis, has pleiotropic effects, including reduced primary adherence to a polymer surface and reduced biofilm production (257).

Attachment to biotic surfaces. Shortly after the insertion or implantation of a medical device, it becomes covered with ECM and plasma proteins, such as fibrinogen, fibronectin, thrombospondin, collagen, von Willebrand factor, and vitronectin, or with host cells, such as platelets. Some of these host factors may serve as receptors for specifically attaching staphylococci that express the respective adhesins on the cell surface (258, 259). Thus, in the later steps of the adhesion process *in vivo*, adherence of CoNS to such host factors may be crucial. Moreover, in some instances, CoNS seem to be capable of attaching directly to the host tissue, i.e., to the endocardium in the pathogenesis of native infective endocarditis, which may be caused not only by *S. aureus* but also, occasionally, by *S. epidermidis*.

(i) Noncovalently linked surface-associated proteins. The *S. epidermidis* autolysin/adhesin AtlE not only mediates primary adherence to a polymer surface (see above) but also attaches to vitronectin (239). Moreover, in a CVC-associated infection model in rats, an *in vivo* importance for AtlE was found: only half of the animals challenged with an *atlE*-negative mutant developed an infection, versus 80% of animals challenged with the isogenic wild-type strain (260). The homologous autolysin Aas from *S. saprophyticus* binds to fibronectin and sheep erythrocytes, leading to hemagglutination; AtlC from *S. caprae* has also been shown to bind to fibronectin (244, 261).

Aae from *S. epidermidis* is another multifunctional autolysin/adhesin with bacteriolytic activity that binds to fibrinogen, vitronectin, and fibronectin dose dependently and in a saturable fashion, with a high affinity (262). Aae has a modular structure and harbors three repeats in its N-terminal domain, each having high similarity with the lysine motif (LysM), which confers cell wall attachment to various surface-associated proteins (263). It also contains a cysteine- and histidine-dependent amidohydrolase/peptidase (CHAP) domain in its C-terminal portion, which has bacteriolytic activity in many proteins (264). Interestingly, in the homologous Aaa protein from *S. aureus*, both the LysM and CHAP domains can mediate adherence to fibrinogen, fibronectin, and vitronectin (240).

Another example of multi- or bifunctional surface molecules of *S. epidermidis* exhibiting both enzymatic and adhesive functions is the GehD lipase. GehD seems to be surface associated, at least in part, and mediates binding of bacteria to collagen (265). Moreover, a putative elastin-binding protein from *S. epidermidis* RP62A, containing a LysM domain, was identified by whole-genome sequencing (266).

The 1,100-kDa giant extracellular matrix-binding protein, Embp, which is probably attached to the cell surface via a C-ter-

minal, transmembrane anchor, has at least two adhesive functions: fibronectin binding and intercellular adhesion (see below) (267). Originally, Embp was identified as a fibronectin-binding protein by use of the phage display technique (268). Embp contains numerous partially alternating repeat domains, i.e., 59 domains termed "found in various architectures" (FIVAR) and 38 domains termed "protein G-related albumin-binding" (GA) domains. Functional analyses indicated that the Embp FIVAR domains harbor the fibronectin-recognizing activity (267). Therefore, the fibronectin-binding site of Embp is distinct from that of the *S. aureus* fibronectin-binding proteins A and B (FnBPA and FnBPB).

(ii) Covalently linked surface proteins. The information on surface adhesins of CoNS that recognize human host factors and are surface located due to a covalent linkage to the cell wall peptidoglycan of the bacteria has greatly increased in past years (235). Such proteins are classified as "microbial surface components recognizing adhesive matrix molecules" (MSCRAMMs). The MSCRAMMs share a similar modular structure, which is represented by an export motif (signal peptide) at the N terminus followed by a host factor-recognizing region, one or more repeat domains, a cell wall-spanning domain, and a cell wall anchorage domain, with the last containing an LPXTG sequence. Recently, it was suggested to divide the CWA proteins into four different groups based on their structure-function properties, with the MSCRAMM family being the most prevalent family (237). According to this classification, the use of the term "MSCRAMM" should now be restricted to those CWA proteins that possess at least two adjacently located IgG-like folded domains in their N-terminal A portion that bind their ligands via the "dock, lock, and latch" mechanism (237).

The anchorage of the MSCRAMM to the cell wall is realized by an enzyme termed sortase A, which is located in the cytoplasmic membrane. It solves the linkage between the amino acids threonine and glycine within the LPXTG sequence and introduces a covalent linkage between the threonine and the peptidoglycan (269, 270). The *S. epidermidis* RP62A genome contains 11 genes encoding LPXTG-containing CWA proteins (266, 271). There is a considerable redundancy in functions: CWA proteins can bind to one or several human host factors, such as fibrinogen, fibronectin, thrombospondin, collagen, or vitronectin, and one human factor can be bound by several attachment factors. So far, not all binding partners of all CWA proteins have been elucidated.

The best-characterized MSCRAMM from *S. epidermidis* is the fibrinogen-binding protein Fbe (also referred to as SdrG), which shows similarity to the cell wall-bound fibrinogen receptor (clumping factor; ClfA) from *S. aureus* (272, 273). Heterologous expression of *fbe* in *Lactococcus lactis* and analysis of an *fbe*-deficient mutant demonstrated a role for Fbe in the interaction of *S. epidermidis* with fibrinogen (274, 275). *In vivo* studies suggested Fbe to be a virulence factor, because an *fbe* deletion mutant was attenuated in an intravascular catheter-associated rat infection model (276). Recently, it was reported that SdrG/Fbe also promotes platelet adhesion and platelet aggregation (277). SdrG/Fbe contains its host factor-recognizing domain in its N-terminal region (278). The "dock, lock, and latch" model has been suggested as the mechanism of binding, based on analysis of cocrystals of SdrG/Fbe and synthetic peptides representing the binding site in fibrinogen (279). The model describes that fibrinogen "docks" inside a cleft of two IgG-like folded regions of the protein. Subsequently, the protein changes its conformation so that the ligand "locks" in the cleft. The complex is then stabilized by a C-terminal "latch" (271).

Like some other CWA proteins, SdrG/Fbe contains a characteristic membrane-spanning region that consists of SD repeats. Other surface proteins containing SD repeats identified in *S. epidermidis* are SdrF and SdrH (280). Antibodies against SdrG and SdrH were found in 16 convalescent-phase patient sera, implying that these proteins are produced during infection (280). SdrF binds to type I collagen via its B repeats (281). Because binding to collagen is mediated by the SdrF B repeats but not by the putative ligand-binding N-terminal domain A, it was assumed that SdrF might be a multiligand adhesin and that further ligands have yet to be identified. Furthermore, it was shown that SdrF contributed to the initiation of ventricular assist device driveline-related infections with *S. epidermidis* by adhering to host collagen deposited on the surfaces of the drivelines (281). Anti-SdrF antibodies were able to reduce the *S. epidermidis* attachment to the drivelines.

The CWA protein SesC, whose gene is highly prevalent among clinical *S. epidermidis* isolates, also seems to mediate attachment to fibrinogen, because transformants expressing *sesC* showed increased attachment to fibrinogen-coated surfaces compared to their wild-type strains. Antibodies against SesC were able to reduce the *S. epidermidis* adherence to fibrinogen *in vitro* as well as *in vivo*, using a catheter-associated rat infection model (271, 282). Moreover, anti-SesC antibodies were able to decrease the number of *S. epidermidis* cells in biofilms *in vivo*. The expression of *sesC* was elevated in cells grown in a biofilm in comparison with planktonically grown *S. epidermidis* cells. Together, these findings suggested SesC to be a promising target for the prophylaxis and treatment of biofilm-associated *S. epidermidis* infections (282). Indeed, it was shown recently that active vaccination against recombinant SesC inhibited *S. epidermidis* biofilm production in a subcutaneous foreign body-associated infection model in rats (283).

Another well-characterized CWA protein from *S. epidermidis* is the accumulation-associated protein Aap, which confers intercellular adhesion (see below). Recently, it was reported that the Aap N-terminal domain A mediates adherence to human corneocytes, supporting a role for Aap in skin colonization (284). The roles of other LPXTG-containing surface proteins of *S. epidermidis* remain to be clarified.

(iii) Teichoic acids. In addition to proteins, teichoic acids are also involved in the adherence of *S. epidermidis* to host factors: teichoic acids significantly and dose dependently promoted the attachment of *S. epidermidis* to surface-bound fibronectin (285). Preincubation of either fibronectin-coated surfaces or bacteria with teichoic acid enhanced the attachment of *S. epidermidis*, suggesting that teichoic acid can act as a bridging molecule between fibronectin-coated polymer material and bacteria.

Biofilm accumulation and maturation. After succeeding in primary attachment to biotic or abiotic surfaces, bacteria multiply and accumulate in multilayered cell aggregates, in a process that necessitates intercellular adhesion. Intercellular adhesion may be mediated by different specific macromolecules, such as polysaccharide adhesins and certain proteins that induce cell aggregation. Moreover, due to its anionic character, eDNA generated by lysed cells and teichoic acids may interact with the positively charged polysaccharide adhesins, thereby increasing biofilm accumulation by additionally acting as a "glue."

(i) Polysaccharide adhesins. Transposon mutants that were

unable to aggregate in multicellular layers had lost the production of a polysaccharide termed polysaccharide intercellular adhesin (PIA) (sometimes also referred to as poly-*N*-acetylglucosamine [PNAG] or polysaccharide/adhesin [PS/A]) (286, 287). PIA/PNAG was purified and chemically analyzed, which revealed a unique composition to that point. PIA/PNAG is basically represented by a linear glucosaminoglycan containing no fewer than 130 β-1,6-linked 2-deoxy-2-amino-D-glucopyranosyl residues, with 15 to 20% being de-N-acetylated (228). Some years later, PIA/PNAG synthesis was also found to be a feature of *S. aureus* (288). In an early report, PIA/PNAG from *S. aureus* was termed poly-*N*-succinyl β-1,6-glucosamine (PNSG), because *N*-acetylglucosamine residues were found to be succinylated (289). However, this finding was later identified as an artifact (290).

The biological activity of PIA/PNAG in biofilm formation and immune evasion is determined by its positive charge, which results from partially deacetylating the *N*-acetylglucosaminyl residues, mediated by IcaB (see below) (291). Most likely, the underlying mechanism of the PIA/PNAG-mediated intercellular adhesion is characterized by the electrostatic attraction of its positive charges to the negative charges of the surface-exposed teichoic acids. Polysaccharides composed like PIA/PNAG not only were identified in Gram-positive staphylococci but also were shown to be involved in biofilm formation of Gram-negative pathogens, for instance, *Escherichia coli* and *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans*, and therefore might represent a general concept (292).

The *S. epidermidis* genes that mediate intercellular adherence and production of PIA/PNAG are organized in an operon (*icaADBC*) and have been characterized functionally (293, 294). IcaA confers the proposed *N*-acetylglucosaminyltransferase activity. However, IcaA alone shows only low transferase activity. Coexpression of the catalytic enzyme-encoding *icaA* gene together with *icaD* leads to a significantly increased activity and to the production of *N*-acetylglucosamine oligomers with a maximal length of 20 residues. IcaAD catalyzes the synthesis of long-chain oligomers, which react with anti-PIA/PNAG antiserum only in the presence of *icaC*. IcaB is the cell surface-located enzyme that catalyzes the partial deacetylation of *N*-acetylglucosaminyl residues (291). The partial deacetylation of PIA/PNAG seems to be crucial for its virulence potential, because an *icaB* mutant was significantly less persistent in a model of foreign body-associated infection in mice (291).

In a mouse model as well as a rat model of device-related infections, a PIA/PNAG-negative mutant was significantly less pathogenic than its wild type, delineating the role of PIA/PNAG as an important pathogenicity factor (260, 295, 296). A study analyzing the pathogenic features of strains isolated from polymer-associated septicemic disease compared with saprophytic skin and mucosal isolates revealed that biofilm production and the presence of the *ica* operon essentially correlated with the disease isolates (297).

Interestingly, the *icaADBC* genes were also identified in a collection of biofilm-forming *S. lugdunensis* clinical isolates (298). However, despite the presence of the *ica* gene cluster, the biofilms produced by the *S. lugdunensis* isolates were sensitive to protease treatment but resistant to dispersin B and sodium metaperiodate, which dissolve polysaccharides. Moreover, by using a PIA/PNAG-specific antibody or wheat germ agglutinin, the authors could not detect PIA/PNAG, strongly suggesting that *S. lugdunensis* biofilm formation is mediated predominantly by protein factors rather than by PIA/PNAG (298). Another study also indicated that biofilm formation, PIA/PNAG production, and the presence of the *ica* locus do not seem to correlate among clinical *S. lugdunensis* isolates and other CoNS species, such as *S. capitis*, *S. hominis*, and *S. warneri* (299).

(ii) Proteinaceous adhesins. Biofilm accumulation in *S. epidermidis* may also be mediated by proteins. Thus, Bap and the Bap-homologous protein Bhp may confer accumulative growth (see above) (253). A biofilm-defective mutant was shown to lack a 140-kDa surface protein, the accumulation-associated protein Aap. Aap is essential for biofilm accumulation on polymeric surfaces in certain *S. epidermidis* strains (300, 301). Biochemical and functional properties clearly differentiate Aap from other factors known to mediate biofilm production. Aap can induce accumulative growth in a completely PIA/PNAG-independent manner and was found to be highly prevalent among clinical *S. epidermidis* strains (229, 302, 303). Aap contains a domain A within its N-terminal portion, which is followed by a repeat domain B. The latter is characterized by a variable number of repeats with 128 amino acids each, which mediate cell-to-cell adhesion and biofilm accumulation. Interestingly, the repeat domain B becomes active as an intercellular adhesin only upon removal of the Aap domain A via proteolysis, mediated by either endogenous staphylococcal or host proteases (229). Aap-based intercellular adherence is dependent on the divalent cation Zn^{2+}, and a "zinc zipper" mechanism was implicated for the interaction of the Aap B repeats, which are also designated G5 domains, on neighboring cells (304, 305). Upon transmission electron microscopic evaluation, Aap turned out to have a fibrillar structure, which might explain its function (306). Moreover, analysis of the crystals of a Zn^{2+}-bound construct from the self-associating region of Aap recently provided the basis of the structure of Zn^{2+}-dependent biofilm accumulation of *S. epidermidis* (307). Antibodies against *S. epidermidis* Aap inhibit biofilm formation to some extent, indicating that Aap may be a vaccine candidate for reducing *S. epidermidis* biofilm infections (308). Formerly, it was suggested that Aap plays a role in biofilm accumulation via attaching PIA/PNAG to the bacterial surface. Although Aap clearly can confer accumulative growth in a completely PIA/PNAG-independent manner, an additional mechanism involving PIA/PNAG cannot be ruled out, considering that the G5 domains represent potential *N*-acetylglucosamine recognition domains (305).

The giant *S. epidermidis* protein Embp (see above) not only binds to fibronectin but also mediates biofilm accumulation (267).

Biofilm detachment. Upon biofilm maturation, individual bacteria or clusters of bacteria may dissociate and disperse via the bloodstream. Following this step, further locations in the body may be colonized by circulating bacteria, leading to metastasis of infection. The disintegration of biofilms may be mediated by different mechanisms, such as a variety of extracellular enzymatic activities or the so-called phenol-soluble modulins (PSMs).

(i) Extracellular enzymes. Biofilm detachment may be mediated by different enzymes conferring breakdown of the complex matrix that allows cells to stick together. Depending on the chemical composition of the respective macromolecules gluing the cells together, enzymes such as proteases (cleaving proteins, such as Bap, Aap, and Embp), sugar hydrolases (disintegrating PIA/

PNAG), or nucleases (disintegrating eDNA) are likely to participate.

The Gram-negative pathogenic bacterial species *A. actinomycetemcomitans* synthesizes an extracellular polysaccharide, the linear β-(1,6)-*N*-acetylglucosamine PGA, which is a macromolecule composed similarly to PIA/PNAG (292). Interestingly, *A. actinomycetemcomitans* produces a sugar hydrolase, termed dispersin B, which can degrade PGA (292). Moreover, dispersin B can disintegrate *S. epidermidis* biofilms formed by clinical isolates (292, 309). However, no such enzyme seems to be present in *S. epidermidis*.

eDNA is another significant macromolecule found in staphylococcal biofilms (232, 247, 310). Hence, the presence of a nuclease reduces the production of *S. aureus* biofilms and induces the dispersal of biofilms that preexisted (232). Thus, the secretion and activity of staphylococcal nucleases may also contribute to biofilm detachment. Indeed, it was recently demonstrated that the secreted thermonuclease Nuc has an inhibitory effect on *S. aureus* biofilm development (311). Additionally, a second thermonuclease, Nuc2, also limits the biofilm formation of *S. aureus*, at least under certain *in vitro* conditions (312, 313). In contrast to *S. aureus*, in *S. epidermidis*, DNase I merely reduces biofilm production and cannot disintegrate preexisting biofilms (232). Therefore, because of protein and polysaccharide factors involved in *S. epidermidis* accumulation, nucleases may predominantly affect initial adherence to a surface and detach only young biofilms. However, some studies showed that in many cases of staphylococcal biofilms, the bacterial cells are held together by protein factors and teichoic acids rather than by PIA/PNAG (314, 315). In these cases, treatment with DNase I and protease dissolved the biofilms, although sometimes only partially (315–317). Thus, eDNA has a stabilizing function in PIA/PNAG-negative backgrounds, highlighting the importance of nucleases in biofilm detachment in *ica*-independent biofilm formation. The protease-dependent dispersal of *S. aureus* biofilms depends on the function of the regulatory QS system *agr* (318). Although a role for *S. epidermidis* proteases in the detachment of *S. epidermidis* biofilms has not been confirmed so far, a contribution of such proteases to biofilm detachment seems likely.

The gene encoding the 27-kDa extracellular serine protease GluSE, also known as SspA or Esp, has been cloned and sequenced (319–321). Surface-attached *S. epidermidis* cells were found to produce GluSE, while planktonic cultures were not, indicating a possible role for GluSE in *S. epidermidis* colonization and tissue damage (321). However, it was recently reported that Esp produced by commensal *S. epidermidis* strains interferes with the biofilm production of *S. aureus* and its colonization of the anterior nares and that purified Esp is able to disassemble preformed *S. aureus* biofilms (42). Moreover, there is a correlation between the colonization of the anterior nares of healthy individuals by *S. epidermidis* producing Esp and the absence of colonizing *S. aureus* bacteria, suggesting a mechanism of bacterial interference (42). Another study indicated that *S. epidermidis* Esp interferes with *S. aureus* biofilm production by degrading a variety of proteins, among them specific proteins associated with *S. aureus* biofilms, i.e., FnBPA/FnBPB, protein A, Eap, and Emp (322). Additionally, Esp seems to interfere with host-pathogen interactions, as it cleaves fibrinogen, fibronectin, and vitronectin (322). Furthermore, Esp was shown to degrade Atl-associated bacteriolytic activities, thereby preventing the release of eDNA as a main component of the biofilm matrix and mediator of initial adherence (323–325).

Additional or alternative *S. epidermidis* proteases may be involved in proteolytic degradation of protein factors mediating attachment and intercellular adhesion, and thus in biofilm detachment of *S. epidermidis*. Possible proteases involved include the following: an extracellular metalloprotease with elastase activity, SepA, whose gene has been cloned and sequenced (326, 327); an extracellular serine protease, EpiP, that is involved in epidermin processing (324); and an extracellular cell wall-associated cysteine protease with elastase activity (Ecp) (319, 328) (see below).

However, although all factors mentioned above play a proven or potential role in biofilm detachment or dispersal *in vitro*, *in vivo* proof demonstrating the involvement of the respective factors in such functions in animal models has been lacking.

(ii) PSMs. Another strategy that leads to biofilm disintegration depends on the synthesis and release of small peptides called phenol-soluble modulins (PSMs). PSMs are short, amphipathic peptides which are secreted in an *agr*-controlled manner (see below) (329). They were first described as proinflammatory agents in *S. epidermidis* (330). According to their length, PSMs can be divided into α-type peptides, which are approximately 20 to 25 amino acids long, and β-type peptides, which are 40 to 45 amino acids long. In *S. epidermidis*, five α-type PSMs (PSMα, PSMγ, PSMδ, PSMε, and PSM-mec) and two β-type PSMs (PSMβ1 and PSMβ2) have been identified (331). PSMγ consists of 25 amino acids and was identified as δ-toxin. The δ-toxin is encoded by *hld*, which is a component of the regulatory *agr* system (see below), and it differs from the *S. aureus* δ-toxin in only three amino acids (332). The recently discovered PSM-mec peptide is encoded by some SCC*mec* elements that cause methicillin resistance (333).

A preliminary indication that PSMs are involved in preventing biofilm formation came from the investigation of a significant number of *S. aureus* clinical strains with respect to their *agr* phenotype (production of δ-toxin) and the ability to form a biofilm. It turned out that the δ-toxin-negative and, consequently, *agr*-defective strains predominantly built biofilms, delineating the importance of *agr* in biofilm production (334). Externally adding δ-toxin to biofilm-positive strains suppressed biofilm formation. Because of their amphipathic nature, PSMs probably act as surfactants, thereby leading to biofilm dispersal (335). Indeed, a recent study indicated that the β-type PSMs promoted the structuring and dispersal of *S. epidermidis* biofilms *in vitro* as well as *in vivo*, in a murine catheter-associated infection model (336).

Internalization by and Persistence in Host Cells

Internalization by nonprofessional phagocytes. As already widely accepted for *S. aureus*, CoNS may also be ingested by human host cells, leading to evasion of the patient's immune defense and antibacterial therapy by "hiding" within nonprofessional phagocytes. It was recently demonstrated that AtlE not only binds to host factors but also mediates *S. epidermidis* adherence to and internalization by human endothelial cells, representing the first and possibly sole internalization mechanism employed by CoNS (337).

S. epidermidis strains were also shown to be internalized by bone cells (338). However, in contrast to *S. aureus*, *S. epidermidis* orthopedic device infection strains exhibited only a low internalization rate (compared to commensal, nasal carriage isolates), suggesting that bone cell invasion is not a major pathophysiolog-

ical mechanism in *S. epidermidis* orthopedic device infections (339).

For *S. saprophyticus*, internalization by a human urinary bladder carcinoma cell line was reported (340).

Intracellular persistence—the SCV concept. The term "small-colony variant" (SCV) reflects a specific phenotype resulting from a switch from the normal (wild-type) phenotype (see Clinical Significance and Infections). SCVs have been described for several Gram-negative and Gram-positive species. While most work has been done on *S. aureus* SCVs (216), similar general characteristics may be assumed for SCVs of CoNS.

Irrespective of the species, the SCV phenotype is characterized by drastic changes in cellular metabolism, reflected by a reduced growth rate and substantial quantitative and qualitative modifications of the transcriptome, metabolome, and proteome (341–343). These changes determine the auxotrophism expressed by almost all SCV isolates (344–348). Metabolic changes also influence the colonial morphotype of SCVs, which are characterized by tiny colonies, reduced or lost pigmentation, and hemolysis compared to their wild-type counterpart (216).

Their intracellular location provides a survival niche in the host environment, shielding SCVs from host defenses and, additionally, from antimicrobial agents (347, 349–351). The resulting habitation in an intracellular environment necessitates an adaptation to the anaerobic milieu (341). Moreover, virulence and pathogenic behaviors are modified; for instance, *S. epidermidis* mutants displaying the SCV phenotype demonstrated augmented expression of PIA (222).

Interference with the Human Immune System

Cell wall components. A serious consequence of *S. epidermidis* FBRIs is septicemia. In the pathophysiology of inflammatory events in septicemia, the production of cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and IL-6, plays a major role. Cell wall components, such as peptidoglycan and teichoic acid purified from *S. epidermidis*, stimulated human monocytes to release TNF-α, IL-1, and IL-6 in a concentration-dependent manner (352). Further studies demonstrated that human serum strongly increased peptidoglycan-induced TNF-α release by human monocytes (353).

Factors involved in biofilm formation. A recent study investigated the contributions of different mechanisms involved in biofilm accumulation, i.e., PIA/PNAG and the proteinaceous adhesins Aap and Embp, to interference with the phagocytosis of *S. epidermidis* and the activation of mouse J774A.1 macrophages (231). Although marked morphological differences were noticed, depending on the factor mediating accumulative growth, PIA/PNAG, Aap, and Embp were similarly efficient in protecting *S. epidermidis* against phagocytosis. Additionally, biofilm-positive *S. epidermidis* strains induced a considerably lower inflammatory J774A.1 macrophage response than that with respective isogenic biofilm-negative mutants, leading to significantly reduced NF-κB activation and reduced IL-1β production (231).

Earlier phagocytosis assays revealed that biofilm-associated, PIA/PNAG-producing *S. epidermidis* cells were more resistant to killing by neutrophils or human polymorphonuclear leukocytes (PMNs) than their planktonically grown, *ica*-negative counterparts (354, 355). Characterization of the underlying mechanisms revealed that a reduced deposition of IgG and complement on the cell surface of PIA/PNAG-positive *S. epidermidis* cells contributes to the biofilm-mediated protection of *S. epidermidis* against killing by PMNs (354). Furthermore, the partial deacetylation of PIA/PNAG mediated by IcaB determined its biological activity in immune evasion, since it was essential for resistance to phagocytosis by PMNs and to human antimicrobial peptides (AMPs) (291).

The importance of PIA/PNAG as an immunoprotective factor has also been studied in a *Caenorhabditis elegans* infection model (356). In this model, a PIA/PNAG-producing *S. epidermidis* wild-type strain has a significant survival advantage in the worm intestinal tract compared to its *ica*-negative mutant. This advantage, however, is found only with wild-type *C. elegans*, not with immunocompromised *C. elegans*. Moreover, immunocompromised nematodes are equally sensitive to *S. epidermidis* wild-type and *ica* deletion strains, suggesting that PIA/PNAG enhances virulence by providing immunoprotection during colonization of the *C. elegans* intestine (356).

Antibodies against the LPXTG-containing surface protein SdrG/Fbe significantly increased macrophage phagocytosis and reduced the severity of systemic infections; SdrG/Fbe was therefore suggested as a potential vaccine candidate (357). Furthermore, SdrG/Fbe inhibited thrombin-induced fibrinogen clotting by interfering with the release of fibrinopeptide B (278). It was suggested that the reason for the fibrinogen-binding activity of SdrG/Fbe might be to inhibit the release of chemotactic elements, such as fibrinopeptide B. This may limit the influx of phagocytic neutrophils, thereby helping the bacteria to survive in the host.

Extracellular enzymes. Extracellular enzymatic activities not only may be involved in biofilm detachment (see above) but also may determine the establishment of an infection and aid in the survival of bacteria in the host by enabling bacteria to invade host tissues and to evade host defense systems, respectively. In this regard, CoNS have developed multiple mechanisms, including the production of a variety of extracellular proteins and enzymes, such as lipases, proteases, esterases, and phospholipases, as well as the production of hemolysins and other toxins.

In particular, proteases may play an important role in (i) proteolytic inactivation of host defense mechanisms, such as antibodies, platelet microbicidal proteins, and AMPs; and (ii) the destruction of tissue proteins, thus causing increased invasiveness. The extracellular serine protease Esp can degrade a wide spectrum of proteins, including complement protein C5 and fibrinogen, thereby providing *S. epidermidis* with the ability to evade the complement defense system and to dysregulate the coagulation cascade (320, 322). The 33-kDa extracellular metalloprotease SepA has a high capacity to inactivate AMPs by proteolytic cleavage (326, 327) and also significantly promotes *S. epidermidis* resistance to killing by PMNs (331). Moreover, Ecp, an extracellular cell wall-associated cysteine protease with elastase activity from *S. epidermidis*, degrades—among other proteins—human elastin, fibrinogen, and fibronectin; it is assumed to be a virulence factor that contributes to the colonization and infection of human tissue (319, 328).

Two homologous lipases (GehC and GehSE1, from *S. epidermidis* strains 9 and RP62A, respectively) exhibit a high degree of similarity (97.8% identical deduced amino acids); they are hypothesized to be involved in skin colonization (358, 359). Most *S. epidermidis* strains seem to possess two lipase genes. The second lipase gene, *gehD*, encodes a mature protein of approximately 45 kDa which is 51% identical to GehC (360).

PSMs. Aside from their function in biofilm detachment, PSMs

(see above) induce cytokine release and stimulate NF-κB production in cells of macrophage lineage (330). Furthermore, in human neutrophils, PSMs induce cellular degranulation, prime cells for an enhanced respiratory burst, and inhibit spontaneous apoptosis (361). PSMs are also chemoattractants for both neutrophils and monocytes (361). Because of these pronounced proinflammatory properties, PSMs may contribute to sepsis caused by *S. epidermidis*. The production of PSMs is controlled by the *agr* QS system (see below). In contrast to its parental strain, an *agr* mutant did not produce any of the PSM peptides (362). Moreover, the *agr* mutant failed to induce the production of TNF-α by human myeloid cells and displayed significantly reduced induction of neutrophil chemotaxis. Therefore, an *agr* QS mechanism was proposed that facilitates growth and survival in infected patients by adapting production of the proinflammatory PSMs to the stage of infection (362). Some PSMs also exhibit moderately cytolytic activity (see below).

Aggressive Capacities

Compared to *S. aureus*, CoNS are characterized by low aggressiveness. Thus, either no or rather lowly aggressive virulence factors have been described for CoNS. Moreover, CoNS are still not generally accepted as producers of toxin superantigens.

Cytolytic toxins. While some *S. epidermidis* PSMs are related to those of *S. aureus*, with a marked capacity for lysing human neutrophils, *S. epidermidis* has, in general, a less cytolytic potential. Nevertheless, *S. epidermidis* produces cytolytic toxins, such as the δ-toxin (PSMγ), which acts by forming pores in the cell membrane, leading to the lysis of erythrocytes and other mammalian cells (332). PSMγ is suggested to be involved in necrotizing enterocolitis of neonates (363). Other α-type PSMs with cytolytic activities include PSMε and the potent leukocyte toxin PSMδ (331). In contrast, β-type PSMs are much less cytotoxic (331, 336). Thus, *S. epidermidis* has the potential to produce an effective cytotoxin; however, the production of strongly cytolytic PSMs is low, explaining why culture supernatants of *S. epidermidis* have little or no capacity to lyse PMNs (331). These data indicate that the strategy of *S. epidermidis* to evade the human immune system depends on passive defense mechanisms mediated by enzymatic activities, such as the protease SepA that cleaves AMPs, rather than on being an aggressive pathogen that produces a variety of potent cytotoxins, as in the case of *S. aureus* (331).

PTSAgs and exfoliative toxins. The capability of CoNS to possess members of the pyrogenic toxin superantigen (PTSAg) family, comprising staphylococcal enterotoxins (SEs) and toxic shock syndrome toxin 1 (TSST-1), has been a matter of debate since the report of a TSS case in 1986, with the recovery of vaginal and labial CoNS isolates which were not specified (364). However, these isolates and other presumed TSST-1-positive CoNS were later found not to be able to produce TSST-1 (365). Later, upon application of PCR technology, clinical CoNS isolates were shown not to harbor classical PTSAg-encoding genes (*sea* to *see* and *tst*) (366, 367). Thus, so far, reasonable data are lacking to confirm the secretion of detectable amounts of classical PTSAgs in a significant proportion of CoNS isolates recovered from human specimens, or their involvement in clinical cases of TSS or food poisoning (365, 368). However, an *S. epidermidis* isolate from a human source was recently shown to harbor a pathogenicity island (SePI) containing genes encoding the SEC variant SEC3 and the SE-like toxin L (SElL) (369). Some reports of CoNS with PTSAg production have been published for isolates recovered from animal or food specimens (370, 371). However, other food- and animal-related studies failed to detect PTSAg-equipped CoNS (372, 373). In general, cross-reactivities of immunological assays and possible misidentifications in the premolecular era may hinder an accurate assessment of respective study results. For detailed information on the staphylococcal PTSAg family itself, please see the review recently published in this journal (368). Clinical CoNS isolates possessing exfoliative toxins have not been reported so far.

Production of Lantibiotics

In particular, commensal staphylococci are known to produce antibiotic-like peptides that also fulfill the criteria for bacteriocins, namely, the so-called lantibiotics (374). Lantibiotics belong to the class of cationic antimicrobial peptides (CAMPs) and are active against Gram-positive bacteria. Their production may play a considerable role in bacterial interference on skin and mucous membranes, thereby creating an ecological niche for *S. epidermidis* and other CoNS. These antibiotic peptides contain the rare, nonproteinogenic thioether amino acids lanthionine and/or methyllanthionine, hence their designation as "*lant*hionine-containing an*tibiotic* peptides," i.e., lantibiotics (375). Type A lantibiotics induce pores in the cytoplasmic membrane. Lantibiotics produced by *S. epidermidis* are the well-characterized epidermin and Pep5. Later, epilancin K7, epidermicin NI01, and epicidin 280 were identified. Further lantibiotics produced by CoNS were detected in *S. gallinarum* (gallidermin), *S. hominis* (hominicin), and *S. warneri* (nukacin ISK-1) (374).

Regulation of Pathogenic Processes

Knowledge concerning the regulation of *S. epidermidis* virulence factors has increased significantly in recent years. For *S. epidermidis*, 2 QS systems, the *agr* (accessory gene regulator) (376, 377) and *luxS*/AI-2 systems (378), have been reported. Another global regulator controlling *S. epidermidis* pathogenicity factors is the staphylococcal accessory regulator (*sar*) locus. The expression of *agr* and *sar* is influenced by the alternative transcription factor σ^B, which is the global regulator of stress responses in many bacterial species. Furthermore, various other regulators were recently identified.

QS in staphylococcal biofilms. QS systems are bacterial cell-cell communication systems in which small pheromone peptides or autoinducing peptides (AIPs) are used to communicate. At low cell densities, the concentration of AIPs is low. With increasing cell densities, the concentration of AIPs becomes elevated. The QS system is induced by the activation of a transcriptional regulator when a certain AIP threshold concentration is reached, which typically occurs in the late exponential growth phase. The transcriptional regulator then regulates the expression of the target genes, which may be up- or downregulated.

(i) The accessory gene regulator (*agr*) QS locus. The regulatory factor of the staphylococcal *agr* QS system is an RNA, called RNAIII, that also encodes the gene for δ-toxin (PSMγ) (see above). RNAIII regulates the transcription of virulence genes, i.e., it stimulates the expression of extracellular pathogenicity determinants, such as enzymes, toxins, and PSMs, and downregulates the expression of CWA proteins (376). The components of the *agr* QS system and their features and functions have been described previously in great detail (376, 379).

agr homologues have also been identified in other CoNS and

CoPS, such as *S. intermedius*, *S. warneri*, and *S. lugdunensis* (376, 380–382). The similarity among the *agr* systems of *S. aureus* and *S. epidermidis* is considerable. Nevertheless, the sequences of *S. aureus*, *S. epidermidis*, and *S. lugdunensis* AIPs are not very similar and differ in length.

The process of staphylococcal biofilm production is influenced by *agr* in a versatile manner. Generally, the *agr* QS system downregulates biofilm production: *S. epidermidis* as well as *S. aureus agr* mutants build stronger biofilms than those of the respective wild types (329, 334, 383, 384). Furthermore, *agr* transcription is considerably repressed during biofilm accumulative growth of *S. epidermidis* (335). Congruently, it was observed that *agr* mutants are found more often among disease strains causing FBRI (35%) than among strains from human volunteers (5%). This implicates that a nonfunctional *agr* system increases the chance of causing an *S. epidermidis* infection associated with foreign bodies (384). The stronger biofilm-forming capacity of the *agr* mutant of *S. epidermidis* correlated with an elevated production of AtlE and subsequently increased adherence to polystyrene (see above) (329). Increased biofilm formation could also be explained by a decreased detachment rate, as thicker biofilms of the *agr* mutant may result from a lack of upregulation of different genes involved in biofilm detachment, such as proteases, nucleases, and PSMs, by *agr* (318, 362, 376).

The regulatory mechanisms controlling the colonization factors seem to differ in *S. aureus* and *S. epidermidis*: in *S. aureus*, *agr* downregulates some CWA proteins, while in *S. epidermidis*, several CWA proteins are produced to a larger extent in the stationary phase (271). Observed, partially conflicting findings may result from different experimental settings (385).

The function of the staphylococcal *agr* system in the growth phase-dependent regulation of protein synthesis and biofilm formation may be summarized as follows. In an early stage of infection, cell density is low and surface and surface-associated proteins with adhesive functions are expressed, allowing attachment to biotic and abiotic surfaces. Upon proliferation of the cells on a surface, AIPs accumulate and eventually reach the critical concentration necessary for the activation of RNAIII synthesis. RNAIII then downregulates the expression of surface protein genes (although species-specific differences exist) and upregulates the production of PSMs, proteases, nucleases, and lipases, which facilitates the maintenance of the infection and/or biofilm detachment.

(ii) The *luxS*/AI-2 system. Many Gram-positive and Gram-negative bacteria harbor the *luxS* QS system. In *S. epidermidis* and *S. aureus*, *luxS* codes for the synthesis of a furanone derivative called autoinducer AI-2 (378, 386). AI-2 is synthesized growth dependently, predominantly in the exponential growth phase. Mutation of *S. epidermidis luxS* resulted in a phenotype similar to that observed with the mutation of *agr*: the *luxS* mutant built a thicker biofilm than its parental counterpart. The *S. epidermidis luxS* system downregulates the production of biofilm via repressing the *icaADBC* operon as demonstrated by transcriptional analysis. Consequently, the *luxS* mutant revealed increased PIA/PNAG synthesis in comparison with its parental strain (378). For comparison, expression of *icaADBC* and synthesis of PIA/PNAG are not affected by *agr*. Furthermore, the *luxS* mutant had a more pronounced capability to colonize and to initiate disease in a CVC-associated rat model of infection (378). *luxS* also controls the expression of pathogenicity-related factors, such as PSMs and lipase, suggesting that the increased biofilm production in the *luxS* mutant may be due, at least partially, to less synthesis of PSMs and, consequently, a diminished biofilm detachment rate. The *luxS* QS system has a pronounced effect on biofilm production and virulence in *S. epidermidis* but not in *S. aureus* (386). Therefore, at least in the case of *S. epidermidis*, the known QS systems *agr* and *luxS* repress biofilm formation.

The staphylococcal accessory regulator (*sar*) locus. The Sar family of transcriptional regulators includes at least 12 paralogs in *S. aureus*, among them SarA. A global regulator, *sarA*, controls exoprotein synthesis by modulating the expression of *agr*. SarA of *S. epidermidis* is very similar (84% identical amino acids) to the SarA protein of *S. aureus* (387). SarA is a positive regulator of *S. epidermidis* biofilm production by direct binding to the *icaA* promoter region, thereby inducing *icaADBC* expression and subsequent PIA/PNAG production (388, 389). Recently, additional mechanisms of *sarA*-dependent biofilm regulation have been identified. Inactivation of *sarA* in *S. epidermidis* led to an induction of biofilm formation, probably via at least two distinct mechanisms (390): first, the expression of the giant extracellular matrix binding protein Embp, conferring intercellular adhesion, is induced in the *sarA* mutant; and second, the expression of the metalloprotease SepA may also be induced in the *sarA* mutant, which would lead to the elevated processing of AtlE and thus, indirectly, to the increased availability of autolysin-dependent eDNA and subsequent biofilm formation (390). Thus, SarA represents a key element inversely controlling PIA/PNAG-dependent and PIA/PNAG-independent mechanisms of biofilm formation (390). Other Sar paralogs recently identified in *S. epidermidis* include SarZ and SarX (391, 392). SarZ is highly homologous to SarZ from *S. aureus* and is a positive regulator of both phases of biofilm formation: initial attachment and PIA/PNAG-mediated biofilm accumulation (391). Furthermore, *sarZ* influences the expression of other pathogenicity factors, such as proteases and lipases, and plays a role in biofilm-associated infections (391). SarX has also been identified as a positive regulator of biofilm production of *S. epidermidis*, primarily via elevating *icaADBC* transcription and PIA/PNAG synthesis (392).

The sigma factor B (*sigB*) operon. Many bacterial species express various alternative sigma factors when adapting gene expression to changing environmental conditions. Like *S. aureus*, *S. epidermidis* encodes the alternative sigma factor σ^B (393, 394). The gene encoding σ^B is part of an operon (*sigB* operon). Inactivation of *rsbU*, which is a required activator of σ^B, led to a biofilm-negative phenotype due to dramatically decreased PIA/PNAG production (394). Ethanol and salt stresses are both known activators of σ^B. However, the presence of ethanol in the growth medium of the *rsbU* mutant completely restored biofilm formation, whereas salt stress did not. Thus, different regulatory mechanisms seem to be involved in *S. epidermidis* PIA/PNAG production in response to ethanol and salt stress. Further results indicated that *icaR*, which codes for a negative regulator of *icaADBC* transcription, might be responsible for this differential regulation (395). Recent analysis indicated that the decreased expression of the *icaADBC* operon in a *sigB* mutant is mediated via upregulation of IcaR (389).

LABORATORY DETECTION AND IDENTIFICATION

The isolation and cultivation of CoNS are relatively easy and straightforward, as is also the identification of frequently encountered CoNS species. From a diagnostic and clinical point of view, it

is an essential requirement to make a clear and valid distinction between CoNS species and CoPS species, with the latter being overwhelmingly *S. aureus* in human clinical specimens. Species-level identification of CoNS associated with infection, especially in the case of a pure culture, has become customary (396). Among CoNS, the accurate recognition of *S. lugdunensis* is of particular importance.

The standard approach for detection and identification includes culturing on a nonselective blood agar plate as well as in enrichment broth, followed by biochemical and other related procedures, including the use of commercial systems for identification purposes. Today, biochemical identification approaches are increasingly being replaced by the application of matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS).

The most challenging problem in CoNS diagnostics is the assessment of their clinical relevance. Thus, the major diagnostic task is to assess whether a given CoNS isolate represents (i) a contamination of the specimen during sampling and processing, (ii) physiological colonization of the skin or mucous membranes, or (iii) clinically significant infection. This challenging situation becomes even more complicated in the case of polymicrobial infections by CoNS, particularly for the choice of antibiotics for therapy if the isolates exhibit different susceptibility patterns. Finally, this cardinal diagnostic and clinical dilemma can be solved only with close cooperation between clinicians and microbiology laboratory specialists.

In the following section, only the main aspects of the detection and identification of CoNS are given; for further details, please refer to respective textbooks and manuals (396–398).

Isolation

Standard procedures. Regardless of the species, Columbia or tryptic soy blood agars containing 5% defibrinated sheep (or horse) blood are the primary culture plates used for the isolation of staphylococci from clinical specimens. The recovery rate can be increased by the simultaneous use of an enrichment broth (e.g., dextrose broth), with streaking onto blood agar after 24 and 48 h of growth. Usually, growth of most CoNS species occurs within 18 to 24 h. Isolates displaying the SCV phenotype, in contrast, often need about 48 to 72 h to display visible colonies.

Specific procedures for detection of foreign body-related infections. (i) Quantitative approaches for catheter-related bloodstream infections. Since clinical findings alone have limited sensitivity and specificity in the diagnosis of CRBSIs, various semiquantitative or quantitative laboratory techniques have been developed. The traditional approach, i.e., the semiquantitative roll-plate catheter culture, necessitates that the distal segment of the central venous catheter be cut and rolled across the surface of a Columbia blood agar plate at least four times. After overnight incubation, a colony count of ≥15 CFU/plate may indicate catheter colonization (399). To detect bacteria not only from the external surface but also from the intraluminal surface, the catheter can be flushed with broth. Alternatively, by counting the absolute number of CFU per volume, examination of paired quantitative blood cultures drawn simultaneously from the catheter and a peripheral vein overcomes the necessity of catheter removal. This approach has been enhanced by the analysis of differential time to positivity (400, 401). CRBSI is probable if the catheter sample becomes positive first and the time difference between both samples is ≥2 h. A pooled sensitivity and specificity of 88% and 87%, respectively, were found in a meta-analysis of this approach (402).

(ii) Implant-associated infections. Detachment of biofilms from an implant surface by sonication may improve the diagnosis of the respective FBRI. For explanted hip and knee prostheses, the culture of samples obtained by sonication of prostheses was more sensitive than conventional periprosthetic tissue culture, particularly for patients who had received antibiotics within 2 weeks prior to surgery (403). Also, for other implants, such as removed electrophysiological cardiac devices and spinal and breast implants, an advantage of sonication prior to culturing has been shown (404–406).

Identification

The application of the extensive and labor-intensive scheme originally published by Kloos and Schleifer in 1975, and subsequently supplemented several times (407), has been replaced in clinical microbiology laboratories by commercial identification systems based on biochemical procedures, including the use of (semi)automated systems. Nowadays, routine pathogen diagnostics are turning to MALDI-TOF MS approaches. In addition, nucleic acid-based molecular methods have become standard, in particular for the verification of ambiguous identification results.

However, it still makes sense to test the basic criteria for the identification of CoNS: Gram-positive, catalase-positive, mostly oxidase-negative (for exceptions, see Fig. 3), coagulase-negative, and facultative anaerobic cocci occurring mainly in clusters. This holds true in particular for plausibility control purposes or in the case of ambiguous results, if doubts arise as to whether a given isolate belongs to the genus *Staphylococcus* or the CoNS group, respectively.

Direct examination of specimens. As with all staphylococci, CoNS are Gram-positive, nonmotile, non-spore-forming cocci. They are usually arranged in pairs or tetrads but also occur singly, in irregular (grape-like) clusters, or in short chains of about three or four cells. Direct microscopic examination may be helpful for analyzing normally sterile fluids (e.g., cerebrospinal fluid and joint aspirates).

Colony morphology and variation. Typically, most CoNS species display nonpigmented, smooth, entire, glistening, and opaque colonies. Strong slime producers may display a mucoid colony appearance. After 2 to 3 days of incubation, colony diameter reaches 3 to 6 mm. More or less gray-yellow, yellow, or yellow-orange pigmented colonies are a characteristic of the following CoNS species: *S. chromogenes*, *S. devriesei*, *S. lugdunensis*, *S. sciuri*, *S. vitulinus*, *S. warneri*, and *S. xylosus*. Other CoNS species may show a kind of yellowish pigmentation. Some CoNS species (e.g., *S. haemolyticus* and *S. lugdunensis*) display a hazy or distinct zone of beta-hemolysis around the colonies (Fig. 5).

SCVs of CoNS, like those of *S. aureus*, are characterized by pinpoint colonies reaching only 10% of the size of the wild-type colonies (216). The colonies are mostly less or nonhemolytic and less or nonpigmented (Fig. 6). Note that they often give the appearance of a mixed culture because colonies displaying the normal phenotype and those exhibiting the SCV phenotype coexist. Upon subculture, SCVs may remain stable or revert to the wild type (408). Normal growth may be restored if the isolate is grown in the presence of the components involved in their auxotrophy, such as hemin, menadione, and thymidine, and/or with CO_2 supplementation (216).

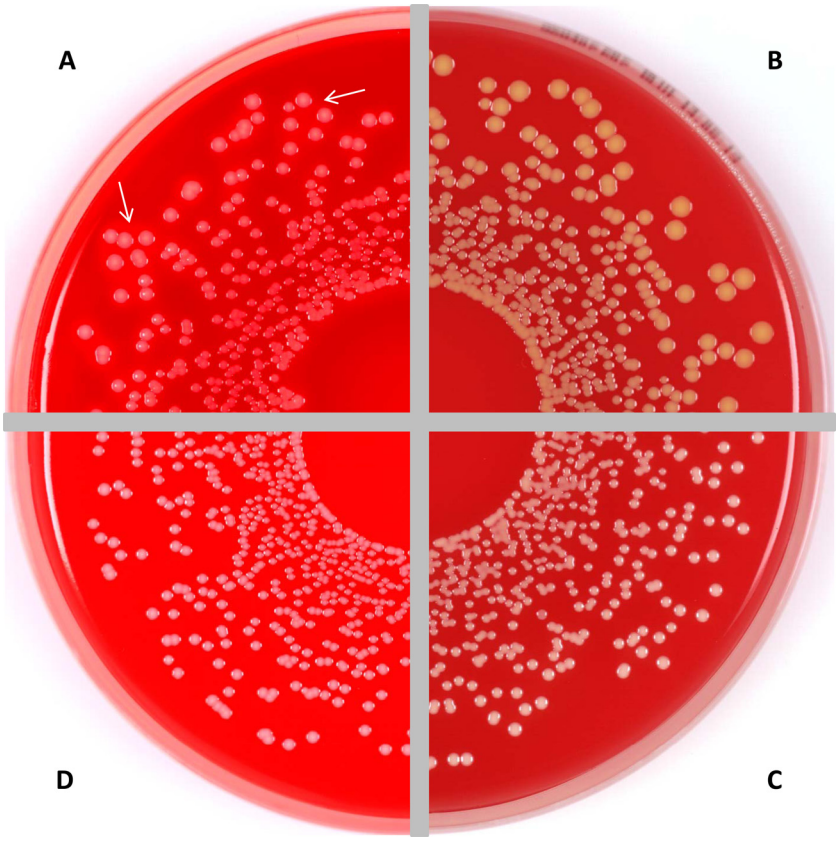


FIG 5 Sections of Columbia blood agar plates showing grayish, hemolytic colonies of *S. haemolyticus* (the color of this photograph was modified to enhance visibility of the weak hemolysis zones [arrows] surrounding the colonies, resulting in a nonnatural reddish tinge) (A); orange, nonhemolytic colonies of *S. chromogenes* (B); creamy, nonhemolytic colonies of *S. lugdunensis* (C); and whitish, nonhemolytic colonies of *S. saprophyticus* subsp. *saprophyticus* (D).

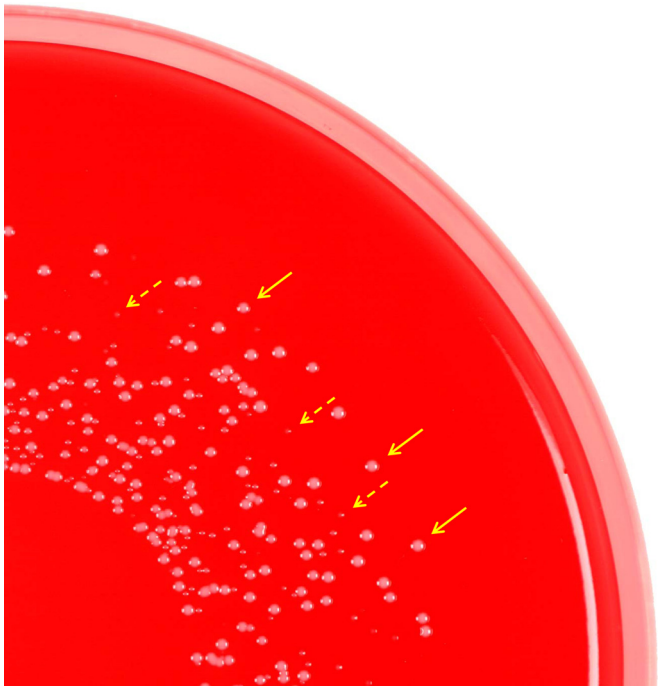


FIG 6 Columbia blood agar plate showing an isogenic *S. epidermidis* strain pair displaying both the normal (arrows) and SCV (dashed arrows) phenotypes. The normal phenotype (NP) on this plate was the result of a spontaneous reversion of the SCV back to the NP.

Separation of CoNS from *S. aureus* and other coagulase-positive or coagulase-variable staphylococci by classical approaches. The traditionally used approach in the clinical laboratory for the differentiation of *S. aureus* (but more precisely, all CoPS) and CoNS is the tube test, based on the clotting of plasma by extracellular free staphylococcal coagulase that converts fibrinogen to fibrin. The detection of the cell wall-bound—historically also designated "coagulase"—clumping factor by the slide agglutination test is obsolete due to low sensitivity and specificity.

To overcome these limitations and the long incubation time of the tube coagulase test, rapid latex and hemagglutination assays allowing presumptive identification of *S. aureus* have been developed based on the detection of clumping factor, protein A, and capsule types 5 and 8. These recent, so-called third-generation tests are characterized by a higher sensitivity (>98 to 100%) and somewhat lower specificity (72 to 99%) than those of earlier assay generations (409). In particular, coagulase-negative but clumping factor-positive species, such as, in particular, *S. lugdunensis*, but also *S. schleiferi* subsp. *schleiferi*, *S. sciuri* subsp. *carnaticus*, and *S. sciuri* subsp. *rodentium*, may be responsible for the lower specificity (410). Lowered specificity may be the result of false-positive reactions occurring with some CoNS strains, due to their possessing, for example, the type 8 capsular polysaccharide as known for *S. haemolyticus* and *S. hominis* isolates (411, 412). The frequency of isolation of CoNS that express these capsular types has been shown to be about 2% and 16% for human and livestock isolates,

respectively (413). For *S. epidermidis*, high expression of a noncapsular, proteinaceous antigen may give false-positive agglutination test results (412). Testing of *S. saprophyticus* strains may also result in a false-positive outcome due to a specific cell wall hemagglutinin (414).

Grouping of CoNS by novobiocin testing. In the case of CoNS isolates recovered from urinary tract specimens, testing for resistance to novobiocin (415) is routinely and almost exclusively used as a simple approach to distinguish the intrinsically resistant organism *S. saprophyticus* subsp. *saprophyticus* from other clinically important CoNS of the *S. epidermidis* group. Other novobiocin-resistant CoNS (Table 2) are rather seldom found in human-derived specimens. The method used is based on the disc diffusion test, using a 5-μg novobiocin disc on Mueller-Hinton agar or tryptic soy-sheep blood agar (for details, see reference 396).

Differentiation by biochemical and related procedures, including the use of commercial systems. Subsequent to the era of classical tests for fermentation, oxidation, degradation, and hydrolysis of various substrates, i.e., the Kloos and Schleifer classification schema and its amendments in the case of staphylococci (407), commercial manual and automated biochemical test systems dominated the laboratory landscape for some decades. These systems are still a cornerstone of many routine laboratories and comprise the following: *Staphylococcus*-specialized API Staph and ID32 Staph strips (bioMérieux, La Balme Les Grottes, France) and the Rapidec Staph (bioMérieux) system, as well as more general systems, such as Vitek 2 (bioMérieux), the Pos ID Panel family (Siemens Healthcare Diagnostics, Deerfield, IL), the BBL Crystal identification system's Rapid Gram-Positive ID kit (BD Diagnostic Systems, Sparks, MD), the Phoenix automated microbiology system (BD Diagnostic Systems), and the Biolog systems (Biolog, Hayward, CA). The Sherlock microbial identification system (MIDI, Newark, DE) combines cellular fatty acid analysis with computerized high-resolution gas chromatography.

These systems are fairly successful at differentiating common CoNS, such as *S. epidermidis*, *S. haemolyticus*, and *S. saprophyticus*, while the accurate identification of less common species, especially *S. hominis* and *S. warneri*, is more variable (89, 416–420). For some of these systems, reliability depends on the performance of additional tests as recommended by the manufacturers. Their accuracy of identification is about 70 to >90%. However, these assays may have also failed to distinguish commonly encountered CoNS species, in particular if isolates were recovered from livestock and food or if uncommon strains were isolated (89, 419, 421). This also holds true in the case of the differentiation of phenotypic variants (422).

The testing of volatile organic compounds (VOCs) in clinical samples appears to be a promising future tool for the noninvasive detection and monitoring of infectious diseases; it is based on VOC biomarker profiles representing metabolites of both the infecting pathogen and pathogen-induced host responses (423). VOC-based procedures for CoNS may be relevant, for example, for the detection of *S. saprophyticus* in urine samples.

Identification by nucleic acid-based approaches. Nucleic acid-based assays specifically designed for direct CoNS detection from clinical specimens are not available on the market, with the exception of those kits developed for the PCR-based detection of pathogens directly from blood, such as the LightCycler SeptiFast test MGRADE (Roche Diagnostics, Mannheim, Germany). Note that a semiquantitative analytical cutoff value for CoNS has been set in this assay to avoid false-positive results due to CoNS contamination during blood sampling procedures. One could speculate that these CoNS-adjusted multiplex PCR assays might underreport CoNS, particularly for patient groups where CoNS-positive findings frequently indicate true bloodstream infections, such as neutropenic hematological patients and preterm newborns (424).

For the identification of cultured CoNS, several nucleic acid-based approaches have been developed and evaluated based on amplification, hybridization, and sequencing procedures.

(i) Amplification-based methods. Overwhelmingly, in the case of CoNS, conserved regions with embedded species-specific sequences of universally occurring genes are amplified, followed by sequencing and analysis of the part(s), allowing differentiation at the species or subspecies level. Note that the validity of results depends strongly on the quality of the database used for sequence analysis (422). Universal targets commonly used for CoNS identification by PCR plus sequencing comprise ribosomal genes (16S and 23S rRNA genes and their spacer sequences), the glyceraldehyde-3-phosphate dehydrogenase-encoding gene (*gap*), the gyrase gene (*gyrA*), the manganese-dependent superoxide dismutase gene (*sodA*), the RNA polymerase beta subunit gene (*rpoB*), the elongation factor TU gene (*tuf*), and the gene for a 60-kDa heat shock protein (HSP60/GroE) (422, 425–432). Sequencing of partial *rpoB* gene sequences was shown to be superior to partial 16S rRNA gene sequencing for the differentiation of *Staphylococcus* subspecies (432). Several commercial tests are available, mainly for the molecular verification of cultured *S. aureus* isolates, which often also allow the detection of the *mecA* and toxin genes. Additionally, some of these are able to identify some of the most clinically relevant CoNS (e.g., GenoType Staphylococcus and GenoType MRSA tests [Hain Lifescience, Nehren, Germany], the StaphPlex panel [Qiagen, Germantown, MD], AccuProbe *S. aureus* culture [Gen-Probe, San Diego, CA], and the *S. aureus* Evigene test [AdvanDx, Woburn, MA]).

(ii) Oligonucleotide microarrays. Microarray-based diagnostics may combine the advantages of high-throughput screening with the possibility of the identification of different genes useful for species determination and, in parallel, the identification of a multitude of virulence, drug resistance, and subtype-determining signatures. These assays have been tested successfully on clinical isolates (433, 434).

(iii) Nucleic acid hybridization approaches (PNA FISH). A qualitative nucleic acid hybridization assay (*S. aureus*/CNS PNA FISH; AdvanDx) targeting rRNA gene sequences, based on peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH), has been developed for the rapid identification of *S. aureus* and several CoNS species in smears prepared from positive blood cultures (435).

Identification by spectroscopic and spectrometric methods. Spectroscopic methods, such as Fourier transform infrared (FT-IR) and Raman spectroscopy, offer an alternative approach for the rapid identification of staphylococci (436). This nondestructive technology also allows discrimination between phenotypes, as shown for the SCV phenotype (408).

Comparable to the introduction of PCR, but with many fewer infrastructure requirements and much less necessity of specific skills, MALDI-TOF MS has become a revolutionary new diagnostic tool, leading to a fundamental shift in routine microbiological diagnostics (437). In contrast to DNA amplification-based approaches, which never became established in routine practice,

MALDI-TOF will soon be implemented as a routine technique for the universal identification of microorganisms, including for CoNS differentiation. This rapid, high-throughput diagnostic approach is based on peptidic spectra obtained by molecular weight determination for individual, specific fragments. The capability of this method for valid identification has been demonstrated in the last few years for many microorganisms, including staphylococcal species. Most studies have reported specificities of >97% for the identification of staphylococci, including CoNS, at the species level (438, 439). To reach this high specificity, the quality of the database and the standardization of variable parameters, such as culture conditions, are crucial.

Another method for high-throughput identification and further molecular characterization is an approach coupling PCR technology, based on universal and target gene-specific primer sets, to electrospray ionization-mass spectrometry (ESI-MS) (440).

Reporting and Interpreting the Isolation and Identification of CoNS

The main question to be answered in the reporting of CoNS recovered from a clinical specimen is whether their detection reflects a true infection or only contamination or colonization. Since in our experience a large proportion of the patient population with presumed false-positive CoNS findings is treated with antimicrobial agents, additional costs of treating patients and, in particular, unnecessary antibiotic selection pressures occur (441).

Factors helpful in the prediction of true infections include the isolation of a strain in pure culture from the infected site and the repeated isolation of the same strain over the course of an infection (1, 396, 442, 443). To reduce the misclassification of nosocomial BSIs due to CoNS, the following algorithm was defined: at least two blood cultures positive for CoNS within 5 days or one positive blood culture plus clinical evidence of infection (444). This was corroborated by a 3-year retrospective cohort study based on data prospectively collected through hospital-wide surveillance; this revealed that a single positive blood culture, if associated with signs of sepsis, should also be considered clinically relevant (445). In a prospective study, multivariate analysis-based predictors of clinically significant CoNS bacteremia included the following: time to positivity of <16 h, identification of *S. epidermidis*, presence of CVC, more than two CoNS-positive bottles from different blood culture sets, and relevant clinical scores (446). The best algorithm (sensitivity, 62%; specificity, 93%; positive predictive value, 83%; and negative predictive value, 81%) for determining the clinical significance of CoNS in this study comprised a Charlson score of ≥3, a Pitt score of ≥1, neutropenic patients, presence of CVC, identification of *S. epidermidis*, and time to positivity of <16 h (446). For further details and strategies (e.g., measurement of time to positivity, in the case of blood cultures, and sampling strategies for the detection of low-grade FBRIs), refer to diagnostic textbooks (396–398).

ANTIMICROBIAL SUSCEPTIBILITY

In regard to resistance to antibiotics and disinfectants, one can divide CoNS into two main groups: (i) those that "haven't seen a hospital from the inside" and are susceptible to the usually administered or applied agents and (ii) those that have been exposed to antibiotic selection pressure in the health care environment. This holds analogously true for animal-adapted strains and their contact with veterinary medicine and/or abuse of antimicrobial agents in husbandry. For clinical CoNS isolates, our sharpest and most efficient weapon—the bactericidal β-lactams—has become progressively blunt. This deteriorating situation is further aggravated by the phenomenon of multiresistance.

Resistance Mechanisms and Susceptibility Patterns

In previous decades, a continuous loss of susceptibility toward most of the available antibiotics was recorded for CoNS. Strong and sometimes dramatic increases in the percentage of resistant isolates were noted particularly for penicillin, oxacillin, ciprofloxacin, clindamycin, erythromycin, and gentamicin (447–449). A selection of recent studies concerning the percentage of resistant CoNS is given in Table 5. For newer compounds without or with just recently established interpretative criteria, examples of CoNS studies analyzing their MIC values are listed in Table 6. Note that given the reduced susceptibility breakpoints for CoNS (with the exception of *S. lugdunensis*) specified in past years by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), susceptibility categorization of older studies may underreport the resistant parts of CoNS populations (450, 451).

CoNS of both animal and human origins are thought to represent an important reservoir of genetic elements leading to resistance not only to the β-lactam antibiotics but also to other antibiotic classes. This is of the utmost importance for human and veterinary medicine, because these genetic elements are mobile by nature. Thus, they may transfer into the medically most significant staphylococcal species, *S. aureus*, leading to problems related to the emergence of MRSA as seen after the introduction of the penicillinase-stable penicillins.

Resistance to β-lactamase activity. Highly penicillin-resistant *S. epidermidis* (*S. albus*) isolates, responsible for fatal subacute bacterial endocarditis, were being reported as early as 1949 (452). This phenotype is caused by penicillinases, first described by Kirby in 1944 (453). They represent a plasmid-mediated staphylococcal β-lactamase encoded by the *blaZ* gene. Penicillinases show specificity for penicillins and act via hydrolysis of the β-lactam ring. Today, as a result of huge selection pressures, CoNS isolated from clinical specimens are significantly more resistant to single-antibiotic and biocidic compounds, often appearing as multiresistant isolates, and penicillin-susceptible *S. epidermidis* and *S. haemolyticus* isolates occur only very rarely (<10%) among isolates recovered from hospitalized patients (75, 454).

Resistance to β-lactams by expression of an additional penicillin-binding protein. In staphylococci, including CoNS species, the expression of an additional penicillin-binding protein (PBP), designated PBP2a (or PBP2′), leads to complete β-lactam resistance (to penicillins, most cephalosporins, and carbapenems), with the only exception being recently introduced cephalosporins with MRSA activity, such as ceftobiprole and ceftaroline. The reason for this is that PBP2a has considerably reduced binding affinities for β-lactam antibiotics, in contrast to the intrinsic set of staphylococcal PBPs (PBP1 to -4) (455). In contrast to the simply structured molecular background of penicillinase genetics, the molecular organization of staphylococcal β-lactam resistance is much more complex and is characterized by an increasingly recognized diversity spanning polymorphisms at the gene level to the composition of the responsible mobile genetic element, the SCC*mec* element, and its relatives within the large SCC family (Fig. 7). Shortly

TABLE 5 Percentages of clinical CoNS isolates categorized as antibiotic resistant toward various antibiotic agents

Parameter	Value or description in study for given species[a]												
	Hellmark et al., 2009 (499)	Mendes et al., 2010 (497)[b]		Putnam et al., 2010 (543)	Kresken et al., 2011 (75)[c]		Mendes et al., 2012 (64)	Gordon et al., 2012 (65)[d]	Barros et al., 2012 (573)	Flamm et al., 2013 (534)[e]		Zhanel et al., 2013 (496)	
	S. epidermidis	MS-CoNS	MR-CoNS	CoNS	*S. epidermidis*	*S. haemolyticus*	*S. epidermidis*	*S. epidermidis*	*S. haemolyticus*	MS-CoNS	MR-CoNS	MS-SE	MR-SE
Study design parameters													
No. of isolates	33	420	1,388	2,510	148	102	71	100	64	278	483	475	85
Country	Sweden	Europe	Europe	Worldwide	Germany	Germany	USA	USA	Brazil	USA	USA	Canada	Canada
Source	PJI	Diverse	Diverse	Mainly BSI, also cSSSI	Diverse	Diverse	Mainly BSI	Diverse	Mainly BSI	Diverse	Diverse	Diverse	Diverse
% Resistant isolates													
Penicillin	ND	ND	ND	ND	91.1/88.0/94.6	95.9/93.9/93.1	ND	98.0	95.3	ND	ND	ND	ND
Oxacillin	84	0.0	100.0	76.4	82.7/83.1/85.5	90.4/90.9/89.2	73.2	79.0	87.5	0.0	100.0	0.0	100.0
Gentamicin	79	5.5	58.8	ND	65.5/56.3/60.8	80.8/84.8/87.3	40.8	46.0	73.4	3.6	24.6	34.7	78.8
Erythromycin	67	35.7	72.3	66.1	ND	ND	69.0	86.0	64.1	39.9	68.3	ND	ND
Clindamycin	67	5.5	37.3	33.4	ND	ND	40.9	74.0	46.9	13.0	34.6	37.6	86.7
Q/D	ND	0.0	1.6	0.5	ND	ND	ND	ND	ND	ND	ND	ND	ND
Clarithromycin	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	64.4	84.7
Ciprofloxacin	79	ND	ND	ND	ND	ND	70.4	ND	71.9	23.0	61.1	47.2	96.5
Levofloxacin	ND	8.6	67.9	54.1	ND	ND	ND	77.0	ND	21.9	59.6	47.0	95.6
Moxifloxacin	64	ND	ND	ND	42.3/52.1/47.3	57.5/51.5/60.8	ND	ND	ND	ND	ND	39.0	94.1
SXT	82	9.1	48.6	ND	ND	ND	47.9	73.0	53.1	20.1	44.7	33.9	80.0
Chloramphenicol	ND	ND	ND	ND	ND	ND	ND	ND	25.0	ND	ND	ND	ND
Fusidic acid	39	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Rifampin	39	ND	ND	ND	ND	ND	ND	35.0	10.9	ND	ND	ND	ND
Doxycycline	ND	ND	ND	ND	10.1/9.2/6.1	12.3/12.1/5.9	ND	ND	ND	ND	ND	ND	ND
Tetracycline	ND	10.5	19.9	ND	ND	ND	11.3	18.0	18.7	7.6	18.6	ND	ND
Tigecycline	0	ND	ND	ND	0.0/0.0/0.7	1.4/4.5/0.0	ND	ND	ND	ND	ND	0.0	0.0
Daptomycin	3	0.0	0.1	0.0	ND	ND	ND	ND	ND	ND	ND	0.0	0.0
Linezolid	0	0.2	0.4	0.8	0.0/0.0/0.0	0.0/0.0/0.0	18.3	2.0	ND	0.4	1.7	0.0	0.0
Vancomycin	0	0.0	0.0	0.0	0.0/0.0/0.0	0.0/0.0/0.0	0.0	ND	ND	0.0	0.0	0.0	0.0
Teicoplanin	ND	3.3 (0.0)[f]	12.2 (0.5)[f]	0.4	ND	ND	ND	ND	ND	0.0	0.0	ND	ND
Mupirocin	ND	ND	ND	ND	ND	ND	ND	ND	7.8	ND	ND	ND	ND

[a] Abbreviations: ND, not done; Q/D, quinupristin-dalfopristin; SXT, trimethoprim-sulfamethoxazole; SE, *S. epidermidis*; MS, methicillin susceptible; MR, methicillin resistant; BSI, bloodstream-related infection; cSSSI, complicated skin and skin structure infection; PJI, prosthetic joint infection.

[b] Besides those for other and unidentified CoNS species, mainly *S. epidermidis* ($n = 953$), *S. haemolyticus* ($n = 114$), *S. hominis* ($n = 176$), *S. lugdunensis* ($n = 25$), *S. saprophyticus* ($n = 30$), *S. warneri* ($n = 36$), and *S. xylosus* ($n = 24$) data have been included. Only EUCAST interpretative criteria-based data are given; for CLSI criteria-based data, see the relevant publication.

[c] Data are shown for three collection periods, as follows: 2005/2007/2009.

[d] Data are shown only for isolates characterized as most disseminated.

[e] For methicillin-susceptible CoNS, besides those for other and unidentified CoNS species ($n = 188$), mainly *S. capitis* ($n = 15$), *S. epidermidis* ($n = 57$), *S. haemolyticus* ($n = 5$), *S. hominis* ($n = 6$), and *S. warneri* ($n = 5$) data are shown; for methicillin-resistant CoNS, besides those for other and unidentified CoNS species ($n = 330$), mainly *S. epidermidis* ($n = 102$), *S. haemolyticus* ($n = 5$), *S. hominis* ($n = 10$), *S. lugdunensis* ($n = 18$), and *S. saprophyticus* ($n = 6$) data are shown.

[f] Percentages given in parentheses show prevalences according to CLSI interpretative criteria.

after the introduction of the first penicillinase-stable penicillin as a therapeutic agent in the early 1960s, about 10% of *S. epidermidis* (*S. albus*) isolates tested resistant to methicillin (marketed as "cellbenin" or "staphcillin") (456). Today, the vast majority of clinical CoNS isolates possess SCC*mec* elements.

(i) The *mec* gene polymorphism. PBP2a is encoded by the *mecA* gene, which is part of a mobile genetic element designated SCC*mec* (457). Once detailed characterization of PBP2a structure and function became available at the end of the 1980s (458, 459), proteins with very similar characteristics were described for CoNS (460). As a few homologs of the *mecA* gene became known, this warranted a proposed nomenclature revision (461) (Table 7). Results of bioinformatic analysis of the *mecA* gene polymorphisms revealed 32 unique alleles that clustered into four distinct branches (462). Forming one branch, the vast majority of all methicillin-resistant CoNS isolates (and the common MRSA lineages) contain the "classical" *mecA* gene. Two further branches correspond to allotypes of the *mecA* gene, which have been described for subspecies of *S. sciuri* (*mecA1*) and for *S. vitulinus* (*mecA2*) among animal-derived isolates (Table 7) (463–465). Both members of the *S. sciuri* species group have been proposed as the origin and/or reservoir of the *S. aureus mecA* gene (465, 466). Note that although the *mecA1* gene is ubiquitously present among *S. sciuri* strains, these strains are uniformly susceptible (or heterogeneously resistant) to β-lactams (463, 467, 468). The same holds true for the branch that includes *mecA* alleles from *S. vitulinus* and for some *S. capitis* and *S. kloosii* isolates (462). Only the upregulated form, in isolates with a mutation or an IS element in the *mecA1* promoter region, showed resistance to β-lactams (465). For intrinsically resistant *S. fleurettii*, it is known that the *mecA* gene ($mecA_{Sf}$) is located on the chromosome not associated with an SCC*mec* element (465). However, it is postulated that the original chromosomal locus contained by *S. fleurettii* must have served as the template for the *mec* gene complex, which may have then combined with a *mecA* gene-free SCC element in other staphylococcal species.

Regarding the other known *mec* types, *Macrococcus caseolyticus* strains isolated from chicken meat were found to harbor a *mec* homolog, now categorized as *mecB* (Table 7) (469). The *mecC* gene represents the fourth of the hitherto known phylogenetic branches of the *mec* genes, comprising isolates that have been detected in the past few years in MRSA (SCC*mec* type XI) strains isolated from diverse human, livestock, and wildlife sources (470–472); one *mecC* CoNS isolate (probably *S. stepanovicii*) was also recovered from a Eurasian lynx (473). A hybrid SCC*mec*-*mecC* element, consisting of SCC*mec* type VII, which carries *mecA*, and a separate *mecC* region, was recently found in two *S. sciuri* subsp. *carnaticus* isolates (468). For *S. xylosus*, a *mecC* gene allotype, designated *mecC1*, was described. However, the isolate was phenotypically oxacillin susceptible due to a truncation of PBP2a by frameshift mutation (474). Another *mecC* allotype, *mecC2*, was recently reported for methicillin-resistant *S. saprophyticus* subsp. *saprophyticus* (475).

(ii) SCC*mec* diversity. The *mec* genes are harbored by an SCC*mec* mobile genetic element inserted into the chromosome (457) (Fig. 7). This cassette is composed of three major elements: the *mec* gene complex, the *ccr* gene complex, and the joining ("junkyard" or J) regions. The *mec* gene complex comprises the *mecA* gene itself and, when present, its regulatory genes, *mecI* (a repressor) and *mecR1* (a sensor inducer), as well as an insertion sequence,

TABLE 6 *In vitro* activities of clinical CoNS isolates toward newer antibiotic agents

Parameter	Value or description in study for given species[a]								
	von Eiff et al., 2005 (500)				Kratzer et al., 2007 (525)		Hellmark et al., 2009 (499)	Karlowsky et al., 2011 (501, 526)	
	MS-SE	MR-SE	MS-SH	MR-SH	MS-SE	MR-SE	*S. epidermidis*	MS-SE	MR-SE
Study design parameters									
No. of isolates	14	21	17	15	15	87	33	83 (501), 202 (526)	19 (501), 34 (526)
Country	Germany	Germany	Germany	Germany	Austria	Austria	Sweden	Canada	Canada
Source	Diverse	Diverse	Diverse	Diverse	BSI of BMTRs	BSI of BMTRs	PJI	Diverse	Diverse
MIC_{90}, MIC range									
Ceftaroline	ND	ND	ND	ND	ND	ND	ND	0.25, ≤0.12–0.5	0.5, 0.25–1
Ceftobiprole	0.5, 0.13–1	2, 0.5–4	0.5, 0.13–1	4, 1–4	ND	ND	1.5, 0.094–1.5	1.0, ≤0.06–2	2, 1–4
Linezolid	1.0, 0.5–1	1, 0.5–1	1, 0.5–1	1, 0.5–1	ND	ND	0.25, 0.047–0.38	1, ≤0.12–2 (501), and 1, ≤0.12–2 (526)	1, 0.5–1 (501), and 1, 0.25–1 (526)
Daptomycin	ND	ND	ND	ND	0.25, <0.01–0.25	0.25, <0.01–0.5	ND	0.25, ≤0.03–0.25 (501), and 0.25, ≤0.03–1 (526)	0.25, 0.12–0.25 (501), and 0.25, 0.12–0.5 (526)
Tigecycline	ND	ND	ND	ND	0.5, 0.06–0.5	0.5, <0.01–0.5	0.25, 0.047–0.5	0.5, ≤0.03–0.5 (501), and 0.5, ≤0.03–0.5 (526)	0.25, 0.06–0.25 (501), and 0.25, 0.06–0.5 (526)
Dalbavancin	ND	ND	ND	ND	ND	ND	0.047, 0.003–0.047	0.06, ≤0.03–1	0.06, ≤0.03–0.06
Telavancin	ND	ND	ND	ND	ND	ND	ND	0.5, ≤0.06–1	0.5, 0.12–1

[a] Abbreviations: ND, not done; SE, *S. epidermidis*; SH, *S. haemolyticus*; MS, methicillin susceptible; MR, methicillin resistant; PJI, prosthetic joint infection; BMTRs, bone marrow transplant recipients; BSI, bloodstream-related infection.

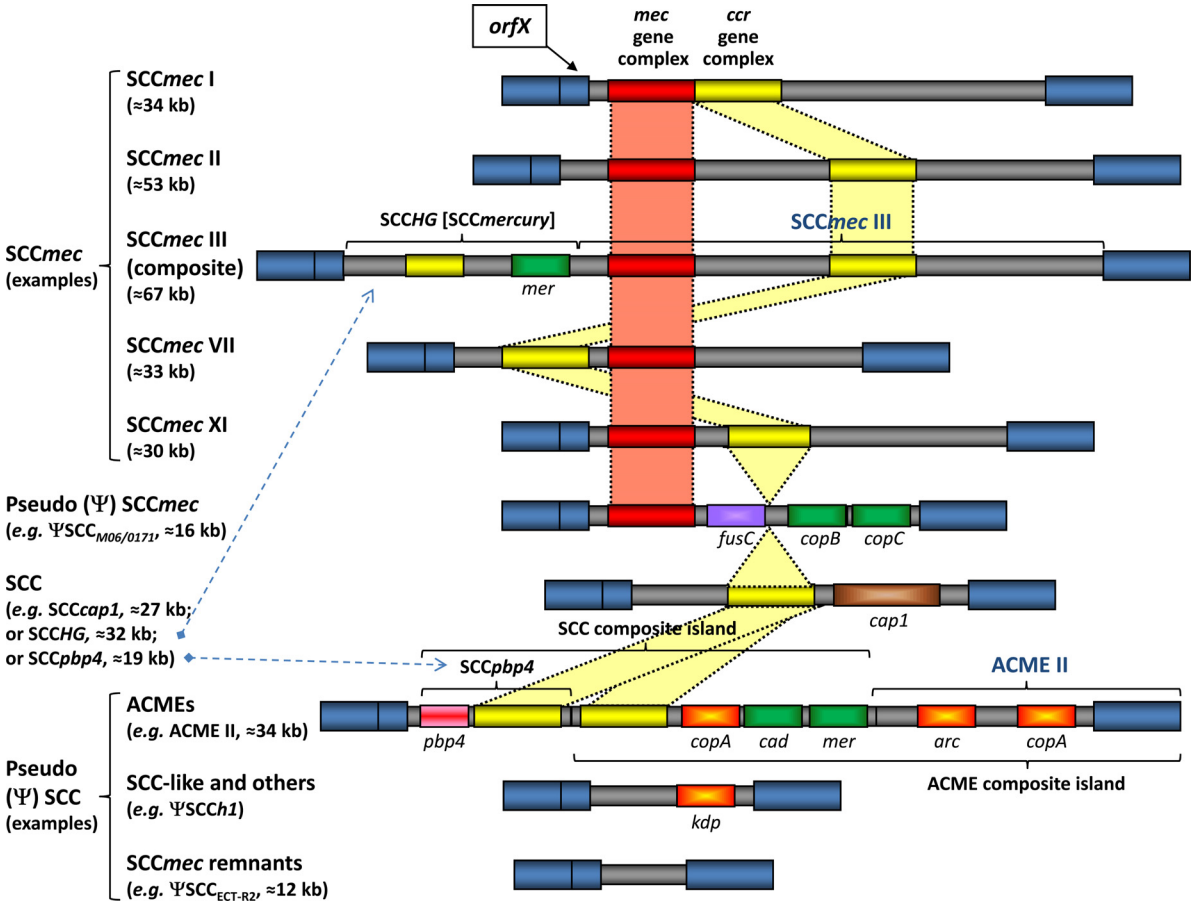


FIG 7 Highly simplified schema (not true to scale) of the composition of the SCC family integrated into the *S. aureus* chromosome (blue). Some examples of various SCC types, including those organized in composite islands, are given. Basic structures comprise the *mec* gene complex (red), the *ccr* gene complex (yellow), and the joining regions (gray). Some SCCs additionally contain (i) resistance operons acting against antibiotic agents (violet), such as fusidic acid (*fusC*); (ii) resistance operons for metalloids and transition metals with toxic/bactericidal properties (green), such as arsenic (*ars*), cadmium (*cad*), copper (*copB* and *copC*), and mercury (*mer*); (iii) virulence genes (brown), such as the capsule polysaccharide gene (*cap1*); (iv) other genes (orange), such as the genes composing the arginine catabolic mobile element (*arc*), the copper-translocating P-type ATPase gene (*copA*), and the potassium-transporting ATPase genes (*kdp*); (v) further penicillin-binding protein 4 (PBP4) genes (pink), such as *pbp4*; and (vi) pseudogenes.

IS*431mec* (476–478). The cassette chromosome recombinase genes *ccrAB* and *ccrC* encode site-specific integrases catalyzing the integration or excision of the entire SCC*mec* into or from the *orfX* locus at its 3′ end in the staphylococcal genome (476).

As discovered in the past few years, the intra-SCC*mec* diversity is enormous and very complex. This holds true not only for the J regions (J1 to -3), which contain diverse virulence, resistance, and other genes, as well as pseudogenes, and which vary in length, but also for the *mec* and *ccr* gene complexes essential for the function of the SCC*mec*. To describe an MRSA or MR-CoNS strain in terms of its SCC*mec* composition, a complex nomenclature has been established by the International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements (IWG-SCC) (479).

To date, 11 types and several subtypes have been reported for the SCC*mec* element. In CoNS, SCC*mec* types III, IV, and V, either alone or in various combinations, are the most prevalent types (62, 69–71) (Table 8). In particular for MR-CoNS, a highly diverse population of SCC*mec* elements has been discovered, and it can be assumed that the assortment of SCC*mec* types and subtypes will be enlarged further.

(iii) SCC family variety. SCC*mec* is part of a unique SCC family with an increasingly recognized structural diversity (Fig. 7). Besides the SCC*mec* elements, characterized by the possession of both *mec* and *ccr* gene complexes, other, diverse elements occur that lack one or both of these complexes (480). (i) SCC elements such as SCC_{12263}, which was found in *S. hominis*, possess a *ccr* complex but lack *mecA* (481). For *S. hominis* and *S. haemolyticus*, it was shown that these species might contain many other potential SCC elements as putative reservoirs of SCC*mec* structural elements (482, 483). (ii) As a result of deletion events or representing precursors of known SCC*mec* elements, pseudo (Ψ)-SCC*mec* elements harbor *mecA* but lack the *ccr* gene complex; an example is the *S. xylosus* $\Psi SCC\mathit{mec}_{S04009}$ element, which carries the class E *mec* gene complex, similar to type XI SCC*mec*, but lacks the *ccr* gene complex and both J regions (474). (iii) Elements lacking both *ccr* and *mec* genes have been designated ΨSCC elements. They are part of many different composite islands and can be differentiated into the following three groups: (i) arginine catabolic mobile elements (ACMEs); (ii) SCC-like elements, chromosome cassettes, or SCC*mec* insertion site genomic sequences; and (iii) SCC*mec* remnants (480). ACMEs are highly prevalent among CoNS strains

TABLE 7 Overview of *mecA* homologues and prototype strains according to the classification of the IWG-SCC

Proposed new designation[a]	Reported gene name (reference)	Prototype strain	Strain origin	Size (bp)	% Identity[b]
mecA	*mecA* (477)	*S. aureus* N315	Human (Japan)	2,007	100
	mecA	Staphylococcal strains that carry *mecA*	Diverse hosts and sources	2,007	98.3–100
	$mecA_{Sf}$ (465)	*S. fleurettii* SFMP01 (CCUG 43834^T)	Goat (goat milk cheese)	ND[c]	99.8
mecA1	*mecA* (*mecA1*) (463)	*S. sciuri* subsp. *carnaticum* K11[d]	Cattle (veal leg, sliced)	2,001	79.1
	mecAs, $mecA_{Ss}$ (465, 466)	*S. sciuri* subsp. *rodentium* ATCC 700061	Norway rat	2,001	80.2
mecA2	*mecA* (464)	*S. vitulinus* CSBO8[c]	Horse	2,007	91
mecB	*mecAm* (626)	*M. caseolyticus* JCSC5402[c]	Domestic chicken (skin swab)	2,025	61.6
mecC	$mecA_{LGA251}$ (470)	*S. aureus* LGA251[c]	Cattle (bulk milk sample)	1,998	68.7
mecC1	*mecC1* (474)	*S. xylosus* S04009	Bovine mastitis	1,997	69.9[d]
mecC2	*mecC2* (475)	*S. saprophyticus* subsp. *saprophyticus* 210	Common shrew	1,998	92.9[e]

[a] According to the proposed nomenclature for reporting novel *mecA* gene homologues (461), as follows: *mec* gene type, ≥70% nucleotide sequence identity with the respective prototype (hitherto described genes are *mecA*, *mecB*, and *mecC*); and *mec* gene allotypes, ≥70% to <95% nucleotide sequence identity to the respective *mec* gene prototype strains, designated with a numeral based on the chronological order of discovery (e.g., *mecA1*, *mecA2*, and *mecC1*).
[b] Unless otherwise stated, percent identity with the *mecA* gene in *S. aureus* N315.
[c] ND, no data given.
[d] Percent identity with the *mecA* gene of *S. aureus* MRSA252. The gene has 93.5% nucleotide identity to *mecC* in *S. aureus* LGA251.
[e] Percent identity with the *mecC* sequence of *S. aureus* LGA251. The gene has 94.5% identity to the *mecC1* sequence of *S. xylosus* S04009.

and are characterized by genetic diversity, with intact or truncated forms (454, 484–486). There is evidence for an interspecies transfer of ACME from *S. epidermidis* into an MRSA USA300 clonal lineage (485).

SCC elements, including their pseudo-elements, often carry additional antibiotic resistance genes, mostly as part of integrated transposons and plasmid copies (e.g., *pbp4* and erythromycin, tetracycline, spectinomycin, and fusidic acid resistance-encoding genes). Moreover, genes mediating resistance to metalloids and transition metals with toxic/bactericidal properties, such as arsenic, cadmium, copper, and mercury, have frequently been found in SCC elements of *S. epidermidis*, *S. haemolyticus*, and other staphylococcal species (Fig. 7) (74, 472, 487–490). In addition, other genes or loci, such as those involved in virulence, colonization, transmission, and cell wall synthesis, have been detected in these elements (484, 485, 488, 491).

TABLE 8 Occurrence of SCC elements in a selection of CoNS species

CoNS species	Source(s)	SCC*mec* (sub)type(s)[a] [reference(s)]
S. capitis	Humans, dogs	I, IA, II, III, IV, IVa, V, NT (627–630)
S. cohnii	Humans, dogs	NT (629, 630)
S. chromogenes	Humans	IV (630)
S. epidermidis	Humans, cats, dogs, horses, pigs, poultry	I, IIa, IIb, III, III (variant), IV, IVa, IVb, IVc, IVd, IVe, IVg, V, VI, NT (63, 70, 627–635)
S. haemolyticus	Humans, cats, horses, pigs	I, II, II.1, III, III (variant), IV, V, NT (70, 627–630, 632, 634–637)
S. hominis	Humans, dogs, pigs	I, III, IV, NT (627–630, 633–635)
S. lentus	Cattle, goats, sheep	III (631)
S. pasteuri	Pigs	IVc (634)
S. rostri	Pigs	III, IVa, NT (634)
S. saprophyticus	Humans	III, NT (498, 638)
S. sciuri	Humans, cattle, goats, pigs, sheep	I, III, IIIA, V, VII, NT (468, 627, 631, 634)
S. warneri	Humans, dogs, pigs, fish food	IV, IV.1, IVb, IVE, NT (629, 632–634, 637)
S. xylosus	Cattle	III, XI[b] (474, 631)

[a] NT, nontypeable and/or novel nondesignated types.
[b] Harbors the *mecC* gene or its allotype (*mecC1*).

(iv) Methicillin resistance. In comparing *S. epidermidis* and *S. haemolyticus*, publications from the 1980s reported high percentages of methicillin-resistant isolates of both species, but an even higher prevalence of MR *S. haemolyticus* strains exhibiting higher MICs (492). Since then, the percentage of MR-CoNS has continuously increased. For instance, over the course of a 20-year study (1986 to 2005) in Zurich, Switzerland, the percentage of MR-CoNS isolates recovered from burn patients increased from 11% to 55% (493). Comparing CoNS isolates ($n = 2,905$) recovered in 2001 from the SSTIs of hospitalized patients in the United States and four European countries, the proportion of CoNS resistance to oxacillin varied from 51.4% in France to 75.2% in the United States (494). In recent studies, the prevalence of clinical *S. epidermidis* and, in particular, *S. haemolyticus* isolates resistant to oxacillin has now reached about 80% or more (Table 6) (65, 75, 495). In contrast, in healthy persons in northern Sweden, a near absence of oxacillin resistance was reported, and isolates of common hospital-associated clones of multidrug-resistant *S. epidermidis* were not found (66). As occurs with MRSA, oxacillin-resistant CoNS isolates are, in general, more often multiresistant than oxacillin-susceptible isolates (496, 497).

In contrast to *S. epidermidis* and *S. haemolyticus*, other clinically important CoNS are mostly less resistant to oxacillin. In a Japanese study, *mecA*-positive *S. saprophyticus* was found in 7.9% of mostly nonisogenic isolates recovered from the genitourinary tract (498); however, in other studies, a much higher rate of resistant isolates was found (495). For *S. lugdunensis*, for which a different susceptibility breakpoint has been defined, 7.9% of isolates were categorized as resistant in an international study (495).

(v) Susceptibility to anti-MRSA cephalosporins. The so-called "fifth-generation" cephalosporins with MRSA activity comprise ceftobiprole and ceftaroline fosamil. Ceftobiprole was approved for use in Switzerland and Canada, but sales were—possibly tem-

porarily—discontinued in response to regulatory recommendations not to approve this substance in the United States and the European Union. Ceftaroline is approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and complicated skin and soft tissue infections (cSSTI), respectively, and by both authorities for treatment of community-acquired pneumonia (CAP).

A ceftobiprole MIC range of 0.094 to 1.5 mg/liter was reported for *S. epidermidis* isolates from PJIs (499). MIC ranges of 0.13 to 1 and 1 to 4 μg/ml were found for isolates of *S. haemolyticus* categorized as methicillin susceptible (MS) and resistant (MR), respectively (500). Also for *S. epidermidis*, a tendency for higher ceftobiprole MIC values was noted (501, 502). In a large U.S. hospital study, ceftaroline demonstrated potent *in vitro* activity against CoNS (MIC_{90}, 0.5 μg/ml), including those CoNS that tested methicillin or linezolid resistant (each MIC_{90}, 0.5 μg/ml) or daptomycin nonsusceptible (MIC range, 0.03 to 0.12 μg/ml) (503). In a Canadian multicenter study, ceftaroline demonstrated a 2-fold greater potency against MR *S. epidermidis* than against MRSA (501). In this study, 83 MS and 19 MR *S. epidermidis* isolates displayed low MIC range values when tested for ceftaroline (≤0.12 to 0.5 and 0.25 to 1 μg/ml, respectively) and ceftobiprole (≤0.06 to 2 and 1 to 4 μg/ml, respectively).

Resistance to glycopeptides, lipopeptides, and lipoglycopeptides. The exact mechanism of glycopeptide resistance among CoNS is still unclear. Heterogeneous susceptibility profiles, including reduced susceptibility for teicoplanin, may suggest some general predisposition to an intrinsic resistance to this antibiotic class (504). Three phenomena leading to therapy failure after administration of glycopeptides have been discovered or postulated, mostly for *S. aureus*. (i) The first phenomenon is the development of so-called vancomycin-intermediate *S. aureus* (VISA) isolates and putative precursor subpopulations, termed heterogeneous VISA (hVISA) strains (505). Since VISA isolates may also be resistant to teicoplanin, the term glycopeptide-intermediate *S. aureus* (GISA and hGISA, if heterogeneous) is also used. Their complex resistance mechanisms include cell wall alterations, resulting in reorganization and thickening, in addition to reduced autolytic activity (506–508). Furthermore, hVISA and VISA may represent a bacterial evolutionary state favoring persistence in the environment of the host (509). Also, cell wall thickening has been reported for glycopeptide-resistant CoNS (*S. epidermidis* and *S. haemolyticus*) (510, 511). Some glycopeptide-resistant CoNS may possess an excess of glycopeptide-binding sites by virtue of the overproduction of cell wall peptidoglycan material (512). Thus, one can consider that the basic mechanisms leading to a reduced susceptibility to glycopeptides may be similar in CoNS and *S. aureus*. (ii) In 2002, the first vancomycin-resistant *S. aureus* (VRSA; also designated glycopeptide-resistant *S. aureus* [GRSA]) strains containing the *vanA* gene were reported in the United States (513). Up to the present, *van* gene-possessing *S. aureus* isolates, all of the *vanA* type, have been found infrequently (513). Presently, the significance of a recent report on highly vancomycin-resistant CoNS isolates (13/15 isolates had MICs of ≥256 mg/liter, as tested by Etest) recovered in 2006 from the saliva of migratory songbirds in Kansas is unknown (514). Of potential importance, 6 of these 15 CoNS isolates (*S. succinus* [$n = 5$] and *S. saprophyticus* [$n = 1$]) were characterized as harboring *van* genes (*vanA* [$n = 5$] and combined *vanA*, *vanB*, and *vanC* [$n = 1$]). The *S. saprophyticus* isolate was *vanA* positive. These highly mobile wild songbirds may act as a vector to spread vancomycin resistance genes over a wide area (514). A recent observation of 3 isolates carrying *vanA* and *vanB1* genes, which were detected by PCR within a collection of 30 *S. epidermidis* isolates from ICU patients in Kampala, Uganda, needs further corroboration (515). (iii) A phenomenon called "vancomycin MIC creep" was postulated to describe an overall population drift in clinical *S. aureus* isolates toward reduced vancomycin susceptibility, but with MIC values that are still below the susceptibility breakpoint (516, 517). This issue is a matter of debate, since other studies noted no changes or even reductions in vancomycin MIC values (518, 519). So far, the creep phenomenon has not been reported for CoNS. A Swedish study analyzing bloodstream isolates of *S. epidermidis* and *S. haemolyticus* isolated from hemato-oncological patients did not show any statistically significant increase of vancomycin MIC values during the 3-decade study period (1980 to 2009) (520).

Following the introduction of vancomycin into clinical practice in 1958, clinical CoNS isolates with reduced susceptibility to vancomycin did not come to widespread attention for more than 2 decades, until the 1980s (521, 522). During this time, resistant *S. epidermidis* and *S. haemolyticus* isolates were reported long before the advent of the first *S. aureus* isolates with reduced glycopeptide susceptibility, in 1997 (523). Both species have been found to be the commonest CoNS species exhibiting reduced susceptibility to glycopeptides (524). However, despite extensive, unabated vancomycin use, the vast majority of CoNS isolates tested have been shown to still be susceptible to vancomycin (64, 75, 495–497, 499, 501, 525–527). In an Italian study of BSI-related CoNS (of these, 77% were MR-CoNS), 87/1,609 (5.4%) isolates displayed reduced susceptibility to glycopeptides; of these, 11 *S. epidermidis* and 2 *S. haemolyticus* isolates were proven to be causative BSI microorganisms (528).

Including clinical isolates of *S. epidermidis* and *S. haemolyticus* isolated from patients with hematological malignancies, no long-term glycopeptide MIC creep was observed over a period of 3 decades; however, a standard Etest was used for MIC determinations (520).

Early studies certified comparable activities of vancomycin and teicoplanin (teichomycin) against CoNS, some with lower MIC values (529). With time, it became evident that teicoplanin-resistant CoNS isolates were more common than those exhibiting resistance to vancomycin. In addition to some earlier reports on evaluated teicoplanin MICs (530), the first teicoplanin-resistant CoNS were reported in 1986 among a selection of methicillin-resistant *S. haemolyticus* strains isolated in the United States (Charleston, SC) between 1980 and 1985 (531). The first (clinically silent) case associated with a teicoplanin-resistant *S. haemolyticus* isolate, obtained from a pacing wire tip, was later reported (532). In the same year, a letter describing a real clinical case due to an *S. epidermidis* isolate from a patient with peritonitis undergoing CAPD was published (533). Nowadays, in the very large, worldwide SENTRY Antimicrobial Surveillance Program (2002 to 2010) study, 0.4% of all CoNS isolates tested were teicoplanin resistant (MIC_{90}, 8 mg/liter; MIC range, ≤2 to >16 mg/liter) (495). Comparable results were attained in other studies if tests were conducted according to CLSI criteria (497, 534). Notably, in testing the same isolates according to EUCAST interpretative criteria, higher resistance percentages were found for teicoplanin (e.g., CLSI/EUCAST percentages for MS-CoNS isolates, 0.0%/

3.3%; and those for MR-CoNS isolates, 0.5%/12.2%) (497). However, study populations with a higher prevalence of teicoplanin-resistant isolates have been reported, such as in a recent Polish study (16.2% teicoplanin resistance; MIC_{90}, 4.0 mg/liter; MIC range, 0.094 to 8.0 mg/liter) (535). In a collection of clinical MR *S. epidermidis* strains ($n = 300$), most of which were contaminants of blood cultures or noninvasive colonizers, a total of 55% were found to be resistant to teicoplanin (536). This French study found that the prevalence of teicoplanin resistance increased in *S. epidermidis*/MR *S. epidermidis*, from 7.2%/20% in 2000 to 30.4%/60.9% in 2004, with a peak of 46.1%/84.4% in 2003, while there was a very low prevalence of teicoplanin resistance in *S. aureus*/MRSA during the same time (range, 0.9% to 2.8%/2.7% to 6.7%). In a United Kingdom study, 20.8% of all CoNS isolates tested ($n = 1,214$) were not susceptible to teicoplanin, but only one vancomycin-intermediate CoNS isolate was found (537). The percentage of teicoplanin-resistant CoNS isolates recovered within 1 year in an Italian prospective case-control study that enrolled 535 patients with CoNS bacteremia was 8% in intensive care units and 3% and 2% in medical and surgical wards, respectively (524). Only one isolate in this study exhibited resistance to both vancomycin and teicoplanin. Overall, *S. haemolyticus* shows a kind of predisposition among CoNS to acquire resistance to glycopeptides, and within this antibiotic class, teicoplanin exhibits less satisfactory MICs than those of vancomycin.

For daptomycin, a bactericidal, cell membrane-targeting cyclic lipopeptide, diverse but not fully elucidated mechanisms leading to resistance have been assumed and have been studied mostly in *S. aureus*. Through the accumulation of single nucleotide polymorphisms in several gene loci, especially the multipeptide resistance factor gene (*mprF*) and the *yycFG* components of the *yycFGHI* operon, cell membrane phenotypic changes occur in addition to other perturbations of the cell membrane (538, 539). Also, modifications of the cell wall, including increased cell wall teichoic acid production, enhanced expression of the *dlt* operon, which is involved in D-alanylation of cell wall teichoic acids, and progressive cell wall thickening, may contribute to daptomycin resistance (539–541). Daptomycin demonstrated high activity against more than 20 CoNS species, as shown in a study of more than 22,000 isolates from 42 countries as part of the SENTRY program (2002 to 2010) (495). In that study, daptomycin inhibited 99.8% (MIC_{90}, 0.5 mg/liter) of isolates. A substantial number of isolates with an MIC above the susceptibility breakpoint (1 mg/liter) were found for *S. sciuri* only (13/46 isolates [28.3%]); low or marginal numbers were noted for *S. auricularis* (4.9%), *S. warneri* (1.2%), *S. capitis* (1.0%), *S. saprophyticus* (0.4%), *S. hominis* (0.2%), and *S. epidermidis* (<0.1%). Species having the highest MIC values for both glycopeptides in that study, such as *S. epidermidis*, *S. haemolyticus*, and *S. xylosus*, were very susceptible to daptomycin (495). Bloodstream isolates of *S. epidermidis* from bone marrow transplant patients showed an MIC_{90} of 0.25 mg/liter for daptomycin (525).

For lipoglycopeptides, potent *in vitro* activity against *S. epidermidis* isolates, regardless of their susceptibility to methicillin, was shown in a comparative review summarizing several studies (MIC_{90} values [MS *S. epidermidis*/MR *S. epidermidis*] were as follows: dalbavancin, 0.06/0.06 mg/liter; oritavancin, 0.05/0.05 mg/liter; and telavancin, 1.0/1.0 mg/liter); the review demonstrated lower lipoglycopeptide MIC values than those of vancomycin (MIC_{90} values [MS *S. epidermidis*/MR *S. epidermidis*], 2.0/4.0 mg/liter) (542). For PJI-associated *S. epidermidis* isolates, an MIC range of 0.003 to 0.047 mg/liter was reported for dalbavancin (499). In a global study comprising 2,510 CoNS isolates, the telavancin MIC_{90} was 0.25 mg/liter, which was lower than those of both vancomycin (2 mg/liter) and teicoplanin (8 mg/liter) (543). However, CoNS that had reduced susceptibility to vancomycin and resistance to teicoplanin presented a ca. 2-fold, species-unrelated reduction in susceptibility to telavancin, but still within an MIC range of 0.25 to 0.5 mg/liter (544).

Resistance to oxazolidinones. After many decades, the oxazolidinone linezolid represented the first (and so far only) of a novel antibiotic class available on the market with activity against Gram-positive microorganisms, including staphylococci. So far, three mechanisms have been discovered that result in oxazolidinone resistance in staphylococci: (i) successive accumulation of single point mutations in the linezolid 23S rRNA (domain V)-binding site in at least two copies of the rRNA gene operons; (ii) rarely, mutations in the *rplC* and *rplD* genes, encoding the 50S ribosomal proteins L3 and L4, respectively, of the peptide translocation center of the ribosome; and (iii) acquisition of the plasmid-borne ribosomal methyltransferase gene, *cfr*, leading to posttranscriptional methylation of adenosine at position 2503 of 23S rRNA in the large ribosomal subunit (545–548). Point mutations in the 23S rRNA gene (e.g., G2447T, T2504A, C2534T, and G2576T) as an underlying mechanism leading to linezolid resistance have also been found for *S. epidermidis* and other CoNS (549–551).

In contrast to the first two mechanisms, *cfr*-mediated resistance is of serious concern, due to its possible high horizontal transfer capability, its origin from animal-associated staphylococcal species, and its association with a $PhLOPS_A$ phenotype, exhibiting resistance to several antibiotic classes, including phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A (552). A multicity outbreak of a *cfr*-containing linezolid-resistant *S. epidermidis* strain has already been reported (553). An isolate has been described in Spain with cooccurrence of all three mechanisms leading to linezolid resistance (554). To date, more than seven different *cfr*-carrying plasmids and several types of chromosomal *cfr* segments have been identified in CoNS (e.g., *S. cohnii*, *S. lentus*, *S. saprophyticus*, *S. simulans*, and *S. warneri*) isolates recovered mostly from swine specimens, but also from cattle, horses, and poultry (555). Moreover, the phenomenon of linezolid dependence may additionally contribute to the escalating emergence of linezolid-resistant isolates (550).

In time-kill experiments, linezolid displayed a predominantly bacteriostatic activity against staphylococci (556). Since its introduction in approximately 2000, linezolid has proven to be at least as effective as glycopeptides for the treatment of patients with Gram-positive infections; however, the majority of data are derived from MRSA patients with SSTIs, supplemented by a few studies on pneumonia (557, 558). Despite more than a decade of clinical use, linezolid resistance is still a rare phenomenon, but concerns are growing. Overall, MIC_{90} values for CoNS are low, and generally 50%, compared to those for *S. aureus* (559). Within a surveillance study enrolling Canadian hospital-associated patients in 2009, *S. epidermidis* isolates offered low MIC_{90} values irrespective of their categorization as methicillin resistant or susceptible (each 1 mg/liter; MIC range, ≤0.12 to 2 mg/liter) (501). Also, results of the 2011 U.S. LEADER surveillance program revealed an overall linezolid MIC_{90} of 1 mg/liter for CoNS (534).

The same value was found within the global 2011 ZAAPS program, which included 266 MS- and 702 MR-CoNS isolates (559).

The incidences of linezolid resistance among CoNS isolates from the U.S. LEADER (2004 to 2010) surveillance programs ranged from 1/496 (0.2%) isolates in 2004 to over 18/1,020 (1.8%) isolates in 2007 and 8/676 (1.2%) isolates in 2010 (560). Other recent studies confirmed a still low prevalence of linezolid resistance among CoNS isolates (559, 561, 562). Besides the species mentioned below (see next paragraph), linezolid-resistant isolates among CoNS were also reported for *S. simulans* and *S. pettenkoferi* (563, 564).

In the 2011 ZAAPS program, a mobile *cfr* gene was noted in an *S. haemolyticus* isolate with an elevated MIC (4 mg/liter) (559). However, isolates with linezolid MICs of >256 mg/liter have been reported (554). An *S. sciuri* isolate with *cfr* was originally identified in a calf (565). Besides *S. aureus*, *cfr* has also been identified in other clinical CoNS isolates from humans, including *S. capitis*, *S. cohnii*, *S. hominis*, *S. epidermidis*, and *S. haemolyticus*, in many parts of the world (559, 566–568). On Chinese pig, chicken, and duck farms, *cfr*-carrying isolates were found among *S. arlettae*, *S. cohnii*, *S. haemolyticus*, *S. lentus*, *S. rostri*, *S. saprophyticus*, *S. sciuri*, and *S. simulans* isolates (569). The justified concern surrounding linezolid resistance, whether *cfr* mediated or not, is underlined by reports of outbreaks and nosocomial spread of linezolid-resistant *S. aureus* and CoNS isolates (554, 563, 568, 570). An impressive example is the regular recovery of linezolid-resistant strains of *S. epidermidis* in an ICU within 4 years following an outbreak of infection by *cfr*-mediated linezolid-resistant *S. aureus* (554). Notably, 58% of colonized patients and 90% of infected patients had previously received linezolid for at least 10 days (554).

Resistance to tetracyclines and glycylcyclines. Resistance to tetracyclines is based primarily on the acquisition of mobile *tet* and *otr* genes, leading to ribosomal protection through dissociation of tetracyclines from their ribosomal binding sites and to drug efflux through active transportation of the agents out of the bacterial cell (571, 572). In a U.S. study from 2011, the percentage of tetracycline-resistant isolates was higher for MR-CoNS (18.6%) than for MS-CoNS (7.6%) (534). About 18% tetracycline-resistant CoNS isolates were found in two other recent studies (65, 573). Within the multicenter German Tigecycline Evaluation Surveillance Trials (G-TEST I to III), in 2005, 2007, and 2009, the percentage of doxycycline-resistant CoNS isolates decreased from 10.1% to 9.2% to 6.1% for *S. epidermidis* isolates and from 12.3% to 12.1% to 5.9% for *S. haemolyticus* (75). Along with the significant decrease of tetracycline administration for outpatients in Europe (574), this phenomenon seems to be a continuation of an earlier trend, as 20.4% of CoNS isolates in 1990, and 18.5% in 1995, exhibited resistance to doxycycline in Germany (447).

The minocycline derivative tigecycline is the prototype compound of a new class of glycylcyclines with bacteriostatic broad-spectrum activity overcoming resistance development of classical cyclines due to not being substrates for tetracycline efflux pumps (575). For staphylococci, the mechanism(s) of tigecycline resistance remains to be elucidated. *In vitro*, overexpression of the MATE family efflux pump (*mepA*) in a wild-type *S. aureus* background caused a decrease in susceptibility to tigecycline, although it was not sufficient to significantly increase the MIC of tigecycline (576). In studying *S. epidermidis* bloodstream isolates, the MIC_{90} of tigecycline, the first available glycylcycline, was 0.5 mg/liter, with no differences if isolates were stratified regarding their methicillin susceptibility (525). Comparing the results from two German multicenter trials conducted prior to and after the introduction of tigecycline, no differences were found in the tigecycline susceptibility of *S. epidermidis* isolates recovered from at least two consecutive blood samples (562). However, three *S. haemolyticus* isolates (4.5%) were categorized as tigecycline resistant, exhibiting an MIC level above the breakpoint of 0.5 mg/liter. All other included CoNS isolates showed an MIC_{90} range of ≤0.125 to 0.5 mg/liter (562). In three global regions, Europe, Latin America, and the Asia-Pacific region, MS-CoNS ($n = 192$) and MR-CoNS ($n = 646$) exhibited an MIC_{90} of 0.5 mg/liter, with all isolates being categorized as susceptible (577).

Resistance to fusidic acid, fosfomycin, and rifampin. Fusidic acid, fosfomycin, and rifampin represent "old" antibiotic agents—nowadays increasingly being reintroduced—with activity against Gram-positive microorganisms (fusidic acid) or activity against both Gram-positive and Gram-negative microorganisms (fosfomycin and rifampin); rifampin is primarily known as an antituberculosis drug. In contrast to the case for *S. aureus*, little is known regarding resistances of CoNS to these compounds, with the data being inconsistent and different breakpoints applied. Although these three agents belong to different classes of antibiotics, they have one thing in common: a rapid development of resistance if administered as monotherapy. Thus, they are used principally in combination therapy. However, combined medication with these agents is based on clinical experience rather than proven evidence and thus is a matter for debate (578).

Spontaneous mutations in the *fusA* gene leading to an altered ribosomal translocase (i.e., elongation factor G [EF-G]) represented the first discovered resistance mechanism class (FusA), leading to resistance to fusidic acid in staphylococci (579). A FusB mechanism in staphylococci includes an acquired chromosomal or plasmid-mediated *fusB* gene, encoding an inducible EF-G-protecting protein (580, 581). Among *S. aureus* and *S. saprophyticus* strains, *fusC* and *fusD* homologs, respectively, have been described (582). Interestingly, mutants of a further class, termed FusE, and some mutants of the FusA class display some phenotype characteristics of staphylococcal small-colony variants (583). In testing of 41, 10, and 11 clinical CoNS strains from the United States, Canada, and Australia, respectively, 7.2%, 20.0%, and 10.8% fusidic acid-resistant strains were noted (584). In Europe, large differences in fusidic acid resistance were found among 3,134 CoNS isolates, ranging from 12.5% in Poland to more than 40% in Belgium, France, Ireland, Switzerland, and the United Kingdom (585). In both studies, the percentage of fusidic acid-resistant isolates was by far higher in the CoNS group than in the *S. aureus* isolates. A notable increase in resistance to fusidic acid (from 10 to 40%) despite the low usage of these agents was shown in a study from Finland (449).

Resistance to fosfomycin (phosphonomycin) can be mediated by either chromosomal or plasmid-borne mechanisms. In contrast to the case for Gram-negative microorganisms, little is known about the chromosomally mediated resistance, which is based on defects in the L-alpha-glycerophosphate (*glpT*) or hexose phosphate (*uhpT*) transport system that takes up fosfomycin (586). In plasmid-mediated resistance, *fosA* encodes a glutathione *S*-transferase that inactivates fosfomycin by forming a covalent bond between fosfomycin and a sulfhydryl group in glutathione (587). In staphylococci, a homolog, *fosB*, has been described (588). Summarizing data from three studies evaluating fosfomy-

cin susceptibility, 31.6% of MR-CoNS isolates were resistant (589). In a 2008 study of 961 nonurinary Greek CoNS isolates, comprising *S. epidermidis*, *S. saprophyticus*, and *S. haemolyticus*, 22.5% exhibited *in vitro* resistance to fosfomycin (590).

Rifampin resistance in staphylococci is most frequently based on point mutations in the highly conserved regions of the *rpoB* gene, which encodes the beta subunit of the bacterial RNA polymerase, resulting in amino acid substitutions at or near the binding site for the drug (591, 592). In a 2009 Swedish study, approximately 39% of PJI-related *S. epidermidis* isolates were found to be rifampin resistant (MIC_{90}, >32 mg/liter) (499). About 15% of CoNS isolates tested resistant in a multicenter study performed in Colombia in 2001 to 2002 (527). Data from Germany revealed 6.7% rifampin-resistant CoNS isolates ($n = 885$) in the mid-1990s (447).

Resistance to mupirocin. In the case of CoNS, little is known about the real prevalence of resistance toward mupirocin, a topically administered antibiotic. In a German study performed in 2001, rates of low- and high-level resistance were shown to be 9.4% and 3.3%, respectively, in *S. epidermidis* (593). About 8% of *S. haemolyticus* isolates tested resistant in a recent Brazilian study (573). However, reports on the elevated prevalence of high-level mupirocin resistance in CoNS, with rates of low- and high-level resistance reaching 22 and 61%, respectively, as a result of increased use of this substance (77, 594), are alarming because mupirocin represents the cornerstone of decolonization efforts for nasally colonized MRSA patients. What is especially worrying is that this resistance is mediated by plasmids carrying the *ileS2* gene, also designated *mupA*, which could be transferred to *S. aureus*. Moreover, these plasmids are recognized as being associated with resistance to other agents, such as clindamycin, erythromycin, levofloxacin, and tetracycline.

Resistance to biocides/antiseptics. Relatively little is known regarding the resistance of CoNS to antiseptics. In a recent study in a French neonatal ICU, 41.2% of CoNS isolates recovered from CRBSIs in very preterm neonates exhibited decreased susceptibility to at least one antiseptic (chlorhexidine, 12%; benzalkonium, 24%; and acriflavine, 33%) (77). Note that quaternary ammonium compound (QAC) resistance determinants are transferable and are located on plasmids and transposons together with antibiotic resistance genes encoding resistance to aminoglycosides, penicillin, and trimethoprim (595).

In Vitro Susceptibility Testing

As with *S. aureus*, the main task for *in vitro* susceptibility testing of CoNS is the unambiguous identification of methicillin resistance. For empirical (calculated) antibiotic therapy of CoNS—at least for *S. epidermidis* and *S. haemolyticus*—methicillin resistance can reasonably be expected. Nevertheless, valid methicillin resistance determination is a necessity for CoNS, since in several circumstances, such as endocarditis and other invasive processes, the use of the most efficient therapeutic option, i.e., the application of β-lactams, should not be excluded *a priori*. Of particular importance is the determination of methicillin susceptibility for *S. lugdunensis*, as the aggressive nature of this CoNS species necessitates the administration of the most efficient (preferably bactericidal) antibiotic agents. Conversely, misidentification of MR-CoNS isolates as methicillin susceptible may lead to fatal treatment failure. Furthermore, valid determination of glycopeptide susceptibility of CoNS isolates may have increasing future significance.

Phenotypic approaches. Conventional antimicrobial susceptibility testing of CoNS is based on reference methods of the CLSI (http://www.clsi.org) or EUCAST (http://www.eucast.org), increasingly replacing national standards.

It is noteworthy that traditional phenotype-based methods have reduced sensitivity and specificity for recognition of methicillin resistance in CoNS. This is caused by heteroresistance of respective isolates, a phenomenon also recognized in MRSA. Heteroresistance describes the fact that only a minority of cells of a given methicillin-resistant isolate express the genetically encoded capability of methicillin resistance under *in vitro* conditions, thus suggesting a false-susceptible result. However, with the enhanced discriminatory power of applying cefoxitin as a test substance for detecting MR staphylococci, most of the diagnostic problems caused by heteroresistance have disappeared. According to the recent CLSI *Performance Standards for Antimicrobial Susceptibility Testing* (version M100-S23) and EUCAST breakpoint tables for the interpretation of MICs and zone diameters (version 3.1), cefoxitin screening based on a disc diffusion assay (disc content of 30 μg) is used as a surrogate method for the determination of *mecA*-mediated oxacillin resistance, reliably predicting methicillin resistance for CoNS (450, 451). Note that the EUCAST zone diameter breakpoints given for CoNS (susceptible, ≥25 mm; and resistant, <25 mm) are modified for *S. lugdunensis* and *S. saprophyticus* to those for *S. aureus*, i.e., ≥22 mm and <22 mm for interpretation as susceptible and resistant, respectively. The CLSI interpretative criteria are basically the same. For CoNS other than *S. lugdunensis*, the cefoxitin MIC has been assumed by EUCAST to be an inferior predictor of resistance to methicillin compared to the disc diffusion test (450). CLSI lists a cefoxitin MIC breakpoint for *S. lugdunensis* (and *S. aureus*) of ≥8 mg/liter. If oxacillin MICs are determined, the MIC breakpoint for CoNS given by both CLSI and EUCAST (with the EUCAST notation in parentheses) is ≥0.5 (>0.25) mg/liter, with the exception of the respective value for *S. lugdunensis* being ≥4 (>2) mg/liter (like that for *S. aureus*) (451).

MICs for glycopeptide testing are method dependent. According to EUCAST (ISO 20776), they should be ascertained by broth microdilution (450). The disc diffusion method is considered unreliable because it is not able to distinguish between isolates exhibiting the wild-type phenotype and those characterized by non-*vanA*-mediated resistance. Serious GISA infections are not treatable with high doses of glycopeptides. Consequently, the resistance breakpoints have been reduced by EUCAST to 2 mg/liter in order to avoid GISA isolates being reported as intermediate (450). Thus, from the susceptibility testing point of view, there is no further reporting in terms of differentiation between VISA/GISA and VRSA/GRSA isolates. For CoNS, the EUCAST MIC breakpoints are ≤4 and >4 for reporting susceptibility and resistance, respectively, to both vancomycin and teicoplanin (450). CLSI criteria still distinguish between being susceptible, intermediate, and resistant toward glycopeptides, and specific MIC interpretative criteria are given for CoNS (breakpoints for vancomycin, ≤4 mg/liter for susceptibility, 8 to 16 mg/liter for intermediate, and ≥32 mg/liter for resistance; and breakpoints for teicoplanin, ≤8 mg/liter for susceptibility, 16 mg/liter for intermediate, and ≥32 mg/liter for resistance) (451). For the detection of heterogeneous resistance to glycopeptides, a modified population analysis profile-area under the curve (PAP-AUC) method is needed (596). A PAP-AUC adaptation for CoNS testing has been described (597). Since this method is laborious, complicated, and

not suited for routine use, a number of screening assays have been developed for *S. aureus*, including antibiotic-containing agar media and specialized gradient tests (macro-Etest) (508). This approach has also been applied for *S. epidermidis* and *S. haemolyticus* (520).

Nucleic acid detection-based approaches. Rapid PCR-based approaches have been introduced only for the detection of MRSA directly from surveillance swabs for screening purposes. Commercial assays specifically developed for the detection of methicillin resistance in CoNS are not available. However, several in-house PCR approaches for the species differentiation and simultaneous methicillin resistance determination of cultivated CoNS isolates, together with detection of biofilm formation genes, have been reported (598, 599).

TREATMENT AND MANAGEMENT

Key points that have to be considered for the treatment and management of CoNS infections include the species (*S. epidermidis* group versus *S. lugdunensis* versus *S. saprophyticus*), the site of infection, the immune status of the patient, and, as a special objective, the presence of inserted or implanted foreign bodies.

Therapeutic Options for Treatment of CoNS Infections

Therapeutic options for the treatment of CoNS are limited because the vast majority of clinically recovered isolates are methicillin resistant. Thus, most infections by CoNS of the *S. epidermidis* group require treatment with a glycopeptide, with vancomycin given preference. Replacement of vancomycin by β-lactamase-resistant penicillins and cephalosporins (first or second generation) is advisable for methicillin-susceptible isolates. Alternatively, cotrimoxazole, if isolates are susceptible, or newer antibiotic agents, such as daptomycin, linezolid, or cephalosporins with MRSA activity, may be administered, in particular if methicillin resistance is probable or was detected.

When used simultaneously, antibiotics with cell wall activity combined with rifampin were shown to act synergistically. Further combination therapies in the case of administration of glycopeptides and β-lactams include aminoglycosides, fosfomycin, cotrimoxazole, and fusidic acid. However, respective recommendations are based on limited, partly uncorroborated studies and some case reports for the treatment of severe infections, mostly by *S. aureus* (600, 601). For CoNS, even fewer data are available. Thus, a careful risk-benefit assessment is mandatory if combination therapy is applied.

Sufficient controlled clinical study data on the efficacy of antimicrobial agents for *S. lugdunensis* infections and the duration of therapy are lacking. Empirical treatment of *S. lugdunensis* infections with β-lactamase-resistant penicillins and cephalosporins of the first or second generation should be appropriate. Note that in cases of *S. lugdunensis*-caused endocarditis, medical therapy alone is rarely successful and urgent surgical intervention is necessary. A recent analysis revealed that medical treatment alone was an independent risk factor for mortality (189).

For uncomplicated UTIs due to *S. saprophyticus* subsp. *saprophyticus*, cotrimoxazole can be administered. In contrast to the usual 3-day regimen for the treatment of uncomplicated UTIs, infections by this CoNS species may respond better to 7 days of therapy; however, the relevant data are sparse (602). This longer treatment regimen may also be applied if other antimicrobial agents, such as fluoroquinolones, are administered (602).

The treatment approach for CoNS has to be adapted for particular infections, as in the case of FBRIs, including CRBSIs and catheter-associated UTIs (CA-UTIs) (see below), as well as infective endocarditis involving native or prosthetic valves (see respective guidelines and literature) (603, 604).

For detailed treatment information, the annually updated edition of *The Sanford Guide to Antimicrobial Therapy* (605), respective national guidelines, and current manufacturer specifications should be consulted.

Management of FBRIs caused by CoNS

In view of the frequent use of implanted devices, biofilm-associated FBRIs due to CoNS remain a therapeutic challenge. They frequently require removal of the device, often accompanied by the need for additional medical interventions and costs. CoNS-generated biofilms show significant resistance to antibiotics, caused by impaired penetration of the antibiotics and changes in bacterial metabolism and behavior. With the exception of rifampin, approximately 100- to 1,000-fold increases in minimal bactericidal levels have been demonstrated against most antibiotics (606).

Whenever an FBRI is suspected, the following general decisions have to be made: whether to remove the colonized foreign body and/or whether to initiate empirical antimicrobial treatment and efforts to salvage the device (92). For this reason, several key questions have to be addressed for the rational and successful management of FBRIs. They include the relevance of a presumed FBRI to clinical signs and how it can be confirmed, the presence of predisposing factors (e.g., neutropenia and other immunocompromising disorders and the type of medical device), the clinical situation of the patient (e.g., premature infant or sepsis), and cooccurring conflicting clinical imperatives. Further general aspects are given in detail by current Infectious Diseases Society of America (IDSA) practice guidelines (607, 608).

In the case of uncomplicated CoNS-caused CRBSIs without endovascular hardware, the removal of the device is often sufficient for therapy unless fever and/or bacteremia persists. In the case of CRBSIs, the absence of continuing bacteremia should be confirmed by blood culture diagnostics after catheter withdrawal. Alternatively, a short antibiotic treatment (5 to 7 days) subsequent to removal of the catheter might be appropriate for uncomplicated CoNS-caused CRBSIs. If the catheter is retained, antibiotics should be administered for 10 to 14 days, along with antibiotic lock therapy (607, 609). However, the question of whether catheter removal and/or antibiotic therapy is preferred is still a matter of debate because of the lack of controlled study data. For MS-CoNS, β-lactamase-resistant penicillins should be used as preferred agents (alternatively, first-generation cephalosporins, vancomycin, or cotrimoxazole [if isolates are susceptible] may be used). In the case of CRBSIs by MR-CoNS, vancomycin should be used preferentially. Alternative agents include daptomycin, linezolid, and quinupristin-dalfopristin (607).

For PJIs caused by staphylococci, intravenous antimicrobial therapy for 2 to 6 weeks should be administered subsequent to debridement and retention of the prosthesis (608). This is followed by a longer oral course (3 to 6 months) dependent on the nature of the PJI (608). For methicillin-susceptible staphylococci, β-lactamase-resistant penicillin or cephalosporins (cefazolin or ceftriaxone) are recommended as preferred treatment by the IDSA (608). For methicillin-resistant staphylococci, vancomycin

should be given; an alternative treatment, daptomycin or linezolid, or a combination therapy with rifampin is recommended irrespective of whether the isolate is methicillin resistant or not (608). Modified recommendations exist for patients with PJI following a one-stage exchange or for other circumstances (608). For specific entities, such as PVIE and CA-UTIs, we refer to the respective guidelines (603, 604).

CONCLUSIONS

CoNS resemble very heterogeneous and versatile Gram-positive bacteria. Their main ecological niches are skin and mucous membranes of humans and animals, and they are therefore always in a very close, and mainly symbiotic, relationship with their natural hosts. This also holds for the CoNS species preferentially found on humans. Except for *S. saprophyticus* and *S. lugdunensis*, CoNS rarely attack a healthy host, because of a lack of aggressive virulence properties. However, groups of especially susceptible patients are increasing, either due to still undeveloped or impaired host response functions or due to inserted or implanted foreign bodies. Consequently, CoNS have become a major nosocomial pathogen. Despite the normally subacute and low inflammatory course of these infections, they present a substantial clinical burden because of broad and severe treatment difficulties. In the case of foreign body infections, the removal of the infected device is most often ultimately required.

Many questions regarding the phylogeny, ecology, and pathogenesis of CoNS are still not answered. Just recently available new methodological tools will enable further research approaches. This may lead to new measures for effective therapy and for the prevention of CoNS infections.

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