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1 **Role of coagulase-negative staphylococci in human disease.**

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Accepted Manuscript

9 **Abstract**

10

11 Coagulase-negative staphylococci (CNS) are normal inhabitants of human skin and mucous
12 membranes. They have long been dismissed as culture contaminants, but now the potentially
13 important role of CNS as pathogens and their increasing incidence has been recognized.
14 Approximately 55%-75% of nosocomial isolates is methicillin resistant. CNS were the first
15 organisms in which glycopeptide resistance was recognized. In the immunocompetent host, CNS
16 endocarditis and urinary tract infections with *Staphylococcus saprophyticus* are the most common
17 CNS infections. Other patients are usually immunocompromised, with indwelling or implanted
18 foreign bodies. CNS account for approximately 30% of all nosocomial blood stream infections. The
19 majority of these concern catheter-related sepsis. Other important infections due to CNS include
20 central nervous system shunt infections, endophthalmitis, surgical site infections, peritonitis in
21 patients with continuous ambulatory peritoneal dialysis and foreign body infections. CNS are rarely
22 associated with mastitis in humans. *Staphylococcus lugdunensis* is more pathogenic than other CNS
23 as it expresses several potential virulence factors. The distinction between clinically significant,
24 pathogenic and contaminating isolates is a major problem. Several studies show clonal intra and inter
25 hospital spread of *Staphylococcus epidermidis* strains which suggests that infection control measures
26 may be necessary for multiresistant CNS isolates as for methicillin resistant *Staphylococcus aureus*.
27 As a result of medical progress, mainly due to the use of invasive and indwelling medical devices,
28 CNS are now a major cause of nosocomial and health-care related infections.

29 **Keywords:** coagulase-negative staphylococci, human medicine, species distribution, antibiotic
30 resistance, endocarditis, urinary tract infections, blood stream infections, nosocomial infection

31

31 1. Introduction

32

33 Coagulase-negative staphylococci (CNS) are normal inhabitants of human skin and mucous
34 membranes. They were first described in 1884 by Rodenbach as *Staphylococcus albus*, an avirulent
35 staphylococcus. They have long been dismissed as culture contaminants, even in type 1 samples
36 (samples obtained from a normally sterile site by needle aspiration or surgery). Only in 1958 the first
37 report on the potential pathogenicity of CNS in patients with septicaemia was published (Smith et al.,
38 1958). Later on, casuistic reports of CNS endocarditis, wound and urinary tract infections (UTI)
39 appeared (Kloos et al., 1994). Since the 1970s, CNS are recognised as etiologic agents of a wide
40 variety of infections. Patients with CNS infections are usually immunocompromised, with indwelling
41 or implanted foreign bodies. CNS play a role in bacteraemia, central nervous system shunt infection,
42 endocarditis, urinary tract infection, surgical site infections, endophthalmitis, foreign body infection
43 and many other infections. The distinction between clinically significant, pathogenic and
44 contaminating isolates is difficult and remains a major problem.

45 An overview of the medical literature on CNS is given, with special focus on identification,
46 species distribution, virulence factors, antibiotic resistance, epidemiology and specific infections
47 caused by CNS in humans.

48

49 2. Identification

50

51 Before 1975, *S. albus* or *S. epidermidis* was distinguished from *S. aureus* by the inability to
52 clot blood plasma. Today, tests based on coagulase production and the thermonuclease reaction are
53 used for rapid differentiation of *S. aureus* from other staphylococcal species (Huebner et al., 1999).
54 Currently, 39 species of CNS are recognized (Euzéby, 2007). Sixteen of these species have been
55 found in specimens of human origin. They are grouped in novobiocin-resistant species (*S. cohnii*, *S.*
56 *saprophyticus*, *S. sciuri*, *S. xylois*) and novobiocin-susceptible species (*S. auricularis*, *S. capitis*, *S.*

57 *caprae*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. lugdunensis*, *S. pasteurii*, *S. saccharolyticus*, *S.*
58 *schleiferi*, *S. simulans*, *S. warneri*) (von Eiff et al., 2001).

59 Accurate identification of CNS isolates to species level is difficult to perform and expensive.
60 According to Huebner et al., 1999, identification to species level is, in general, not necessary for
61 good patient management. However, recent literature indicates accurate species identification is
62 necessary to provide a better understanding of pathogenic potential of various CNS species (Heikens
63 et al., 2005; Sivadon et al., 2005).

64 Before 1975, CNS were classified in different biotypes, according to Baird-Parker. In 1975,
65 Kloos and Schleifer proposed a scheme for identification of staphylococci in the routine laboratory.
66 This scheme is based on 13 key characteristics, such as coagulase activity, hemolysis, nitrate
67 reduction and aerobic acid production from carbohydrates (Kloos et al., 1975). Nowadays, besides
68 phenotypic methods, a variety of genotypic methods (16S rRNA, *sodA*, *gap*, *rpoB*, *tuf* gene
69 sequencing) have been developed (Heikens et al., 2005; Layer et al., 2006; Mellmann et al., 2006).
70 Heikens et al. compared phenotypic with genotypic (16S rRNA gene and *tuf* gene sequencing)
71 identification (Heikens et al., 2005). The results showed that *tuf* gene sequencing is the best
72 identification method (5 of 57 isolates misidentified). The API staph ID test (BioMérieux, Marcy
73 l'Etoile, France) appeared to be a reliable alternative (7 of 57 isolates misidentified). The
74 performance of the BD Phoenix system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA)
75 was poor. A recent study (Layer et al., 2006) compared 3 phenotypic, commercial identification
76 methods with a molecular identification method (*gap* based terminal restriction fragment length
77 polymorphism analysis) as reference method. The BD Phoenix ID-13 system (Becton Dickinson
78 Diagnostic Systems) identified 18 of 27 reference strains and 70 of 86 clinical isolates correctly, the
79 VITEK 2 ID-GP system (BioMérieux) 20 of 27 reference strains and 80 of 86 clinical isolates, the ID
80 32 STAPH system (BioMérieux) 23 of 27 reference strains and 19 of 20 clinical isolates. Thus,
81 genotypic methods are superior to phenotypic methods, but some phenotypic methods have a highly

82 acceptable level of identification accuracy when used in routine practice (Heikens et al., 2005; Layer
83 et al., 2006).

84

85 3. Species distribution

86

87 Interpretation and comparison of the species distribution found in different studies is very
88 difficult. The type of identification method used, may influence the species distribution found and
89 some *Staphylococcus* species demonstrate habitat or niche preference. *S. capitis* for example is
90 mainly found on the adult head, *S. cohnii* on the feet. *S. saprophyticus* is found in urine of young
91 women (Kloos et al., 1994; Bannerman, 2003).

92 *S. epidermidis*, *S. haemolyticus* and *S. hominis* are the most frequently encountered CNS
93 species in clinical samples. The isolation frequency of the different CNS species in clinical, human
94 specimens is shown in Table 1. Usually, more than 50% of CNS isolates belong to the species *S.*
95 *epidermidis*. In India, low percentages of *S. epidermidis* were found (13.2%) and high percentages of
96 *S. haemolyticus* (71.9%) (Chaudhury et al., 2007). A Japanese study (Kawamura et al., 1998) found a
97 very high percentage of *S. caprae* (14%), while the frequency of isolation in other studies is very
98 low. In the study by Kawamura et al., 1998, all isolates were identified by a DNA-DNA
99 hybridisation and by conventional, phenotypic identification based on the Kloos and Schleifer
100 method. None of the *S. caprae* isolates was identified correctly by the phenotypic method.

101 In Spanish point prevalence studies in a large group of hospitals, performed from 1986 to
102 2002, showed no major shifts in the distribution of CNS species (Cuevas et al., 2004). When the
103 distribution in 2002 is compared with 1986, there is a decrease in isolation of *S. epidermidis*, *S.*
104 *simulans*, *S. cohnii* and *S. xylois* and an increase in isolation of *S. hominis* and *S. saprophyticus*.

105 *S. epidermidis* is the predominant pathogen in intravascular catheter-related infections, nosocomial
106 bacteremia, endocarditis, urinary tract and surgical wounds infections, central nervous system shunt
107 infections, ophthalmologic infections, peritoneal dialysis-related infections and infections of

108 prosthetic joints (Bannerman, 2003). *S. haemolyticus* has been implicated in native valve
109 endocarditis, septicemia, urinary tract infections, peritonitis and wound, bone and joint infections
110 (Bannerman, 2003). *S. saprophyticus* is associated with urinary tract infections in young females. *S.*
111 *lugdunensis* has been implicated in arthritis, catheter infections, bacteremia, urinary tract infections,
112 prosthetic joint infections and endocarditis (Bannerman, 2003). Other CNS species have been
113 implicated in a variety of infections.

114

115 **4. Virulence factors**

116

117 Already in 1972, the “slime” production of CNS was noted as an important factor in the
118 pathogenesis of infections (Huebner et al., 1999). This “slime” or biofilm is the most important
119 virulence factor of *S. epidermidis*. The biofilm formation enables attachment and persistence of the
120 bacteria on foreign materials. Moreover, bacteria organized in biofilms are protected from the action
121 of antibiotics and the immune system (Costerton et al., 1999; Mack et al., 2007). The first phase in
122 biofilm formation is attachment, in which staphylococcal binding proteins such as the
123 autolysin/adhesins AtlE and Aae, the fibrinogen-binding protein Fbe/Sdrg, the fibronectin-binding
124 protein Embp and the lipase GehD, play an important role (Mack et al., 2007). The most important
125 adhesion molecule is AtlE. The second phase in biofilm formation is accumulation, in which the
126 polysaccharide intercellular protein PIA, encoded by the *icaADBC* locus, is a major functional
127 component (von Eiff et al., 2002; Mack et al., 2007). In strains lacking the *icaADBC* locus, biofilm
128 formation is mediated by the accumulation-associated protein (Aap) or by the biofilm-associated
129 protein (Bap/Bhp) (Ziebuhr et al., 2006). Recently, 2 biofilm producing strains, negative for PIA,
130 Aap and Bhp, have been described (Qin et al., 2007). The regulation of biofilm formation is very
131 complicated and best studied in *S. epidermidis*. Different regulatory systems, such as *sae*, alternative
132 sigma factor σ^B , *sar* and quorum sensing (this is inter and intra species communication, possible
133 when a certain bacterial density has been established) systems play a role (Xu et al., 2006; Mack et

134 al., 2007). The 2 quorum sensing systems in *S. epidermidis*, *agr* and *luxS/AI-2*, repress the biofilm
135 formation: *luxS* system by downregulating PIA production, *agr* system by downregulating AtlE
136 production. *Agr* controls the expression of toxins and secreted virulence factors and the interaction
137 with the immune system (Kong et al., 2006). Quorum sensing systems have potential as therapeutic
138 targets for control of staphylococcal infections (Harraghy et al., 2007). Another important virulence
139 factor of CNS is the antibiotic resistance. Regulation of biofilm formation and methicillin resistance
140 seem to use similar pathways, as insertion of a certain transposon influences both biofilm formation
141 and the expression of methicillin resistance (Mack et al., 2007). Methicillin resistance was found to
142 be significantly higher in slime positive isolates (81%) than in slime negative isolates (57%) (Koksal
143 et al., 2007).

144 The phenotypic variability and heterogeneous gene expression observed in CNS, especially in
145 *S. epidermidis*, is an advantage for adaptation to changing environmental conditions (Ziebuhr et al.,
146 2006).

147 Other potential virulence factors of *S. epidermidis* include the following: extracellular
148 enzymes and toxins: metalloprotease with elastase activity, cysteine protease, serine protease, lipase,
149 fatty acid modifying enzymes (FAME) and the δ -toxin. CNS also produce lantibiotics (von Eiff et
150 al., 2002; Vuong et al., 2002). Lantibiotics are bacteriocins such as epidermin, which are active
151 against other gram-positive bacteria.

152 Several studies tried to discriminate between invasive and commensal *S. epidermidis* strains
153 by the detection of virulence associated genes (Frebourg et al., 2000; Vandecasteele et al., 2003;
154 Rohde et al., 2004). In the study by Rohde et al (Rohde et al., 2004) the virulence genes *icaADBC*,
155 *mecA* and IS256 were all highly prevalent in invasive strains. Commensal strains from healthy
156 individuals almost completely lacked *icaADBC*, *mecA* and IS256. However in the commensal
157 strains isolated from hospitalized bone marrow transplant patients the studied genes had the same
158 distribution as the invasive strains, suggesting replacement of their own commensal flora by hospital
159 strains. As a consequence these genes cannot discriminate between invasive and commensal strains.

160 *S. lugdunensis* and *S. schleiferi* are more pathogenic than other CNS species. Like *S. aureus*,
161 they may express a clumping factor and/or produce a thermostable DNase (von Eiff et al., 2002). A
162 variable percentage of these strains produces extracellular slime or glycoocalix, esterase, FAME,
163 protease, lipase and a haemolysin. *S. lugdunensis* is more likely than other CNS, to be considered a
164 pathogen until proven otherwise (Poutanen et al., 2001; Koziol-Montewka et al., 2006). *S.*
165 *lugdunensis* is often misidentified as *S. aureus*, because slide agglutination tests are often positive.

166 The main virulence factor of *S. saprophyticus* in UTI is the capacity to adhere to uroepithelial
167 cells by means of surface-associated proteins: the autolysin/adhesin Aas, Ssp and Sdrl. Once
168 colonization has been established several invasion factors are produced: urease, elastase, lipase and
169 FAME (von Eiff et al., 2002).

170

171 **5. Antibiotic resistance**

172

173 Resistance to antibiotics in CNS is of major concern. Penicillin resistance in CNS is very
174 high: even in 1968 the resistance rate was 60% (Corse et al., 1968). Nowadays, resistance is around
175 91% in clinical strains (Cuevas et al., 2004; Koksai et al., 2007). Methicillin resistance in
176 staphylococci is caused by expression of PBP2a encoded by the *mecA* gene. *MecA* is located on a
177 genetic element called the staphylococcal cassette chromosome (SCC). There is evidence of
178 horizontal transfer of SCC cassettes between staphylococcal species (Hanssen et al., 2004), which
179 implies that CNS could serve as a reservoir for the spread of resistance genes to *S. aureus*. In clinical
180 samples, rates of methicillin resistance of 55% - 77% and even 86% in ICU settings, have been
181 reported (Del' Alamo et al., 1999; Agvald-Öhman et al., 2004; Cuevas et al., 2004; Chaudhury et al.,
182 2007; Gatermann et al., 2007; Jones et al., 2007a; Jones et al., 2007b; Koksai et al., 2007; Sader et
183 al., 2007;). In continuous ambulatory peritoneal dialysis (CAPD) patients and medical students 38%
184 and 27%, respectively, of colonizing CNS strains were methicillin resistant (de Mattos et al., 2003;
185 Koziol-Montewka et al., 2006; Higuchi et al., 2007). Several studies show an increase of MR CNS

186 over time. In Spain, methicillin or oxacillin resistance remained stable (26%-34% of CNS) between
187 1986 and 1994, increased significantly in 1996 (51%) and reached 61% in 2002 (Cuevas et al.,
188 2004). An increase of methicillin resistant CNS strains was also found in other studies: from 38% in
189 1996 to 68% in 2007 in blood of patients with true bacteremia (Koksal et al., 2007), from 19% in
190 1991 to 74% in 1998 in peritoneal dialysis patients (Zelenitsky et al., 2000). It is generally assumed
191 that approximately 80% of nosocomial isolates and 30-40% of isolates obtained from healthy carriers
192 or patients from the community, demonstrate resistance to methicillin (Huebner et al., 1999; de
193 Mattos et al., 2003; Koziol-Montewka et al., 2006).

194 In Spain, resistance to ciprofloxacin and erythromycin increased progressively in CNS from
195 1% and 41% in 1986 to 45% and 63% in 2002 (Cuevas et al., 2004). Susceptibility percentages to
196 different antibiotics are given in Table 2. Two surveillance studies, performed in 2006, one in the US
197 and one in Europe, Asia, Australia and Latin America show comparable susceptibility results.
198 Susceptibility rates to fluoroquinolones, erythromycin, clindamycin, trimethoprim/sulfamethoxazole,
199 gentamicin, teicoplanin and linezolid are 42%-47%, 30%-34%, 60%-61%, 62%-59%, 71%-58%, 99
200 and 98-99%, respectively (Jones et al., 2007a, Jones et al., 2007b). Methicillin resistant strains have
201 high rates of resistance to other classes of antibiotics. Resistance rates in methicillin susceptible
202 strains are much lower (Reynolds et al., 2004; Biedenbach et al., 2007; Koksal et al., 2007; Sader et
203 al., 2007).

204 CNS were the first organisms in which acquired glycopeptide resistance (vancomycin MIC
205 ≥ 8 $\mu\text{g/mL}$, teicoplanin MIC ≥ 16 $\mu\text{g/mL}$) was recognized (Biavasco et al., 2000). Most of the clinical
206 glycopeptides resistant isolates are resistant to teicoplanin, but susceptible to vancomycin, indicating
207 a heterogeneous expression of glycopeptides resistance (Nunes et al., 2006). The resistance
208 mechanisms to glycopeptides in CNS are not yet fully understood. Most reports show that resistance
209 mechanism in CNS is similar to that described in VISA and hetero-VISA strains (Nunes et al., 2006).
210 This mechanism is multifactorial, expression related and can be selected, in vitro, by exposure to
211 teicoplanin and vancomycin (Biavasco et al., 2000; Nunes et al., 2006). Laboratory detection of

212 glycopeptide-resistance may be problematic, as there is an influence of various technical factors.
213 Susceptibility testing by disk diffusion results in a very high percentage of false susceptible results
214 (very major errors in 80% of the nonsusceptible to teicoplanin strains) (Del' Alamo et al., 1999).
215 Susceptibility rates to vancomycin and teicoplanin of respectively 99%-100% and 68%-100% are
216 found in clinical studies (Del' Alamo et al., 1999; Cuevas et al., 2004; Reynolds et al., 2004;
217 Chaudhury et al., 2007; Koksal et al., 2007; Sader et al., 2007).

218 Novel antibiotics have been developed to overcome the resistance problem in CNS. These
219 antibiotics include for example linezolid, daptomycin, tigecycline and quinupristin/dalfopristin.
220 Susceptibility of CNS isolates towards these agents is usually 100% (Garrison et al., 2005; Sader et
221 al., 2007). In recent surveillance studies the lowest reported susceptibility percentages are 98,4% for
222 linezolid (Jones et al., 2007a), 99% for quinupristin/dalfopristin (Jones et al., 2007b) and 99,9% for
223 daptomycin (Sader et al., 2007). In one institution, 4% of CNS, originating from 25 patients, were
224 found to be linezolid resistant. The majority of these resistant strains showed some genetic
225 relatedness, previous linezolid use was an independent predictor of linezolid resistance and the
226 majority of patients had been accommodated in a single ward (Potoski et al., 2006).

227 The prevalence of resistance varies widely among staphylococcal species. The highest rates
228 of resistance are found in *S. haemolyticus*: 76-96% oxacillin resistant, 80-90% erythromycin
229 resistant, 26-29% teicoplanin nonsusceptible (Gill et al., 1983; Del' Alamo et al., 1999; Chaudhury
230 et al., 2007; Gatermann et al., 2007). Oxacillin resistance rates are also high in *S. hominis* (80%)
231 (Gatermann et al., 2007) and *S. epidermidis* (38-81%) (Gill et al., 1983; Del' Alamo et al., 1999;
232 Gatermann et al., 2007). Teicoplanin nonsusceptible isolates occur in 3% of *S. epidermidis* and in
233 none of the *S. hominis* isolates (Del' Alamo et al., 1999). *S. lugdunensis* has nearly uniform in vitro
234 susceptibility to most antimicrobials, including penicillins, cephalosporins and macrolides (Poutanen
235 et al., 2001; Gatermann et al., 2007).

236

237 **6. Epidemiology**

238

239 Several studies show that most CNS infections are hospital-acquired or health-care related
240 (Rupp et al., 1994; Huebner et al., 1999). Colonization of patients and hospital staff with antibiotic
241 resistant *S. epidermidis* precedes infection with these organisms (Kloos et al., 1994; Nouwen et al.,
242 1998; Widerström et al., 2006). Some clones are probably endemic in the hospital environment. CNS
243 have the ability to survive in the intensive care unit (ICU) surroundings on medical devices and
244 medical equipment for weeks to months (Neely et al., 2000). The clonal spread of identical or closely
245 related methicillin-resistant CNS strains within hospitals and even between hospitals has been
246 demonstrated (Monsen et al., 2000; Widerström et al., 2006). Frequent transmission of CNS between
247 intubated patients was demonstrated in a multidisciplinary ICU (Agvald-Öhman et al., 2004). The
248 spread of CNS strains is well studied in neonatal ICUs, where CNS are the major causative organism
249 of sepsis. A relatively small number of molecular types of CNS can persist in the neonatal ICU for
250 many years. The *mecA* gene carriage in these clusters is usually very high, which suggests that
251 antibiotic resistance is one of the major selective forces (Krediet et al., 2004). Multi locus sequence
252 typing identified a sequence type (ST 27), which contained exclusively *ica*-positive isolates and
253 represented the majority of clinical strains within different hospitals in Germany. The ST 27 clone
254 was also detected in a Norwegian hospital and in medical facilities in the United States (Kozitskaya
255 et al., 2005). The combination of biofilm formation, antibiotic resistance and genetic flexibility (due
256 to multiple copies of IS256) in the ST27 clone may explain why this clone is so predominant in
257 hospital settings. It is tempting to assume that patients who are admitted to hospital are rapidly
258 colonized with this clone and that this newly acquired microflora might represent the origin for later
259 infection (Kozitskaya et al., 2005; Ziebuhr et al., 2006). Hospital personnel can also be responsible
260 for spreading multi resistant CNS isolates (Hira et al., 2007). Clonal types can only be distinguished
261 by genotypic methods and not by phenotypic appearance of the colonies or by antibiotype (Nouwen
262 et al., 1998; Miragaia et al., 2002). Risk factors for the emergence and spread of CNS clones in
263 hospitals include the duration of hospital stay (especially ICU stay), duration of antibiotic treatment,

264 antibiotic pressure in the environment, and hygienic standards (Widerström et al., 2006). The use of
265 contact and hand hygiene precautions is extremely important for preventing nosocomial colonization
266 and infections. Maybe periodic surveillance of patients and staff in specific wards could be useful to
267 avoid the spread of multi resistant CNS. A good antibiotic policy, in order to reduce the antibiotic
268 pressure, will help to reduce the incidence of multi resistant CNS.

269

270 7. Specific infections

271

272 7.1. Urinary tract infections (UTI)

273

274 *S. saprophyticus* is the second (after *Escherichia coli*) most frequent causative organism of
275 uncomplicated urinary tract infections (UTI) in women. Complications, such as recurrent infection,
276 acute pyelonephritis, nephrolithiasis, septicaemia and endocarditis have been documented but are
277 rare (Raz et al., 2005; Widerström et al., 2007). The vast majority of infections occur in young,
278 sexually active women. *S. saprophyticus* can also cause UTI in males of all ages (Raz et al., 2005). *S.*
279 *saprophyticus* is found in 3-9% of cases of uncomplicated acute cystitis (Christiaens et al., 1998;
280 Grude et al., 2005; Nys et al., 2006). Frequency of isolation is age dependent. In a recent study, *S.*
281 *saprophyticus* was isolated from 7%, 4% and 0.5% of subjects in age categories 11-20 years, 21-50
282 years and 51-70 years, respectively (Nys et al., 2006). *S. saprophyticus* can be pathogenic in low
283 numbers ($<10^5$ cfu/mL) (Rupp et al., 1994). *S. saprophyticus* is probably often missed as causative
284 organism of UTI, as the bacteriuria is considered to be nonsignificant, especially when bacterial
285 counts are low.

286 *S. saprophyticus* has also been isolated from 7% of rectal swabs taken from carcasses of
287 cattle and pigs. The micro-organism is a common contaminant of various food samples, especially of
288 raw beef and pork (Raz et al., 2005). In humans, the major reservoir of *S. saprophyticus* is the
289 gastrointestinal tract. The following risk factors have been identified: recent sexual intercourse,

290 outdoor swimming and meat processing (Huebner et al., 1999). Colonization and infection is more
291 frequent during summer and fall.

292 Other CNS species, mainly *S. epidermidis*, are occasionally found as causative organisms in
293 UTI (<5% of UTI in hospital environment). *S. epidermidis* is usually isolated from hospitalized,
294 elderly patients with urinary catheters or other manipulations to the urinary tract (Rupp et al., 1994;
295 Raz et al., 2005).

296

297 7.2. Endocarditis

298

299 The incidence and characteristics of CNS endocarditis were studied in a large cohort of
300 patients from the International Collaboration on Endocarditis Merged Database (Chu et al., 2004).
301 CNS accounted for 7% of cases of definite native valve endocarditis (NVE), excluding endocarditis
302 associated with injection drug use (Chu et al., 2004). Most CNS NVE is caused by *S. epidermidis*
303 (85%). The remainder is caused by *S. hominis* (6%), *S. lugdunensis* (5%), *S. capitis*, *S. caprae* and *S.*
304 *simulans*. Rates of heart failure and mortality were found to be similar between patients with CNS
305 and *S. aureus* NVE (Chu et al., 2004). Patients with NVE caused by staphylococci were significantly
306 more likely to have health-care associated endocarditis than patients with viridans streptococcal
307 NVE.

308 In a study from 1999, streptococci are responsible for 48% of cases of infective endocarditis,
309 *S. aureus* for 23% and CNS for 6% (Hoen et al., 2002). These frequencies were also found in a study
310 conducted between 1951 and 1965: *S. epidermidis* was the third most frequent isolated organism (in
311 10% of cases) in cases of bacterial endocarditis, after viridans streptococci (47%) and *S. aureus*
312 (24%) (Dalton et al., 1967). Injecting heroin users are susceptible to right-sided endocarditis due to *S.*
313 *epidermidis* (von Eiff et al., 2001).

314 Characteristics of patients with prosthetic valve endocarditis (PVE) were studied and
315 compared with NVE patients in the International Collaboration on Endocarditis – Prospective Cohort

316 Study (Wang et al., 2007). Patients with PVE had a higher rate of CNS infection (16.9%) than
317 patients with NVE (8.3%). In literature, higher rates (than in the study by Wang et al., 2007) of CNS
318 in infections of prosthetic valves are found (40-50% of cases) (Huebner et al., 1999; von Eiff et al.,
319 2001).

320 *S. lugdunensis* endocarditis has more features of *S. aureus* endocarditis than of CNS
321 endocarditis. The infection is often aggressive, most cases are community-acquired and only a
322 minority of patients (approximately 25%) has prosthetic valves (Poutanen et al., 2001).

323

324 7.3. Blood stream infections (BSI)

325

326 Almost all cases of bacteremia due to CNS are nosocomial or at least health-care related in
327 origin. Intravascular and cardiovascular devices, such as peripheral and central catheters, vascular
328 grafts, implanted defibrillators and coronary stents, are widely used. Catheter related infections are
329 by far the most common cause of bacteremia due to CNS (Huebner et al., 1999).

330 Throughout the 1960s and 1970s, Gram-negative organisms were the most common pathogens
331 isolated from patients with nosocomial blood stream infections (BSI) (Wisplinghoff et al., 2004), but
332 in one study (Dalton et al., 1967), between 1951 and 1965, *S. epidermidis* accounted for 23% of
333 positive blood cultures in patients with suspected bacteremia. Second and third most frequent
334 isolated organism was *S. aureus* (12%) and *Corynebacterium* species (12%). The high rates of
335 common skin bacteria (such as *Corynebacterium* species and *S. epidermidis*) in the study by Dalton
336 et al., 1967, raise concern about the clinical significance. The incidence of bacteremia caused by
337 CNS rose between 161% and 754%, respectively in large teaching and small non-teaching hospitals,
338 between 1980 and 1989 (Rupp et al., 1994). During 1986 - 1989 CNS were the most frequently
339 reported cause of BSI, accounting for 27% of BSI (Schaberg et al., 1991).

340 In a nation wide surveillance study in the USA, performed between 1995 and 2002, CNS
341 accounted for 31% of all nosocomial BSI (Wisplinghoff et al., 2004). The crude mortality of BSI due

342 to CNS was 25.7% in an intensive care unit (ICU) and 13.8% in a non-ICU ward. In Flanders,
343 Belgium, CNS account for 25.9% of all nosocomial BSI. Forty-eight percent of BSI cases in
344 Flanders were due to catheter related sepsis, 32% to sepsis of unknown origin, and 20% were
345 associated with another infection or an invasive manipulation (Suetens et al., 2002).

346 CNS are the most common pathogens in catheter-related infections (50-70% of cases). In
347 addition to bacteremia, CNS, mainly *S. epidermidis*, can cause exit-site infections, tunnel infections,
348 infected thrombophlebitis, endocarditis and abscesses (Rupp et al., 1994; Huebner et al., 1999). At
349 the time of removal, 8-40% of all catheters are colonized by CNS (Rupp et al., 1994).

350 Positive blood cultures with CNS can be explained by contamination, true bacteremia or transient
351 benign bacteremia (Rupp et al., 1994). It may be very difficult to distinguish between infection and
352 contamination. As the positive predictive value of a blood culture growing CNS varies from 6 to
353 12% (Correa et al., 1999), the criteria used for defining true bacteremia influence reported CNS
354 prevalence. The CDC criteria for defining bloodstream infection (Garner et al., 1988) are used in
355 most of the studies. The intensity of surveillance also influences the reported BSI incidence and
356 prevalence of CNS.

357 There is increasing evidence that the mucosa, rather than skin, is the likely source of CNS
358 bacteremia in cancer patients (Costa et al., 2004; Costa et al., 2006). A recent study showed that
359 among cancer patients with CNS positive blood cultures and an indwelling central venous catheter
360 (CVC), the mucosal sites were the most frequently colonised by CNS (nasal mucosa in 86%, rectal
361 mucosa in 40%). The skin at the CVC site was colonised by CNS in 32% of patients. Among patients
362 with true bacteremia, 6 mucosal isolates and only 1 skin isolate were genetically related to the isolate
363 recovered from blood based on pulsed-field gel electrophoresis (Costa et al., 2006). A review of the
364 literature confirms that CNS colonise mucosal sites including gut, nares and throat and may
365 translocate from mucosal sites to the bloodstream (Costa et al., 2004). This is supported by
366 epidemiological, experimental, clinical and molecular relatedness studies. The assumption that the
367 skin is the primary source of CNS infection has been the reason to try to achieve a reduction of CNS

368 catheter related bacteremia with skin decontamination and the use of maximum barrier precautions at
369 the time of CVC insertion. However, not all studies show a positive effect of these two interventions
370 (Costa et al., 2004).

371

372 7.4. Foreign body-related infections (FBRI)

373

374 Insertion or implantation of medical devices is associated with a risk of bacterial and fungal
375 infections. Medical devices are increasingly used in almost all fields of medicine for diagnostic
376 and/or therapeutic procedures. The contamination of the device occurs most likely by inoculation
377 with only a few micro-organisms from the patient's skin or mucous membranes during implantation
378 or subsequent manipulations (Rupp et al., 1994; von Eiff et al., 2001; von Eiff et al., 2005). The
379 pathogens may also be acquired from the hands of the surgical or clinical staff (von Eiff et al., 2005).
380 Staphylococci, particularly *S. epidermidis*, account for the majority of FBRI (von Eiff et al., 2005).
381 Most CNS isolates causing foreign body-related infections (FBRI) are methicillin resistant.

382 Neurosurgical devices (ventricular shunts, implantable stimulators, intracranial pressure
383 devices) are frequently used. Of the pathogens isolated from ventriculoperitoneal shunt infections in
384 pediatric patients less than 8 years old, 53% were CNS (Filka et al., 1999). Clinical symptoms can be
385 subtle and nonspecific. (Huebner et al., 1999). In a review of CSF shunt infections, caused by a
386 single pathogen, CNS and *S. aureus* were isolated with equal frequency, i. e. in 23% of cases each
387 (Wang et al., 2004). Others reported that CNS are the most common cause of shunt infections (40-
388 60% of infections) (Rupp et al., 1994). In a retrospective study, pure culture of CNS accounted for
389 11% of cases of adult bacterial meningitis (Huang et al., 2005). All cases had post-neurosurgical
390 states as underlying condition.

391 CNS cause 17-56% of episodes of continuous ambulatory peritoneal dialysis-associated
392 peritonitis (Rupp et al., 1994, Monsen et al., 2000). *S. epidermidis* is the predominant species (78%)
393 followed by *S. haemolyticus* (11%) (Monsen et al., 2000). From 1991 to 1998, the incidence of

394 dialysis-related peritonitis caused by *S. epidermidis* decreased, probably due to the introduction of a
395 new dialysis system. Even so, *S. epidermidis* was still the most common cause of peritonitis in 1998,
396 causing 28% of culture positive cases (Zelenitsky et al., 2000).

397 Up to 60% of vascular graft infections and 20-40% of prosthetic joint infections are caused
398 by CNS (Rupp et al., 1994).

399 CNS are also associated with low grade foreign body infections such as aseptic loosening of hip or
400 other joint prostheses, or fibrous capsular contracture syndrome after mammary augmentation with
401 silicone prostheses (von Eiff et al., 2001).

402

403 7.5. Surgical site infection

404

405 *S. aureus* is the most common pathogen isolated from surgical site infections (SSI) (20%),
406 followed by CNS (14%) and *Enterococcus* species (12%) (CDC, 1996). In a secondary care hospital,
407 CNS were the third (10%) most frequently isolated micro-organism, after *S. aureus* (21%) and
408 *Streptococcus* species (11.2%) (Cantlon et al., 2006). Outbreaks of SSI originating from operating
409 room personnel have been reported, but probably most infections are indogenous (Huebner et al.,
410 1999). Sternal osteomyelitis following median sternotomy is caused predominantly by CNS (Rupp et
411 al., 1994).

412

413 7.6. Endophthalmitis

414

415 CNS are by far the most common pathogens isolated from vitreous biopsies in cases of
416 endophthalmitis. In a review of 67 cases of endophthalmitis, 31% of the culture positive biopsies
417 (only 44%) yielded CNS as pathogen (Karacal et al., 2007). Most cases of endophthalmitis were
418 postoperative (73.5%), mainly after cataract surgery. Other cases were associated with endogenous
419 origin (13%), post-intravitreal injection (6%), keratitis (4%) and post-traumatic (3%). Post-traumatic

420 endophthalmitis, a complication of a penetrating eye injury, is caused by CNS in 28% of cases (Abu
421 El-Asrar et al., 1999).

422

423 7.7. Mastitis

424

425 CNS are rarely associated with mastitis in humans. In lactation mastitis, the agents most
426 frequently cultured from milk are *S. aureus* and CNS (Barbosa-Cesnik et al., 2003). In non
427 lactational breast abscesses, CNS are rarely isolated as sole pathogen. Some cases of non lactational
428 breast abscesses, especially with *S. lugdunensis* have been published in literature (Asnis et al., 2003).
429 *S. aureus* and anaerobes are the most common organisms to cause breast abscesses (Surani et al.,
430 1993).

431

432 8. Conclusions and Outlook

433

434 CNS are a group of micro-organisms that are increasingly implicated as a cause of significant
435 infection. The infection rate has been correlated with the increase in the use of invasive and
436 indwelling medical devices and the growing number of immunocompromised patients. Community
437 acquired, primary CNS infections are rare, except for *S. saprophyticus* UTI, NVE and *S. lugdunensis*
438 infections. The increase of CNS infections is particularly high in bacteraemia. CNS are now a major
439 cause of nosocomial or health care related infections. The consequences of these infections are
440 substantial, both in morbidity and mortality and in financial costs. Clonal spread of CNS clusters
441 within and even between hospitals has been demonstrated. This is of major concern as CNS are often
442 multi-drug resistant and can serve as a reservoir of resistance genes. Implementation of infection
443 control measures similar to those used for MRSA may be necessary to prevent further spread of
444 methicillin and multi-drug resistant CNS.

445

446

447 **Conflict of Interest**

448

449 None of the authors (A. Piette, G. Verschraegen) has a financial or personal relationship with
450 other people or organizations that could inappropriately influence or bias the paper entitled “Role of
451 coagulase-negative staphylococci in human disease”.

452

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689 Table 1

690 Species distribution (%), sample origin, used identification method of CNS in clinical samples in different studies (country and publication date in
691 heading).

	USA 1983 (1)	USA 1993 (2)	Denmark 1996 (3)	Japan 1998 (4)	Brazil 1999 (5)	Spain 2004 (6)	France 2005 (7)	India 2006 (8)	India 2007 (9)	Germany 2007 (10)	Turkey 2007 (11)
<i>S. epidermidis</i>	75	65	58	50	50	56	71	34	13	67	44
<i>S. haemolyticus</i>	7	13	9	16	10	5	2	13	72	12	12
<i>S. hominis</i>	5	7	12	5	12	18	4	2	6	9	9
<i>S. simulans</i>	1	2		6		1	1		2	1	2
<i>S. capitis</i>	2	4	<1	5		3	6	10	1	1	8
<i>S. saprophyticus</i>	1	1	1	5		5				<1	3
<i>S. warneri</i>	3	4	2	3		4	7	1	1	2	4
<i>S. lugdunensis</i>		3	<1	2			3	13	1	3	9
<i>S. caprae</i>				14			2			1	
<i>S. cohnii</i>	<1	1	1	<1	6	0	<1			1	<1
<i>S. auricularis</i>		<1		<1							<1
<i>S. schleiferi</i>								12		1	<1
<i>S. xylois</i>						0		6		1	5
<i>S. pasteurii</i>							2				
sample origin	CS	CS	BSI	CS	BSI		BJI	CS	CS	BSI	BSI
identification method	SP	Vitek1	SP	DNA	Microsc	SP	<i>sodA</i>	SP	Vitek2	SP + <i>sodA</i>	API

692 (1) Gill et al. (2) Kleeman et al. (3) Jarløv et al. (4) Kawamura et al. (5) Del' Alamo et al. (6) Cuevas et al. (7) Sivadon et al. (8) Singhal et al. (9)
693 Chaudhury et al. (10) Gatermann et al. (11) Koksals et al.; CS: clinical specimens, BJI: bone and joint infections; SP: standard procedures (based on
694 Kloos and Schleifer), Vitek1: Vitek GP card (Biomérieux), *sodA*: *sodA* sequencing, DNA: DNA-DNA hybridization, Microsc: Microscan positive
695 combo panel type 6 (DADE MicroScan Inc., Sacramento, CA), Vitek2: Vitek ID 32 Staph (Biomérieux), API: API ID 32 Staph (Biomérieux)

696

696 Table 2

697 Percentage susceptibility of CNS in different studies (in heading country and publication date); MR: % susceptibility in methicillin resistant strains, MS:

698 % susceptibility in methicillin susceptible strains

% susceptibility	Spain	UK, Ireland		Asia_Pacific		USA	Europe, Asia,	Turkey		Europe, Turkey,	
	2002 (1)	2004 (2)		region 2007 (3)		2007 (4)	Australia, Latin	2007 (6)		Israel 2007 (7)	
		24		15,2		23,1	25,7	32,5		28	
		MR	MS	MR	MS			MR	MS	MR	MS
methicillin/oxacillin	39										
penicillin	21	0	24.5			12.1	15.3	0	9		
ceftriaxone						51.1	47.6				
ciprofloxacin	55	40.8	81.6			42.2	46.5	33	77	27.8	86.9
levofloxacin				50.2	89.1	42.3	47.5			28.1	87.3
cotrimoxazole	76			60.8	89.1	61.9	59.3	32	62	52.6	91.8
gentamicin	72	25.7	78.6			71.3	57.7	10	83		
tetracycline		39.2	67.3	83.5	89.1	86.9	83.7	40	55		
erythromycin	37	27.3	62.2	31.8	78.3	28.8	33.8	20	63	27.2	65.7
clindamycin	66	69.1	93.9	68.6	95.7	59.9	60.7	28	82	67	94.8
chloramphenicol	91			87.1	91.3			44	87	86.6	97.4
fusidic acid								75	85		
rifampicin	93									85.3	96.1
teicoplanin	100	65	77.6	96.1	89.1	99.3	99.3	100	100	97.3	99.6
vancomycin	100	99.7	100	100	100	100	100	100	100	100	100
linezolid	100	100	100	100	100	98.4	99.5			100	100
quinupristin/dalfopristin	100			99.6	100	99.3	99			99.3	100
daptomycin						100				100	99.6

699 (1) Cuevas et al. (2) Reynolds et al. (3) Biedenbach et al. (4) Jones et al., 2007a (5) Jones et al., 2007b (6) Koksall et al. (7) Sader et al.