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From Clinical Microbiology to Infection Pathogenesis: How Daring To Be Different Works for *Staphylococcus lugdunensis*

Kristi L. Frank,[1,2]† José Luis del Pozo,[2] and Robin Patel[2,3]*

Department of Biochemistry and Molecular Biology,[1] Infectious Diseases Research Laboratory, Division of Infectious Diseases, Department of Medicine,[2] and Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology,[3] Mayo Clinic College of Medicine, Rochester, Minnesota

* Corresponding author. Mailing address: Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, 200 First Street S.W., Rochester, MN 55905. Phone: (507) 538-0579. Fax: (507) 284-4272. E-mail: patel.robin@mayo.edu.

† Present address: Department of Microbiology, University of Minnesota Medical School, 420 Delaware St., S.E., Minneapolis, MN 55455.

INTRODUCTION

A large number of *Staphylococcus* species distinct from *Staphylococcus aureus* comprise the group known as coagulase-negative staphylococci (CNS), so named for their inability to clot plasma due to the lack of production of the secreted enzyme coagulase (5). CNS, which often occur as skin commensals, were historically considered innocuous or, rarely, opportunistic pathogens of low virulence (84). However, the important role of CNS as pathogens, with particular regard to infections associated with indwelling medical devices, is becoming increasingly appreciated (44, 61, 140). CNS are now a leading cause of bacteremia in the United States, Canada, Latin America, and Europe (61, 140), and many of these CNS are resistant to multiple classes of antimicrobial agents (44). Despite this, and in contrast to the case for *S. aureus*, infections caused by CNS typically manifest as less severe and subacute diseases that are infrequently associated with mortality.

In 1988, Freney et al. described two new coagulase-negative species, *Staphylococcus schleiferi* and *Staphylococcus lugdunensis*, isolated from human clinical specimens (68). Since that time, *S. lugdunensis*, named after Lyon, France, the city where the organism was initially isolated (68), has emerged as an important human pathogen with notable clinical and microbiological characteristics that stand out among those of other CNS. Described previously as "surreptitious" (171) and a "wolf in sheep's clothing," *S. lugdunensis* behaves more like *S. aureus* than other CNS in many respects, including exhibiting an elevated degree of virulence. *S. lugdunensis* is both a skin commensal and a pathogen responsible for nosocomial and community-acquired infections that may proceed aggressively and with a level of severity reminiscent of that of *S. aureus* infections. Unlike *S. aureus*, *S. lugdunensis* does not possess secreted coagulase. However, some isolates produce a membrane-bound form of the enzyme (clumping factor) that yields a positive result in slide coagulase and/or rapid latex agglutination tests, potentially leading to misidentification of the organism as *S. aureus* in the clinical laboratory. *S. lugdunensis* has a propensity to cause native valve endocarditis with a fulminant and highly destructive clinical course that is quite remarkable for a coagulase-negative species, which are otherwise more frequently the etiologic agents of prosthetic valve endocarditis (84). Equally surprising, compared to CNS, most *S. lugdunensis* isolates remain susceptible to a large number of antimicrobial agents (67).

With little doubt, *S. lugdunensis* cannot be considered a "typical" coagulase-negative *Staphylococcus* species, and its successful position as an unusually virulent pathogen deserves attention. In this review, we aim to provide a comprehensive overview of the body of literature on *S. lugdunensis* since its description 20 years ago, with particular emphasis on the aspects of clinical infection, clinical microbiology, antimicrobial susceptibility, and virulence that are unique to this organism.

CLINICAL DISEASE

In 1989, Etienne et al. described two cases of native valve endocarditis and one case of prosthetic valve endocarditis in which *S. lugdunensis* was retrospectively identified as being the causative agent (53). In each case, the infection was aggressive, involving valve destruction and abscess formation, and ultimately resulted in the deaths of two of the three patients. The resemblance of the clinical course of *S. lugdunensis* infections to that of *S. aureus* was apparent in that early report. The full pathogenic potential of and the wide spectrum of diseases caused by *S. lugdunensis* are now unmistakable (Table 1). In this section, we review the role of *S. lugdunensis* as a constituent of the human normal flora as well as a human pathogen.

Characteristics of Colonizing and Infectious Isolates

S. lugdunensis is a constituent of the human normal skin flora and an infrequent, but not rare, human pathogen. Early studies established *S. lugdunensis* as a skin commensal (82, 183). The organism preferentially colonizes the perineal region (111, 183, 186) and has been rarely found in the anterior nares or nasal cavities of hemodialysis patients (97), cardiothoracic patients (9), and healthy subjects (147). Akiyama et al. reported that five of nine *S. lugdunensis* isolates (among a total of 162 CNS of colonizing or infective origin) collected from patients with skin lesions in Japan were considered to be colonizing isolates, although the source of isolation was not reported (1). Van der Mee-Marquet et al. (186) cultured the inguinal folds of 140 consecutive patients in an emergency department over three months and found that *S. lugdunensis* colonized 23% of women and 19% of men, providing supporting data that *S. lugdunensis* is frequently found in the perineal area.

Herchline and Ayers reported the occurrence of 229 *S. lugdunensis* isolates, comprising 10% of all non-*S. aureus*, non-*S. epidermidis* isolates, during a 63-month study at a U.S. tertiary-care hospital and its associated outpatient clinics (82). The majority of isolates (55%) originated from outpatients. In a review of 50 consecutive cases from which *S. lugdunensis* was isolated, both colonizing and infectious isolates were identified; infectious isolates derived predominantly from skin-associated infections and, to a lesser extent, from vascular-related infections (82). *S. lugdunensis* was often found as part of a mixed culture (82). Although *S. lugdunensis* is commonly described in patients with underlying illnesses or undergoing immunosuppressive therapies (82, 121), it can cause both superficial and serious infections in otherwise healthy people (24, 82, 99, 196).

In addition to Herchline and Ayers' study (82), several groups from multiple countries have reported the frequency of isolation of clinical *S. lugdunensis* isolates. In contrast to the 10% rate of *S. lugdunensis* isolation reported by Herchline and Ayers (82), *S. lugdunensis* accounted for fewer than 3% of non-*S. aureus*, non-*S. epidermidis* strains from human clinical

TABLE 1. Reported infections caused by *Staphylococcus lugdunensis*

Infection type	Reference(s)
Cardiovascular infection	
Native valve endocarditis	1, 2, 7, 17, 19, 26, 38, 42, 50, 53, 55, 58, 60, 70, 71, 87, 89, 95, 98, 99, 104–106, 109, 116, 134, 139, 144, 148, 149, 155, 156, 160, 161, 166, 169–171, 180, 183, 187, 189, 193, 195–197
Prosthetic valve endocarditis	2, 37, 53, 60, 96, 164, 183
Pacemaker-related endocarditis	2, 15, 101, 162
Myocarditis	142
Skin and soft tissue infection	1, 60, 83, 177
Abscesses or wounds	10, 60, 82, 131, 177, 186
Nonpuerperal breast abscess	4, 108, 194
Bloodstream infection, sepsis, or septic shock	25, 51, 60, 178
Toxic shock syndrome	133
Acute oral infection (abscesses, osteomyelitis)	200
UTI	24, 79
Bone and joint infection	167
Infective arthritis or osteomyelitis	60, 98, 118, 132, 181
Vertebral osteomyelitis	77, 98, 121, 198
Disk space infection	18, 20, 36, 78
Prosthetic joint infection	154, 158, 182, 198
Central nervous system infection	
Brain abscess	60, 71
Meningitis	88
Ventriculoperitoneal shunt infection	52, 157
Peritonitis	60, 111, 159
Ocular infection	
Suppurative keratitis	141
Postoperative endophthalmitis	6, 29

sources collected in six Japanese hospitals (91). Overall, in that study, *S. lugdunensis* accounted for 1.3% of the 1,230 staphylococci (including *S. aureus*) isolated. *S. lugdunensis* represented only 1 of 499 (0.2%) CNS recovered from blood cultures in several counties in Denmark during a 2-month period (86). Other rates of isolation of clinically significant *S. lugdunensis* among CNS range from 0.8% in Korea (165) to 3% in the United States (92) to 6% in Argentina (43).

Bloodstream Infection, Sepsis, and Toxic Shock Syndrome

S. lugdunensis accounted for only 4 of 1,256 (0.3%) CNS causing community-acquired or nosocomially acquired bloodstream infection during a 12-month period in a worldwide network of hospitals, making it the seventh most common coagulase-negative species isolated (140). A retrospective review of the occurrence of clinically significant cases of *S. lugdunensis* bacteremia at a hospital in the United States over a 12 year period revealed a total of six patients with *S. lugdunensis* bacteremia (51). In each case, the patient had an underlying disease and the illness manifested as fever. Most patients had intravascular catheters that were reportedly infected. A *mecA*-positive *S. lugdunensis* isolate causing catheter-associated bloodstream infection in a premature neonate has been described (178).

Several instances of *S. lugdunensis*-induced septicemia and septic shock, including one that occurred as a result of receiving contaminated platelets, have been documented (25, 60). A female patient developed *S. lugdunensis* bacteremia and toxic shock syndrome 48 h after tooth extraction with foam packing (133).

Skin and Soft Tissue Infection

Skin and soft tissue infections account for a prominent number of the total infections caused by *S. lugdunensis*. In a 63-month study examining the occurrence of *S. lugdunensis* in consecutive cultures, 55% of the 155 specimens collected from 143 patients originated from wounds, abscesses, or cellulitis (82). Others have reported that *S. lugdunensis* represents 5 to 6% of CNS isolated from skin lesions (1, 83). The organism is more likely than *S. epidermidis* or other CNS to be clinically significant when isolated from superficial infections, and it causes suppurative lesions, including furuncles, felons, and sebaceous cysts, at a higher frequency than other CNS (1, 177). Many *S. lugdunensis* skin infections, particularly abscesses, occur in the perineal, inguinal, or pelvic girdle region (10, 81, 131, 177, 186).

There are three reports describing a total of seven cases of breast abscesses caused by *S. lugdunensis* in nonlactating women (4, 108, 194). Abscesses developed in two patients shortly after surgical procedures (108), whereas the remainder presented spontaneously.

Oral Infection

S. lugdunensis, as well as *S. aureus* and other CNS, has been isolated from patients with acute oral infections, including abscesses and osteomyelitis (200). *S. lugdunensis*, but not *S. aureus*, was isolated more frequently from patients with oral infection than from healthy subjects, suggesting that *S. lugdunensis* may be a pathogen when isolated from oral infections (200).

Ocular Infection

S. lugdunensis is an infrequent but significant pathogen in ocular infections. Nearly 6% (31/524) of CNS isolates recovered from the eyelids, anterior chamber fluid, or vitreous fluid of patients with postoperative endophthalmitis were *S. lugdunensis*, which was second only to *S. epidermidis* in terms of frequency of isolation (6). All pairs of *S. lugdunensis* intraocular isolates and eyelid isolates from single patients had identical pulsed-field gel electrophoresis profiles, indicating that the source of infection in these cases was the patient's skin flora (6). Similar results were observed in a more recent study (29), in which there were five cases (5.7%) of *S. lugdunensis* postoperative endophthalmitis among 87 documented infections. *S. lugdunensis* endophthalmitis is associated with a high

rate of complications and a poor functional prognosis (29). *S. lugdunensis* has also been reported as a cause of suppurative keratitis (141).

Peritonitis

S. lugdunensis peritonitis after Caesarean section (60) or in patients undergoing continuous ambulatory peritoneal dialysis has been noted (111, 159). *S. lugdunensis* accounted for 2.3% of CNS recovered from 106 cases of continuous ambulatory peritoneal dialysis-associated peritonitis in 46 patients over a 2-year period (111). *S. lugdunensis* peritonitis closely resembles peritonitis caused by *S. aureus*, both of which may involve catheter tunnel abscesses (159).

UTI

Urinary tract infections (UTIs) caused by *S. lugdunensis* have been observed infrequently in adult and pediatric patients (24, 79). Haile et al. conducted a 3-month prospective study of 4,652 consecutive urine cultures to determine the frequency of detection of *S. lugdunensis* (79). Of 500 CNS cultured, 31 (6%) grew *S. lugdunensis* as part of mixed cultures; it was unclear to the authors whether these isolates were uropathogens or contaminants. *S. lugdunensis* isolated in pure culture was deemed the causative agent of UTI in a child (24).

Infections of the Central Nervous System

S. lugdunensis brain abscesses have been described in patients with dental infection and embolic native valve endocarditis (60, 71). A case of *S. lugdunensis* meningitis in a child subsequent to ventriculostomy was reported (88). Three blood cultures grew *S. lugdunensis*, leading the authors to suggest that community-acquired bacteremia may have resulted in the seeding of the cerebrospinal fluid.

Three *S. lugdunensis* ventriculoperitoneal shunt infections in pediatric and adult patients, of both early and late onset, have been reported (52, 157). In all three cases, the infected shunt was surgically removed. Shunt infections caused by *S. lugdunensis* may present like a shunt infection caused by *S. aureus* rather than like one caused by *S. epidermidis* (157).

Endocarditis

In 1993, Vandenesch et al. reported 11 cases of *S. lugdunensis* endocarditis, 8 of which involved native mitral and/or aortic valves (183). This report brought the number of documented cases of *S. lugdunensis* endocarditis in the literature to 20 during the 5 years following the original species description (183). Based on those cases, those authors concluded that *S. lugdunensis* is an aggressive pathogen when causing endocarditis, based on the findings that most patients had symptoms for less than 3 weeks, that there was a high degree of valve destruction commonly associated with abscess formation, that valve replacement was often required, and that the mortality rate was 70% (14/20 patients died) (183). A further review of several published cases of *S. lugdunensis* endocarditis also revealed a pattern of embolus formation (95).

In a prospective study of 912 consecutive infective endocarditis cases from a Madrid, Spain, hospital occurring between 1990 and 2003, *S. lugdunensis* accounted for 1.1% of cases overall or 1.5% of cases excluding endocarditis in intravenous drug users in whom there were no cases of *S. lugdunensis* endocarditis (2). Four cases of native valve endocarditis (0.8%), two cases of prosthetic valve endocarditis (1.5%), and four cases of pacemaker lead endocarditis (7.8%) were observed (2). Significantly more patients with *S. lugdunensis* endocarditis underwent surgery than did patients with *S. aureus* endocarditis (70% versus 37%, respectively; $P < 0.04$); surgical rates for *S. epidermidis* endocarditis were similar to those for *S. lugdunensis*. The mortality rate associated with *S. lugdunensis* endocarditis (50%) was significantly higher than those associated with *S. aureus* (14.5%; $P < 0.01$) and *S. epidermidis* (20%; $P < 0.04$). In a univariate analysis of data from 69 cases reported in the literature between 1988 and 2003, a diagnosis of *S. lugdunensis* endocarditis after 1995 was associated with decreased mortality (2).

More than 80 cases of endocarditis attributable to *S. lugdunensis* have been reported to date; these are summarized in Table 2. Further characteristics of *S. lugdunensis* native valve, prosthetic valve, and pacemaker-associated endocarditis are discussed separately below. It is noteworthy that, in addition to endocarditis, *S. lugdunensis* myocarditis has been described (142).

Native valve endocarditis. *S. lugdunensis* accounted for nearly 5% of 89 staphylococcal endocarditis isolates recovered from patients at our institution between 1980 and 1999 (134). All *S. lugdunensis* isolates originated from native valves, comprising 44% of the nine CNS in the collection causing native valve endcoarditis. Upon review of 69 published reports of *S. lugdunensis* endocarditis from 1988 through 2003, Anguera et al. reported that native valve endocarditis accounted for 77% of all cases (2). Of the native valve cases, the mitral valve was involved 55% of the time. The disease was characterized by acute onset (54% of cases) with cardiac failure, abscess formation, and embolization arising at rates of 45%, 19%, and 30%, respectively. Fifty-one percent of patients underwent surgery, which was associated with a mortality rate of 29%; the overall mortality rate was 42%.

Many reports of *S. lugdunensis* endocarditis describe cases occurring following surgical procedures or skin trauma in the pelvic region. There have been five reports of *S. lugdunensis* native valve endocarditis that developed 1 to 3 months following vasectomy in men ranging in age from 32 to 45 years (58, 104, 195). Significant valve damage occurred in all cases. Four patients underwent urgent valve replacement (104, 195), while valvular reconstruction was performed on the fifth patient following successful antimicrobial therapy (58). These cases suggest that *S. lugdunensis* endocarditis may be a rare complication of vasectomy. In addition, native valve infection has developed in patients following a scrotal wound (134), kidney transplantation (134), and femoral angiography or angioplasty (17, 116, 144, 189).

Three patients on chronic hemodialysis have developed *S. lugdunensis* endocarditis (89, 160, 166). In each case, the arteriovenous fistula or venous catheter was suspected to be the origin of infection. One patient developed native valve endocarditis of the pulmonary valve (89).

TABLE 2. Reported cases of *Staphylococcus lugdunensis* endocarditis

Authors, yr	Age (yr)/ gender[a]	Comorbidity(ies)	Valve(s)	Suspected source	Outcome	Reference
Smyth et al., 1988	67/F	None	Native aortic	Not stated	Recovered	169
Etienne et al., 1989	72/F	None	Native aortic, mitral, tricuspid	Not stated	Died	53
	65/F	None	Native mitral	Cutaneous finger lesion	Recovered	
	64/M	None	Prosthetic aortic	Not stated	Died	
Fleurette et al., 1989	70/F	None	Not stated	Not stated	Died	60
	64/M	None	Prosthetic aortic	Not stated	Recovered	
Walsh and Mounsey, 1990	32/M	None	Native aortic	Vasectomy 3 mo prior	Recovered	195
Barker et al., 1991	77/M	Congestive cardiac failure; rheumatic fever affecting mitral, aortic, and tricuspid valves	Native mitral	Not stated	Died	7
Cormican et al., 1992	42/F	Mastectomy	Prosthetic aortic	Not stated	Died	37
Sheppard and Jankowski, 1992	59/M	Rheumatic heart disease 13 yr prior	Prosthetic mitral, native aortic	Not stated	Died	164
Shuttleworth and Colby, 1992	60/M	Atherosclerotic disease, aortic aneurysm, end-stage renal disease	Native mitral	Hemodialysis catheter	Died	166
Schonheyder et al., 1993	55/F	Hypertension, mitral valve regurgitation, end-stage renal disease	Native mitral	Not stated	Died	160
Vandenesch et al., 1993	54/M	Not stated	Prosthetic aortic	Cheek infection	Died	183
	71/F	Not stated	Native mitral	Not stated	Recovered	
	57/F	Not stated	Native mitral, aortic	Arm lymphangitis	Recovered	
	81/F	Not stated	Native mitral	Toe infection	Died	
	66/F	Not stated	Prosthetic aortic	Not stated	Recovered	
	65/M	Not stated	Native mitral	Not stated	Died	
	77/M	Not stated	Native mitral	Not stated	Died	
	23/M	Not stated	Native mitral, aortic	Hickman catheter	Died	
	69/F	Not stated	Native aortic	Not stated	Died	
	37/M	Not stated	Native aortic	Not stated	Died	
	74/M	Not stated	Prosthetic mitral	Pacemaker	Died	
Breen and Karchner, 1994	72/F	Coronary artery disease	Native aortic	Coronary angioplasty	Recovered	17
Costello et al., 1995	76/M	Lymphoma	Native mitral	Not stated	Recovered	38
Kralovic et al., 1995	26/M	None	Native aortic	Dental procedure 3 mo prior	Recovered	99
Dupont et al., 1996	88/F	None	Native mitral	Not stated	Died	50
Koh et al., 1996	52/F	None	Native mitral	Not stated	Recovered	95
Lessing et al., 1996	34/M	None	Native aortic	Vasectomy 30 days prior	Recovered	104
	37/M	None	Native aortic	Vasectomy 21 days prior	Recovered	
	42/M	None	Native aortic	Vasectomy 29 days prior	Recovered	
	45/F	None	Native aortic, tricuspid	Inguinal furuncle 30 days prior	Recovered	
De Hondt et al., 1997	33/F	Bicuspid aortic valve	Native aortic, mitral	Not stated	Recovered	42

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TABLE 2—*Continued*

Authors, yr	Age (yr)/ gender[a]	Comorbidity(ies)	Valve(s)	Suspected source	Outcome	Reference
Waterer et al., 1997	62/M	Rheumatoid arthritis, mitral valve regurgitation	Native mitral	Not stated	Died	197
Celard et al., 1997	41/M	None	Native tricuspid	Cardioverter defibrillator-associated infections for 5 yr	Recovered	26
Laguno et al., 1998	68/F	Pacemaker	Endocarditis on pacemaker leads	Pocket infection 1 year prior	Recovered	101
Llinares et al., 1998	70/F	None	Native mitral	Not stated	Died	109
	66/M	None	Native mitral	Not stated	Died	
	60/M	None	Native aortic	Not stated	Died	
Sanchis-Bayarri Vaillant et al., 1999	65/M	Rheumatic fever affecting mitral valve	Native mitral	Not stated	Recovered	156
Bobin et al., 1999	62/M	Pacemaker	Native tricuspid	Pacemaker insertion 1 mo prior	Recovered	15
	65/M	Diabetes mellitus, pacemaker	Endocarditis on pacemaker leads	Cutaneous effraction of a toenail 3 days prior	Recovered	
Burgert et al., 1999	33/M	Bicuspid aortic valve	Native aortic	Not stated	Recovered	19
Fervenza et al., 1999	39/M	None	Native mitral	Vasectomy 2.5 mo prior	Recovered	58
Kamaraju et al., 1999	65/F	Type 2 diabetes mellitus, hypertension, end-stage renal disease, multiple vascular access infections	Native pulmonary	Not stated	Recovered	89
Wasserman et al., 1999	27/F	Pelvic inflammatory disease	Native mitral	Pelvic inflammatory disease 1 wk prior	Recovered	196
Kragsbjerg et al., 2000	79/M	Psoriasis, hypertension, rheumatoid arthritis, prosthetic knee, aortic and mitral valve regurgitation	Native mitral, aortic	Prosthetic joint infection 1 yr prior	Died	98
Patel et al., 2000	49/M	Renal transplant, Mitral valve prolapse	Native mitral	Not stated	Recovered	134
	85/F	Total knee arthroplasty	Native mitral	Prosthetic joint infection 16 mo prior	Recovered	
	67/M	Rheumatic heart disease, cryptogenic cirrhosis	Native mitral	Not stated	Recovered	
Polenakovik et al., 2000	55/M	Dyslipemia	Not stated	Arteriography via right inguinal area 2 wk prior	Recovered	144
Renzulli et al., 2000	51/M	None	Native aortic, mitral	Not stated	Recovered	148
Teong et al., 2000	22/M	None	Native aortic	Not stated	Recovered	180
Sanchez et al., 2000	71/F	Breast cancer, prosthetic hip failure	Native aortic	Not stated	Recovered	155
Farrag et al., 2001	78/F	None	Native mitral	Not stated	Died	55
Jones et al., 2002	16/M	Congenital aortic stenosis	Native aortic	Not stated	Recovered	87

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TABLE 2—*Continued*

Authors, yr	Age (yr)/ gender[a]	Comorbidity(ies)	Valve(s)	Suspected source	Outcome	Reference
Watchler et al., 2002	22/F	None	Native mitral	Not stated	Recovered	193
Sotutu et al., 2002	7/M	Congenital aortic stenosis	Native aortic	Not stated	Recovered	171
Garcia Fernandez et al., 2003	65/F	Breast cancer	Native mitral	Not stated	Died	70
Seenisavan and Yu, 2003	36/F	Cocaine abuse	Native mitral	Not stated	Recovered	161
Rodriguez-Gascon et al., 2003	77/F	Hypertension, diabetes mellitus, vulvar carcinoma	Native mitral	Not stated	Recovered	149
Petzsch et al., 2004	68/M	None	Native aortic	Not stated	Recovered	139
Anguera et al., 2005	77/F	Liver cirrhosis	Native mitral	Not stated	Died	2
	82/F	Ischemic heart disease	Not stated	Not stated	Died	
	68/F	Pacemaker	Endocarditis on pacemaker leads	Not stated	Relapse 1 year later	
	66/M	Pacemaker	Endocarditis on pacemaker leads	Not stated	Died	
	78/M	Pacemaker	Endocarditis on pacemaker leads	Not stated	Recovered	
	70/M	None	Prosthetic aortic	Not stated	Died	
	77/M	None	Prosthetic aortic	Not stated	Recovered	
	43/F	Congenital pulmonary stenosis	Native pulmonary	Not stated	Recovered	
	37/M	None	Native aortic	Not stated	Died	
	63/M	Pacemaker	Endocarditis on pacemaker leads	Not stated	Recovered	
Van Hoovels et al., 2005	66/M	Pulmonary lobectomy	Native mitral	Not stated	Recovered	187
	78/F	Heart failure, gastric ulcers	Native mitral	Not stated	Died	
	19/M	Aortic and mitral valve insufficiency	Native mitral and tricuspid	Not stated	Died	
Seifert et al., 2005	61/M	Nephrectomy for cancer, pacemaker	Endocarditis on pacemaker leads	Battery replacement 3 mo prior	Recovered	162
Gianella et al., 2006	49/F	Bicuspid aortic valve	Native aortic	Not stated	Recovered	71
Sorli Redo et al., 2006	66/M	Chronic obstructive pulmonary disease	Native mitral	Not stated	Recovered	170
Kouberti et al., 2007	33/M	Congenital aortic bicuspid valve	Prosthetic aortic	Aortic valve replacement 40 days prior	Died	96
Viganego et al., 2007	75/M	Aortic valve sclerosis, type 2 diabetes mellitus, hypertension	Native aortic	Femoral endoarterectomy and femoral-popliteal bypass 7 mo prior	Died	189
Matthews et al., 2007	77/F	Coronary artery disease	Native mitral	Cardiac catheterization 3 wk prior	Recovered	116

[a] F, female; M, male.

Prosthetic valve endocarditis. Like other CNS, *S. lugdunensis* also causes prosthetic valve endocarditis (2, 37, 53, 60, 96, 164, 183). Thirteen percent of 69 cases of *S. lugdunensis* endocarditis cases between 1988 and 2003 involved prosthetic valves (2). The aortic valve was affected in over three-quarters of cases (2). Over half of patients underwent surgery; *S. lugdunensis* prosthetic valve endocarditis was associated with a 78% mortality rate (2). Abscess formation, pus, and significant tis-

sue destruction commonly occur in *S. lugdunensis* prosthetic valve endocarditis (2, 37, 164, 183).

Pacemaker-associated endocarditis. *S. lugdunensis* endocarditis due to infected pacemaker systems has been described (2, 15, 101, 162). Pacemaker-associated endocarditis was responsible for 10% of 69 *S. lugdunensis* endocarditis cases reported in the literature between 1988 to 2003 (2). Symptom onset is reported to be acute, and metastatic infection is common (15, 101). Infection with *S. lugdunensis* small-colony variants (SCVs) reportedly caused recurrent symptoms in one patient (162). Surgical removal of infected pacemaker systems, in addition to antimicrobial therapy, has been commonly used (2, 15, 101, 162) and is associated with a mortality rate of 14% (2).

Bone and Joint Infection

S. lugdunensis is a noteworthy cause of bone and joint infection. In a 4-year prospective study of the occurrence of CNS in patients undergoing orthopedic surgery for bone and joint infection, *S. lugdunensis* was isolated at a frequency of 3% in 212 CNS derived from 119 surgeries in 104 patients (167). Another study revealed that during a 40-month period, *S. lugdunensis* accounted for 1% of the 601 CNS obtained from patients with orthopedic clinical infections, including surgical wounds and infected prostheses (3). Temporal bone osteomyelitis and three cases of *S. lugdunensis* infective arthritis following surgical procedures have been reported (60, 118, 132, 181).

Vertebral osteomyelitis and disk space infection. Multiple reports describe vertebral osteomyelitis due to *S. lugdunensis* (77, 121, 198). In one case, the source of infection was not obvious, although the patient was immunosuppressed (121). Infection in immunocompetent hosts has also been reported (77, 198). *S. lugdunensis* disk space infection was reported in a patient receiving chemotherapy for multiple myeloma (20), in a patient with osteoarthritis and bacteremia 1 month following foot surgery, and in an immunocompetent patient following disk surgery (78). A patient who developed *S. lugdunensis* spondylodiscitis several months after the replacement of a pacemaker battery (thought to be the source of infection) was successfully treated with antimicrobial therapy alone (18). Clinical manifestations of *S. lugdunensis* spine-related infections can be severe (20).

Prosthetic joint infection. *S. lugdunensis* should be considered a pathogen when isolated from patients with prosthetic joint infection (63). In a prospective study, *S. lugdunensis* was the causative agent in 4% (3/79) of all prosthetic joint infection cases from patients undergoing hip or knee arthroplasty revision or resection (182). Four other cases of *S. lugdunensis* prosthetic joint infection have been communicated in the literature (154, 158, 198). *S. lugdunensis* prosthetic joint infection has been reported to present from 6 weeks to 4 years after implantation (154). Acute onset occurred in three of the four cases (154, 198).

CLINICAL MICROBIOLOGY

Species Description and Microbiological Characteristics

S. lugdunensis is a gram-positive, nonmotile, catalase-positive coccus (68). Cells are 0.8 to 1.0 μm in diameter and occur singly or in pairs, clusters, or short chains (68). *S. lugdunensis* is a facultative anaerobe that grows well in rich media at temperatures of between 30 and 45°C. Growth is sustained on 10% or 15% sodium chloride after incubation for 24 or 96 h, respectively (68). Colony morphology, pigmentation, and hemolysis vary among strains (60, 68). The species is coagulase negative (Fig. 1A), but a variable percentage of strains are positive for clumping factor (bound coagulase) when tested in a slide agglutination test with human plasma or various commercial latex agglutination kits (discussed further below) (5, 68). *S. lugdunensis* does not possess protein A (68, 135). Isolates are positive for acetoin production, nitrate reduction, and ornithine decarboxylase and pyrrolidonyl arylamidase (PYR) activities (Fig. 1B and C, respectively) but negative for oxidase and alkaline phosphatase (5, 68). *S. lugdunensis* is susceptible

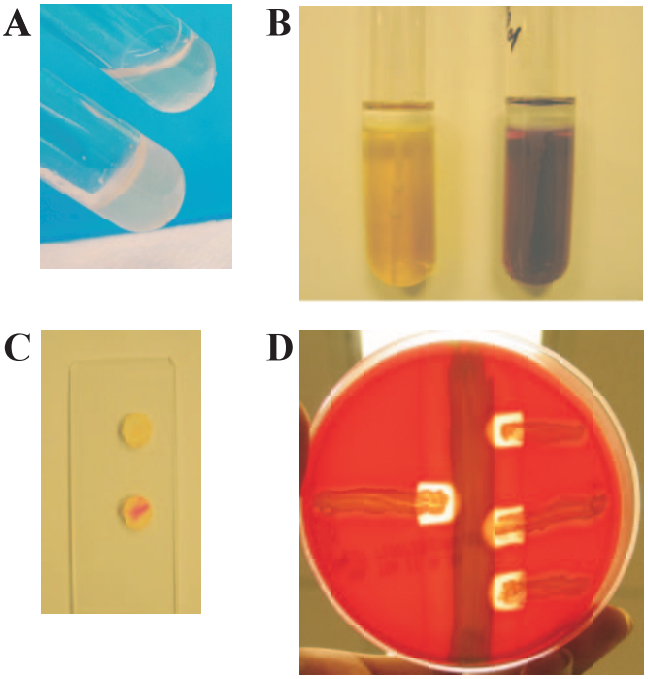

FIG. 1. Key biochemical characteristics of *S. lugdunensis*. (A) Tube coagulase (long coagulase) test. *S. aureus* RN4220 (bottom) clots plasma (BBL rabbit coagulase plasma with EDTA; BD, Franklin Lakes, NJ), whereas *S. lugdunensis* IDRL-5258 (top) is unable to clot plasma. (B) Ornithine decarboxylase test. *S. aureus* RN4220 (left) and *S. lugdunensis* IDRL-5258 (right) were used to inoculate decarboxylase medium agar (BBL Moeller decarboxylase broth base; BD) containing ornithine and overlaid with mineral oil. *S. lugdunensis* demonstrates ornithine decarboxylase activity, causing a change in the medium's pH indicator (bromocresol purple) to a purple color, signifying a positive result. In contrast, a negative result (yellow) is obtained with *S. aureus*. (C) Rapid PYR test. *S. lugdunensis* IDRL-5258 (bottom) produces PYR, exhibiting a positive (pink) reaction in a rapid test (Remel, Lenexa, KS). *S. aureus* RN4220 (top) is PYR negative. (D) Synergistic hemolysis. The δ-like hemolysin of *S. lugdunensis*, mediated by three small peptides produced upon expression of the *slush* locus (see text for details), acts synergistically with the β-hemolysin of *S. aureus* to produce a zone of complete hemolysis on sheep red blood cells. *S. lugdunensis* IDRL-5258 (left) and *S. lugdunensis* IDRL-2414 (right, streaked in triplicate) are streaked perpendicular to, but not touching, *S. aureus* RN4220, which is streaked vertically. In panels A, B, and D, photographs were taken 18 h after inoculation and incubation in ambient air at 37°C. Panel C was photographed approximately 5 minutes after the rapid test was performed.

to novobiocin and variably resistant to polymyxin B (5, 80). Acid is produced under aerobic growth conditions from D-glucose, D-fructose, D-mannose, maltose, D-trehalose, α-lactose, sucrose, *N*-acetylglucosamine, and glycerol (5, 68). The cell wall peptidoglycan is composed of L-lysine-glycine$_{5-6}$, and the cell wall teichoic acids contain glycerol, glucose, and glucosamine (68).

To date, the *S. lugdunensis* genome has not been sequenced. However, the base composition of the genome of the type strain ATCC 43809 (accession no. N860297) has been estimated by thermal denaturation experiments to be 32% G+C (68), which is comparable to the G+C compositions of sequenced *S. aureus* and *S. epidermidis* strains (5). Many strains carry one or more plasmids, some of which confer resistance to cadmium (54, 143). Genomic analyses by restriction endonuclease digestion and pulsed-field gel electrophoresis suggest a relatively low level of genomic variability among *S. lugdunensis* strains (54, 81, 107, 186).

Hemolysis. *S. lugdunensis* may demonstrate hemolysis on blood agar containing rabbit erythrocytes and weak hemolysis after 2 days or more on blood agar containing sheep erythrocytes (60, 68). Additionally, a synergistic hemolytic phenotype resembling the activity of the *S. aureus* δ-hemolysin was observed in 73% of *S. lugdunensis* strains when streaked perpendicular to a β-hemolysin-producing staphylococcal strain (e.g., *Staphylococcus intermedius*) on blood agar containing rabbit erythrocytes (185). Similarly, in a different study, 95% of strains demonstrated a zone of complete hemolysis when streaked in proximity with a beta-hemolytic staphylococcal strain on blood agar containing sheep erythrocytes (Fig. 1C) (80).

Colony variation. Variation in colony morphology and pigmentation among *S. lugdunensis* strains has been described (60, 68, 106, 162). In the original description of the species, colony diameters ranged from 1 to 4 mm (68). Colonies may have yellow to gold pigmentation after 3 to 5 days of incubation or may remain cream-colored or unpigmented (60, 68). Three of the 11 originally described strains exhibited two distinct colony morphotypes, displaying both smooth and glossy or rough and dull morphologies (68). Several colonial morphotypes subcultured from an apparent mixed staphylococcal culture taken from a patient with native valve endocarditis were subsequently all identified as *S. lugdunensis* (106). Subsequent subculturing of single colonies demonstrated colonial variation through three serial passages (106). In a collection of nine *S. lugdunensis* isolates, three displayed colony variation after 48 h, as well as after being subcultured and incubated for 24 h (106).

SCVs are a slow-growing, nonpigmented, and nonhemolytic subpopulation of staphylococci, particularly common in *S. aureus*, that may arise upon culturing of clinical specimens (190). SCVs often grow to only 1/10th of the size expected of a normal colony and present difficulty in identification and susceptibility testing due to their fastidious and auxotrophic growth characteristics (5, 190). *S. aureus* SCVs may have a defect in the electron transport chain (190). Hemin-auxotrophic SCVs of *S. lugdunensis* were isolated from thrombotic material scraped from pacemaker leads in a reported case of pacemaker-related endocarditis (162). In addition to the SCVs, the infecting strain produced at least three other colony morphologies that persisted upon serial subculturing (162).

Identification in the Clinical Microbiology Laboratory

CNS are not routinely identified to the species level in most clinical microbiology laboratories. Typically, cultures positive for staphylococci are tested to identify *S. aureus*, which in many cases can be simply determined with a slide or latex agglutination test for clumping factor and, depending if a commercial kit is used, protein A or other *S. aureus*-specific cell surface antigens. A negative result in a slide agglutination test may be followed with a tube coagulase test, which can confirm whether the organism is tube coagulase negative and therefore classifiable as a CNS. The enhanced virulence and destructive nature of *S. lugdunensis* are compelling reasons for the prompt identification of this organism to the species level when it is suspected during infection, especially when isolated from sterile sites. As discussed below, *S. lugdunensis* is easily identifiable with a relatively few biochemical tests, namely, tests for PYR activity, ornithine decarboxylase activity, and secreted coagulase (via a tube coagulase test). Caution should be exercised when testing staphylococci for clumping factor using rapid methods, as some isolates are clumping factor positive.

Biochemical profile for identification. *S. lugdunensis* can be positively differentiated from other CNS by a negative tube coagulase test, a positive PYR reaction, and positive ornithine decarboxylase activity (Fig. 1). *S. lugdunensis*, along with *S. haemolyticus*, *S. schleiferi*, and *S. intermedius*, is PYR positive (5). While the reference method for staphylococcal PYR testing is with PYR broth, Fig. 1 shows testing of *S. lugdunensis* and *S. aureus* for PYR using the disk test that is commonly used for the identification of streptococci. Due to the pigmentation of some staphylococcal species, the PYR disk test may be difficult to interpret. In our experience, however, we have not encountered difficulties when identifying *S. lugdunensis* with this method. Positive and negative *Staphylococcus* control strains should be included when performing the PYR disk test.

S. lugdunensis is the only *Staphylococcus* species for which ≥90% of isolates are positive for ornithine decarboxylase; a positive result can be obtained in as soon as 8 h (5). It should be noted that a small number of *S. epidermidis* strains reportedly decarboxylate ornithine (5). *S. lugdunensis* can also be identified by the production of acid from trehalose, mannose, maltose, and sucrose but not from mannitol (5).

Several biochemical identification schemes to differentiate multiple CNS species, including other clumping factor-positive staphylococci, incorporate tests to accurately identify *S. lugdunensis* (43, 105, 159). Readers are referred to those publications for further information.

Variable presence of clumping factor. In *S. aureus*, cell wall-associated clumping factor A is a protein adhesin for fibrinogen that mediates bacterial aggregation upon coming into contact with plasma (5). The initial description of 11 *S. lugdunensis* strains reported that all were positive for clumping factor when mixed with human plasma (68). However, only 58% were clumping factor positive with human plasma in a subsequent study of 31 isolates (60).

In addition to human plasma, there exist a large number of commercially available latex agglutination kits containing fibrinogen-coated particles to facilitate visible clumping reactions mediated by clumping factor (5). Some commercial kits have improved their sensitivity of detection of *S. aureus* by

incorporating monoclonal antibodies that detect protein A, capsular polysaccharides, or other cell-associated antigens. It has been repeatedly shown that positive results for clumping factor vary significantly, depending on the type of kit used (67, 80, 183). While we detected clumping factor in only 13% (2/15) of *S. lugdunensis* isolates with the Staphaurex kit (Remel, Lenexa, KS) (67), other investigators have reported positive results ranging from 79% (30/38) with the BBL Staphyloslide kit (BD, Franklin Lakes, NJ) (80) to 82% (9/11) with the Staphyslide kit (bioMérieux, Marcy-l'Etoile, France) (183).

Side-by-side evaluations of *S. lugdunensis* strain collections in multiple commercial latex agglutination systems have been performed (135, 138). Paulsson et al. tested 11 strains of infectious or colonizing *S. lugdunensis* with human plasma and three commercial systems (135). Six of 11 strains were positive under all four conditions tested. The remaining five isolates were negative in all tests. A second study evaluated 30 *S. lugdunensis* isolates in six commercial agglutination kits (138). Positive results ranged from 7% to 60%, depending upon the ability of each kit to detect clumping factor, protein A, and other *S. aureus*-specific antigens.

The *Manual of Clinical Microbiology* states that latex agglutination methods for the detection of clumping factor in *S. lugdunensis* are not as reliable as detection with human plasma (5). However, the use of human plasma in clinical laboratories is discouraged unless it has been determined that it lacks infectious agents and is capable of clotting (5). Overall, this phenotype has varied widely among strains in published studies; results may depend on the testing method used. Collectively, the results of published studies indicate that testing for clumping factor in *S. lugdunensis* is not a dependable method for the identification of this species.

Identification with commercial kits or automated systems. Many clinical laboratories employ commercial identification kits or automated instruments that allow quick determination of bacterial species. Numerous systems exist, and manufacturers continuously update their database systems to improve the accuracy of organism identification as new information becomes available. As would be expected, in the years immediately following the description of *S. lugdunensis*, several identification kits or systems were unable to accurately identify this organism due to incomplete or a general lack of information in the system databases (76, 80, 93, 166). Interestingly, the Microbial Identification System (MIDI, Newark, DE), which identifies organisms based on the analysis of their microbial cellular fatty acid compositions, correctly identified 26/26 *S. lugdunensis* strains as early as 1994 (172). The *Manual of Clinical Microbiology* gives the following list of systems that include *S. lugdunensis* in their databases (23): API-Staph, version 4.0 (bioMérieux); Vitek 2 GP, version 4.01 (bioMérieux) (the older Vitek Legacy did not include *S. lugdunensis*); MicroScan Conventional Pos ID (LabPro version 1.5) and Rapid Pos ID (LabPro version 1.6) (Dade MicroScan, Inc., West Sacramento, CA); BBL Crystal Gram-Pos ID and Rapid Gram-Pos ID (BD); Microbact Staph 12S (Oxoid); Biolog CP2 version 6.11/6.12 (Biolog, Hayward, CA); MIDI version 5.0 (MIDI); and Phoenix-100 GPID PMIC/II-100 (BD Diagnostics). In addition, the RapID Staph Plus (Remel, Lenexa, KS) correctly identifies *S. lugdunensis*. The databases of other systems that are not listed here may also include *S. lugdunensis*; users are advised to consult the manufacturer of their automated identification system for further information on this topic.

Species identification by molecular methods. Methods to differentiate microorganisms by unique nucleic acid sequences are becoming more commonplace in the clinical microbiology laboratory due in part to increasing technological advances, including real-time PCR and high-throughput DNA sequencing systems. Many efforts particularly focus on the timely identification of pathogenic CNS. Several promising nucleic acid targets that provide accurate identification of *S. lugdunensis* have been identified and are discussed below.

The sequence diversity of the 16S rRNA genes of staphylococci enables species-level identification. The 16S rRNA gene represents a ubiquitous, highly conserved gene in which certain regions have accumulated changes during the evolution of individual species. By comparing the 16S rRNA sequence of an unknown organism to a sequence repository, such as the GenBank database maintained by the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/GenBank/index.html), identification can usually be obtained. Thus, PCR amplification and sequencing of this gene have become an option for molecular identification of pathogenic bacteria in the clinical microbiology laboratory (33), and this technique was used to confirm the identity of a *mecA*-positive *S. lugdunensis* isolate upon its isolation from a bloodstream infection in a pediatric patient (178). Real-time PCR assays utilizing fluorescent resonance energy transfer probes that bind to regions of the staphylococcal 16S rRNA gene following amplification with broad-range primers have also been developed (168). Such methods may enable identification of organisms in a shorter time than is needed to amplify and sequence the 16S rRNA gene or other genes.

The internal transcribed spacer (ITS) regions of the prokaryotic rRNA gene locus, which show considerable variability among genera and species, serve to separate the 16S, 23S, and 5S genes and may contain coding sequences for tRNA genes. Staphylococci possess several nonidentical copies of the rRNA locus, and the ITS region of each copy may vary in length and sequence composition. PCR amplification of the ITS regions of a particular species' genome thus yields a polymorphic, species-specific banding pattern. In a study demonstrating the utility of PCR amplification of the ITS region to identify staphylococcal species, two *S. lugdunensis* strains produced banding patterns that were dissimilar from those of the other 28 staphylococcal species examined (39). In this regard, ITS-PCR provides a method that discriminates *S. lugdunensis* isolates from other CNS yet does not require sequencing. ITS-PCR banding patterns must be compared to banding patterns from reference strains in order to obtain a species identification, so inclusion of an adequate variety of reference strains is necessary for successful interpretation. Using this method, coupled with microchip gel electrophoresis for rapid analysis of PCR amplification products, *S. lugdunensis* and other staphylococci were successfully identified from blood culture bottles (69).

Ribotyping, the analysis of rRNA restriction fragment length polymorphisms, provides an alternative method for molecular differentiation of bacterial species. This technique analyzes differences over the entire rRNA locus and may be useful for epidemiological studies. An automated

ribotyping system is commercially available (5) and has been used to evaluate collections of CNS isolated from blood or orthopedic prosthesis infections to determine its ability to correctly identify individual species (21, 22). Ribotyping correctly identified all 11 *S. lugdunensis* strains included in the two published studies (21, 22), indicating the validity of this technique for identification of this species. Interestingly, in both reports, *S. lugdunensis* strains displayed three unique ribotype patterns.

Sequences of several other genes, including *hsp60*, *sodA*, *rpoB*, and *tuf*, have proven useful as targets for molecular identification of CNS. A 600-base-pair region of the *S. lugdunensis* heat shock protein gene, *hsp60* (also called *groEL*), amplified with universal primers, identified *S. lugdunensis* isolates with 100% accuracy in hybridization experiments (72, 73). Over 40 clinical staphylococcal isolates were tested in these experiments; none of the other species tested were falsely identified as *S. lugdunensis* (72, 73). Additionally, restriction fragment length polymorphism analysis of *groEL* following PCR amplification permitted identification of *S. lugdunensis* and 11 other *Staphylococcus* species (8). The *sodA* gene, encoding manganese-dependent superoxide dismutase, is present in and has been sequenced from approximately 40 CNS, including *S. lugdunensis* (145). The *sodA* sequences of CNS share less similarity with each other than do their 16S rRNA gene sequences, providing an alternative target for classifying closely related species (145). Sivadon et al. used this target to prospectively identify *S. lugdunensis* and other CNS causing bone and joint infections (167). Amplification and sequencing of a 751-base-pair region of the RNA polymerase β subunit gene *rpoB* and an 881-base-pair span of the elongation factor Tu (EF-Tu) gene *tuf* have also served to differentiate *S. lugdunensis* from other CNS (47, 113). Sequencing of the *rpoB* and 16S rRNA genes of several isolates recovered from a pediatric patient with meningitis facilitated identification of *S. lugdunensis* as the causative organism (88).

ANTIMICROBIAL SUSCEPTIBILITY

Prevalence of Antimicrobial Resistance in *S. lugdunensis*

S. lugdunensis, unlike most CNS, has remained remarkably susceptible to a wide array of antimicrobial agents. In 2007, we reported that 14 clinical isolates from a variety of sources were susceptible to 10 antistaphylococcal antimicrobial agents representing different drug classes (67). A 15th organism was resistant to trimethoprim-sulfamethoxazole but remained susceptible to the other nine agents tested. The distribution of antimicrobial susceptibilities of these isolates is summarized in Table 3.

The trend that *S. lugdunensis* is generally susceptibility to multiple agents, including pencillins, does not change based on the source of infection. Eleven endocarditis isolates were susceptible to the following 19 antimicrobial agents: penicillin, oxacillin, streptomycin, kanamycin, gentamicin, tobramycin, erythromycin, lincomycin, pristinamycin, tetracycline, minocycline, chloramphenicol, perfloxacin, fusidic acid, vancomycin, teicoplanin, fosfomycin, rifampin, and co-trimoxazole (183). Fifteen bloodstream isolates exhibited susceptibility to many common antimicrobials, including penicillin (51). Fifteen *S. lugdunensis* isolates from diabetic foot infections were susceptible to eight out of nine agents tested, including ceftobiprole, a new broad-spectrum cephalosporin (74).

In a study of non-*S. aureus*, non-*S. epidermidis* staphylococci from orthopedic infections, *S. hominis*, *S. capitis*, *S. haemolyticus*, and *S. warneri* exhibited high rates of resistance (51 to 66% of isolates) to penicillin, ampicillin, cefazolin, and cefamandole (3). In contrast, of eight *S. lugdunensis* isolates studied, only three were resistant to the same β-lactams. In addition, one *S. lugdunensis* isolate was resistant to erythromycin. There have also been single reports of *S. lugdunensis* isolates resistant to streptomycin (86), tetracycline (183), penicillin (183), gentamicin (83), ceftazidime (74), and aminoglycosides and macrolides (60). A single case report described the emergence of resistance to rifampin and ciprofloxacin that correlated with treatment of a persistent *S. lugdunensis* infection that manifested over 3 years as septic arthritis of both knees, vertebral osteomyelitis, and aortic and mitral valve endocarditis (98).

There has been only one reported observation of *S. lugdunensis* isolates that are resistant to multiple antimicrobial agents (200). Six *S. lugdunensis* oral infection isolates collected in Korea were resistant to ampicillin, penicillin, cephalothin, oxacillin, and clindamycin (200). Three of the isolates were also resistant to erythromycin and/or gentamicin, and three harbored plasmids (although it was not determined whether the plasmids contributed to the antimicrobial resistance phenotypes). These organisms are unusual in comparison with other reported collections of *S. lugdunensis*.

Some *S. lugdunensis* strains exhibit resistance to the translation-inhibiting antimicrobial agent fusidic acid, which prevents ribosomal release of EF-G. Fusidic acid-resistant *S. lugdunensis* strains have acquired a chromosomal *fusB* resistant determinant that encodes an EF-G-binding protein located downstream of *groEL* in the genome (130).

Frequencies of β-Lactamase and *mecA*

The frequency of β-lactamase in *S. lugdunensis* is reported to differ between isolates from North American and European countries. This percentage ranges from 7 to 24% in publications originating from French laboratories (60, 186). In contrast, three separate collections of *S. lugdunensis* isolates from laboratories in the United States showed rates of 24%, 29%, and 40% (67, 80, 82). A Spanish study and a Swedish study reported rates of 12% and 15% β-lactamase-positive *S. lugdunensis* isolates, respectively (81). As expected, β-lactamase-positive *S. lugdunensis* isolates demonstrate resistance to penicillin and other related antimicrobial agents.

In accordance with the overwhelming antimicrobial susceptibility exhibited by *S. lugdunensis* isolates, this organism has generally remained susceptible to oxacillin. PCR screening for *mecA* in large collections of *S. lugdunensis* has repeatedly yielded negative results (57, 67, 81, 85, 110). In addition to screening *S. lugdunensis* for oxacillin resistance by *mecA* PCR, a slide latex agglutination test to detect the presence of PBP2a or Mueller-Hinton agar supplemented with 4% NaCl containing 6 μg/ml oxacillin may also be used (110, 115, 199).

Only two descriptions of *mecA* in *S. lugdunensis* presently exist in the English literature (9, 178). A *mecA*-positive

TABLE 3. Distribution of antimicrobial susceptibilities of *Staphylococcus lugdunensis* clinical isolates

Antimicrobial agent and parameter[a]	% of isolates with MIC or MBC at or below the following concn (μg/ml)[b]:												
	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128
CFZ													
MIC			20[c]	67	100								
MBC			7[c]	40	73	93	100						
DAP													
MIC		21	50	93		100							
MBC		14	29	36	79	100							
LZD													
MIC					13	100							
MBC													100[d]
MXF													
MIC			87	100									
MBC			60	80	93	100							
NAF													
MIC				47	100								
MBC				20	73	87	100						
Q-D													
MIC		7	27	60	80	87	100						
MBC					7	13	53	67		73	100[e]		
RIF													
MIC	100[f]												
MBC	20		40					47	53		100[e]		
TET													
MIC		20	27	67	80	100							
MBC											100[e]		
SXT[g]													
MIC			47	67	87	93				100[h]			
MBC						20	27		40	100[h]			
VAN													
MIC					27	87	100						
MBC								7				20	100[d]

[a] CFZ, cefazolin; DAP, daptomycin; LZD, linezolid; MXF, moxifloxacin; NAF, nafcillin; RIF, rifampin; Q-D, quinupristin-dalfopristin; TET, tetracycline; SXT, trimethoprim-sulfamethoxazole; VAN, vancomycin.

[b] Percentage of clinical *S. lugdunensis* isolates (*n* was 15 for all drugs except daptomycin, for which *n* was 14). *S. lugdunensis* isolates and the methods used for susceptibility testing were described previously (67).

[c] MIC or MBC ≤ 0.125.

[d] MBC > 128.

[e] MBC > 32.

[f] MIC ≤ 0.03.

[g] SXT susceptibility values correspond to trimethoprim concentrations.

[h] MIC or MBC > 16.

strain identified as *S. lugdunensis* by conventional phenotypic, automated, and molecular methods was reported as causing a bloodstream infection in a premature neonate with an intravascular catheter in Singapore in 2003 (178). No zone of inhibition was observed with a 5-μg methicillin disk, and the oxacillin Etest MIC was >256 μg/ml. The *mecA* gene was detected by PCR, and the MRSA-Screen latex agglutination test was positive after induction of expression of the oxacillin resistance gene. The patient was successfully treated with vancomycin. Additionally, Becker et al. reported the isolation of a *mecA* PCR-positive *S. lugdunensis* nasal colonizing strain, but no further characterization was performed (9).

Breakpoints for Oxacillin Resistance

In 1999, NCCLS (now the Clinical Laboratory and Standards Institute [CLSI]) lowered the oxacillin resistance breakpoints for CNS from ≥4 μg/ml to ≥0.5 μg/ml in order to improve the sensitivity of identification of *mecA*-positive isolates as oxacillin resistant (122). Subsequently, Hussain et al. demonstrated that while the revised breakpoints accurately classified several *mecA*-positive species of CNS (i.e., *S. epidermidis*, *S. hominis*, and *S. haemolyticus*) as oxacillin resistant, *S. lugdunensis* isolates with MICs of 0.5 to 2 μg/ml but lacking the *mecA* gene, as detected by PCR, were falsely categorized as being oxacillin resistant (85). A patient with native valve en-

docarditis caused by an *S. lugdunensis mecA*-negative isolate, which was classified as oxacillin resistant due to its oxacillin MIC of 1 μg/ml, was successfully treated with ceftriaxone, suggesting that the breakpoints for oxacillin resistance in CNS were not appropriate for *S. lugdunensis* (134). NCCLS later recommended that *S. lugdunensis* isolates should be screened for oxacillin resistance by detection of PBP2a by latex agglutination or *mecA* by PCR (123). Finally, in 2005, the oxacillin breakpoints for *S. lugdunensis* were revised once more to follow those set for *S. aureus*, which should more accurately predict *mecA*-negative *S. lugdunensis* isolates (34). Currently, *S. lugdunensis* strains showing oxacillin MICs of ≤2 μg/ml are considered susceptible, whereas those showing oxacillin MICs of ≥4 μg/ml are classified as resistant (34).

Vancomycin Tolerance

Vancomycin, a glycopeptide antimicrobial agent, exerts bactericidal activity against staphylococci. It is generally recommended that vancomycin be reserved for situations in which other antimicrobials are not viable treatment options. A phenomenon known as vancomycin tolerance, in which organisms with MICs indicating susceptibility are refractory to killing in bactericidal killing assays, has been documented in *S. aureus* (117, 136) and has recently been recognized among *S. lugdunensis* isolates (16, 67). In our collection of vancomycin-susceptible (MIC range, 0.5 to 2 μg/ml) *S. lugdunensis* clinical isolates, 93% ($n = 15$) demonstrated tolerance to vancomycin, as defined by a minimal bactericidal concentration (MBC)/MIC ratio of ≥32 (67). Vancomycin MBCs for 12 isolates were >128 μg/ml (67). Bourgeois et al. reported similar findings when the bactericidal activities of vancomycin and teicoplanin, a related glycopeptide, were tested against clinically significant *S. lugdunensis* isolates using time-kill curve methodology (16). They found that 6/13 *S. lugdunensis* isolates were tolerant to vancomycin or teicoplanin, including three organisms that were tolerant to both antimicrobial agents (16). The killing capacities of vancomycin and teicoplanin against the 13 *S. lugdunensis* isolates were reduced compared to those against 77 other CNS, despite the susceptibility of the isolates to both antimicrobial agents (16).

Optimal treatment of bacterial endocarditis is considered to require a bactericidal antimicrobial regimen. Cases of *S. lugdunensis* native valve endocarditis have been successfully treated with vancomycin, usually in combination with aminoglycosides or rifampin (2, 161, 183). The general susceptibility of *S. lugdunensis* to the β-lactams usually precludes the necessity to rely on vancomycin therapy. The observation that *S. lugdunensis* glycopeptide tolerance may be widespread is concerning and warrants further in vitro and in vivo studies to delineate whether this is a clinically significant finding.

Response of *S. lugdunensis* Biofilms to Antimicrobial Treatment

Most infections caused by CNS are attributable to the formation of biofilms, surface-associated multicellular communities of microorganisms that surround themselves in a self-produced extracellular polymeric matrix, on host tissues or indwelling medical devices (191). Bacterial biofilms exhibit high levels of resistance to antimicrobial therapies and evade host immune defenses, making biofilm-related infections extremely difficult to treat. Several types of documented *S. lugdunensis* infection derive from a biofilm etiology, and the clinical features and pathogenesis of these infections are covered elsewhere in this review. Here we discuss our present understanding of the response of *S. lugdunensis* biofilms to antimicrobial agents.

We investigated the ability of 10 antistaphylococcal agents at concentrations traditionally tested in MIC assays to significantly reduce the number of bacteria recovered from biofilms of 15 *S. lugdunensis* isolates (67). The biofilm bactericidal concentration (BBC) assay, which measures the amount of regrowth in recovery media following the exposure of biofilms to antimicrobial agents, revealed that the BBC_{90}s for all drugs tested were considered to indicate resistance by the breakpoints for planktonic organisms set forth by the CLSI. Seven drugs had BBCs of ≥128 μg/ml, the highest concentration tested in the assay. Interestingly, the BBC range of the quinolone moxifloxacin was ≤0.125 to 2 μg/ml, and BBCs of 73% of biofilms could be considered to indicate susceptibility by the planktonic breakpoints for this drug.

The activity of sodium metabisulfite, a commonly encountered preservative and antioxidant in intravenously administered pharmaceuticals, was tested against staphylococcal biofilms using an in vitro model of biofilm formation (64). Sodium metabisulfite (0.72 mg/ml) caused only a 1.4 $\log_{10}$ drop in *S. lugdunensis* viable biofilm cell counts following 24-hour treatment of established biofilms. However, the same concentration of sodium metabisulfite prevented *S. lugdunensis* biofilm formation in an in vitro microtiter plate biofilm assay, suggesting that sodium metabisulfite may be effective at preventing, but not treating, *S. lugdunensis* biofilms.

Since subinhibitory concentrations of various antimicrobial agents enhance or impair biofilm formation by *S. epidermidis* (49, 146), we performed similar studies using a microtiter plate biofilm formation assay to define the effects of 10 antistaphylococcal antimicrobials at subinhibitory concentrations on *S. lugdunensis* biofilms (67). Tetracycline, which enhances *S. epidermidis* biofilm formation (146), exerted a negative effect on biofilm formation by 93% of the *S. lugdunensis* isolates tested. In contrast, the β-lactam nafcillin significantly increased biofilm formation by 93% of the organisms. Considering the widespread susceptibility of *S. lugdunensis* strains to β-lactam agents, which makes these drugs preferred options for treating *S. lugdunensis* infections, this result is concerning and deserving of further investigation with in vivo studies. Linezolid also caused a decrease in biofilm formation by 80% of the isolates. The effects of several of the other antimicrobial agents varied among strains, although cefazolin, daptomycin, and rifampin did not substantially affect biofilm formation by most of the isolates.

Cadmium Resistance

Widespread resistance to cadmium and arsenate was reported soon after the description of *S. lugdunensis* (60). In a collection of 35 *S. lugdunensis* strains from different European cities, 20 were found to carry plasmids that conferred resistance to cadmium at concentrations of ≥125 μg/ml (143). A

3.2-kb plasmid called pLUG10 is the most frequently occurring plasmid in cadmium-resistant *S. lugdunensis* strains (28, 143). In *S. aureus*, the plasmid pOX6 carries a cadmium resistance gene, *cadB*, which is hypothesized to encode a membrane-associated cadmium-binding protein (137), in association with *cadX*, which encodes a putative transcriptional activator (28). Probes generated from the *S. aureus cadB* gene hybridized to pLUG10 DNA in Southern blot analyses, suggesting that cadmium resistance mechanisms were similar in these two species (143). Subsequent sequence analysis of pLUG10 revealed that the 3,117-base-pair plasmid contains two open reading frames with predicted amino acid sequences that share high degrees of identity with CadB and CadX from pOX6 (28). Inactivation of either *cadB* or *cadX* in pLUG10 decreases bacterial resistance to cadmium, indicating that both gene products are necessary for full expression of cadmium resistance (28). When transformed into *S. aureus* strain RN4220, pLUG10 replicates and confers resistance to cadmium at levels commensurate with those when the plasmid is present in *S. lugdunensis* (28). Interestingly, despite the regions of homologous cadmium resistance between the two plasmids, pLUG10 is a member of the plasmid pT181 family (127) and pOX6 belongs to the distinct family of pC194 plasmids.

The *S. aureus* plasmid pRW001 also carries a cadmium resistance cassette composed of two genes, *cadD* and *cadX** (41). The predicted CadD protein is 84% identical to CadB from pLUG10, and CadX* represents a truncated peptide that is 86% identical to the positive regulatory protein CadX from pLUG10. The cadmium MIC for *S. aureus* carrying pRW001 alone was 20 μg/ml, but introduction of *cadX* from pLUG10 on a second plasmid was found to increase the cadmium MIC to >150 μg/ml, indicating that full-length *cadX* complemented the nonfunctional *cadX** found on pRW001 (41). The *cadD-cadX** resistance determinant of pRW001 is located on a 3.9-kb DNA fragment flanked by direct repeats of the insertion sequence element IS*257*, leading to the hypothesis that this genetic element passed from pLUG10 to pRW001 through a recombination event that resulted in truncation of the C-terminal region of *cadX* (41).

Although the clinical relevance of cadmium resistance in *S. lugdunensis* is unclear, in *S. aureus*, genes for cadmium resistance and β-lactamase have been found together on plasmids (114, 128). In particular, genes related to *cadD* and *cadX* of plasmid pRW001 are present in several *S. aureus* β-lactamase resistance plasmids that demonstrate cadmium resistance (114). In contrast to the case for pRW001, however, this *cadX* homologue is present as a full-length gene and IS*257* sequence elements are absent, suggesting that the recently described family of plasmids acquired the cadmium resistance markers through an alternate evolutionary pathway (114).

PATHOGENESIS AND VIRULENCE FACTORS

Toxins, Hemolysins, and the *agr* Locus

Efforts to identify toxins in *S. lugdunensis* similar to those produced by *S. aureus*, including enterotoxins A to E, toxic shock syndrome toxin 1, and exfoliatin A, have been unsuccessful (60, 133), despite a case of *S. lugdunensis* toxic shock syndrome having been reported (133).

Hemolytic activity due to α-, β-, or γ-hemolysins has not been detected in *S. lugdunensis* (185). Further, probes for *S. aureus* hemolysins did not hybridize to *S. lugdunensis* genomic DNA in Southern blotting experiments (185). Most *S. lugdunensis* isolates produce a heat-stable δ-like hemolysin that shares phenotypic properties with the *S. aureus* delta-toxin, which is encoded by the *hld* gene (185). In *S. aureus*, *hld* is part of the *agr* locus; hybridization experiments have demonstrated the presence of a sequence similar to *hld* in *S. lugdunensis* (185).

***agr* locus.** The staphylococcal *agr* (accessory gene regulator) locus is a quorum-sensing system that acts as a global regulator of virulence factors, particularly secreted exoproteins, including enterotoxins, hemolysins, and numerous host protein-modifying enzymes (126). Regions of homology to *S. aureus agr* have been identified by PCR or Southern blotting in a large number staphylococcal species, including *S. lugdunensis* (46, 48). *agr* loci from *S. lugdunensis*, *S. epidermidis*, *S. saprophyticus*, and the coagulase-positive veterinary pathogen *S. intermedius*, have been characterized in detail (Table 4) (153, 175, 184, 188). The locus is comprised of two divergent transcripts, RNAII and RNAIII, which are expressed from promoters P2 and P3, respectively (126). RNAII encodes four genes, *agrB*, *agrD*, *agrC*, and *agrA*, whose protein products are the machinery of a two-component signal transduction system (126). The propeptide AgrD is processed into a small peptide that serves as the two-component system autoinducer by the membrane protein AgrB. AgrB secretes the autoinducer peptide (AIP), which in turn binds to AgrC, the transmembrane histidine kinase signal transduction component of the two-component system. Upon AIP binding, AgrC phosphorylates the DNA-binding protein AgrA. Extracellular accumulation of AIP to a critical quorum threshold leads to AgrA activation of expression of promoters P2 and P3. In the *S. aureus agr* locus, promoter P3 directs transcription of a 517-nucleotide transcript called RNAIII, which acts as an intracellular effector to upregulate transcription of extracellular protein genes and downregulate that of surface protein genes, and contains the *hld* gene, encoding the 26-amino-acid delta-toxin (126). With the exception of the nonhemolytic *S. saprophyticus* and *S. lugdunensis* (discussed below), the *hld* locus is located within the RNAIII transcription unit (153, 175, 184, 188).

The *S. lugdunensis agr* locus is an actively transcribed genomic region that was initially identified by its homology to *S. aureus* RNAIII in *S. lugdunensis* isolates demonstrating synergistic hemolytic activity (184). Sequence analysis of the *S. lugdunensis agr* gene shows it to be ~63% identical to the *S. aureus agr* locus, with a similar genomic organization, including promoters P2 and P3, *agr-rna*III, a highly conserved intergenic region, and open reading frames matching *agrB*, *agrD*, *agrC*, and *agrA* (184) (GenBank accession no. AF173933). Despite the synergistic hemolytic phenotype frequently associated with *S. lugdunensis* isolates, which was expected to be mediated by a δ-hemolysin homologue, no open reading frames with similarity to the *S. aureus hld* gene are located in the *S. lugdunensis* sequence for RNAIII. Further, in contrast to the observation that RNAIII sequences of other CNS are highly homologous with *S. aureus* RNAIII (179), the homology between the RNAIIIs of *S. aureus* and *S. lugdunensis* is rather low, with the

TABLE 4. *Staphylococcus lugdunensis* virulence factors

Virulence factor	Gene name	Description	Homologue(s) in other species	Reference(s)
Accessory gene regulator system (*agr*) and RNAIII	*agr* locus	Quorum-sensing system that acts as a global regulator of virulence factors	*S. aureus*, *S. epidermidis*, *S. saprophyticus*, *S. intermedius agr* locus	11, 46, 48, 126, 153, 175, 184, 188
SLUSH-A, SLUSH-B, SLUSH-C hemolytic peptides	*slush* locus	Hemolytic peptides with delta-toxin-like activity	*S. haemolyticus*, *S. cohnii* subsp. *cohnii*, *S. cohnii* subsp. *urealyticum*, *S. caprae*, *S. xylosus slush*-like sequences	45, 46, 100, 176
OatA peptidoglycan *O*-acetyltransferase	*oatA*	Membrane-bound enzyme that confers resistance to lysozyme by O-acetylating cell wall *N*-acetylmuramic acid and preventing lysozyme binding	*S. aureus oatA*	12, 13
vWf-binding protein vWbl	*vwbl*	Mediates interaction with vWf-expressing host cells, including platelets and endothelial cells; contains an RGD motif	No sequence similarity with known proteins	125
Fibrinogen-binding protein Fbl	*fbl*	Facilitates binding to fibrinogen in the host, member of the Sdr (SD repeat) family of *Staphylococcus* surface proteins	*S. aureus* clumping factor A (*clfA*)	120, 124
Biofilm formation				
PNAG/PIA extracellular matrix synthesis genes	*icaADBC* locus	Biosynthetic enzymes of a β-1,6-linked *N*-acetylglucosamine polysaccharide polymer commonly found in the extracellular matrix of staphylococcal biofilms	*S. aureus*, *S. epidermidis*, *S. caprae icaADBC*	30, 66
Biofilm extracellular matrix protein(s)	Unknown	Components of the biofilm extracellular matrix	Unknown	27, 66, 94, 152

highest regions of conservation occurring at the 5′ and 3′ ends (11). Nonetheless, full-length *S. lugdunensis* RNAIII was shown to be transcribed at a level equivalent to its native background when heterologously expressed in *S. aureus* from its endogenous promoter (11). This expression pattern was shown to be *agr* dependent, and *S. lugdunensis* RNAIII was capable of transcriptional and phenotypic complementation of several *agr*-regulated exoproteins in an *agr*-null *S. aureus* strain (11). These studies indicate that the absence of the *hld* gene does not impair the ability of *S. lugdunensis* RNAIII to function as a regulatory molecule.

***slush* locus.** Following the finding that the *S. lugdunensis* δ-like hemolysin is not encoded within the *agr* locus (184), Donvito et al. purified three small exoproteins that exhibited synergistic hemolytic activity with *S. aureus* on sheep blood agar (45). Sequencing of the peptide fragments following trypsin digestion generated highly related 10- or 23-amino-acid sequences for each of the three peptides. A degenerate DNA probe based on the amino acid sequence of one of the tryptic fragments was hybridized to *S. lugdunensis* restriction enzyme-digested genomic DNA, and the corresponding hybridizing fragment was subsequently cloned and sequenced in order to determine the genetic locus responsible the synergistic hemolytic peptides. The locus, denoted *slush* for *S. lugdunensis* synergistic hemolysin, contains three open reading frames encoding 43-amino-acid peptides of high similarity, called SLUSH-A, SLUSH-B, and SLUSH-C, which are identical to the sequenced hemolytic peptide fragments (Table 4). An additional open reading frame, ORF-X, encoding a predicted 24-amino-acid peptide of unknown function and lacking sequence similarity to the *slush* open reading frames, lies upstream of *slush*-A. The *slush* locus was detected in 14/14 *S. lugdunensis* strains by Southern blotting, indicating genetic conservation of the locus among strains of this species (46). The same probe also hybridized to DNAs from 4/4 strains of *S. haemolyticus*, *S. cohnii* subsp. *cohnii*, and *S. cohnii* subsp. *urealyticum* and to those of some strains of *S. caprae* (3/4) and *S. xylosus* (1/4) (46). No sequences bound to the *slush* probe when hybridized against *S. aureus* and 11 other CNS species or subspecies (46). Peptides with high degrees of identity to SLUSH-A (~45 to 65%) are found in the genomes of other pathogenic CNS species, *S. saprophyticus* and *S. haemolyticus* (100, 176). Transcriptional regulation of the *slush* locus may be under control of the *agr* locus (46).

Resistance to Lysozyme

Lysozyme is an essential enzymatic component of the human innate immune system that defends against microbial infection. As reported in the species description, *S. lugdunensis* is resistant to 400 mg/ml lysozyme (68). Several other pathogenic staphylococci, including *S. aureus*, display resistance to high concentrations of lysozyme, whereas nonpathogenic staphylococci remain sensitive or display hypersensitive reactions (12). In *S. aureus*, lysozyme resistance is mediated by expression of a membrane-bound peptidoglycan *O*-acetyltransferase (OatA), which O acetylates cell wall *N*-acetylmuramic acid, preventing binding of lysozyme (13). *S. lugdunensis* possesses an *oatA* homologue in its genome and O-acetylated peptidoglycan in its cell wall (Table 4), indicating that the mechanism of lysozyme resistance in *S. lugdunensis* is likely the same as that in *S. aureus* (12).

Experimental Animal Studies

Lambe et al. tested the ability of six strains of *S. lugdunensis* to induce abscess formation in a mouse model of foreign-body infection (102). Pieces of silicone rubber catheter preadhered with each test strain were subcutaneously implanted in mice that subsequently received a subcutaneous injection with the test strain. After 7 days, the six *S. lugdunensis* strains collectively induced abscess formation in 76% of mice. *S. lugdunensis* was cultured from 97% of the explanted foreign bodies and/or the surrounding tissues. The results obtained with *S. lugdunensis* (76% ± 19% abscess formation) did not statistically vary from the collective results obtained from nine *S. epidermidis* strains (91% ± 13% abscess formation) in the same model, suggesting that the ability of *S. lugdunensis* to infect foreign bodies is similar to that of *S. epidermidis*.

To further investigate the relationship of the foreign body to *S. lugdunensis* virulence, Ferguson et al. used the same mouse model described above but compared abscess formation with and without the presence of the foreign body (56). Abscess formation and positive culture of the surrounding tissues were statistically higher when a foreign body was present for 4/5 *S. lugdunensis* strains tested. Similar results were obtained with 3/5 *S. epidermidis* strains examined. *S. epidermidis* induced abscess formation in the absence of a foreign body at a rate of 11 to 88%, whereas abscess formation in the absence of a foreign body occurred in 8 to 46% of infections induced by the five *S. lugdunensis* strains, attesting to the ability of *S. lugdunensis* to cause diseases on par with those of other pathogenic CNS. Virulence was enhanced with most tested strains when a foreign body was involved, suggesting that biofilm formation on implanted foreign devices is a virulence mechanism used by *S. lugdunensis*.

The pathogenicity of a single *S. lugdunensis* strain was also tested in a murine model of implant-associated peritoneal infection (151). Although the strain was essentially unable to adhere to the surface of the implant material in vitro, it was found to persist in the peritoneums of normal or neutropenic mice with peritoneal implants at statistically higher numbers than in normal mice without implants. As observed with two strains of *S. epidermidis* and single strains of *S. haemolyticus* and *S. scheiferi*, high numbers of *S. lugdunensis* organisms disseminated to the liver and kidneys in neutropenic mice with implants, further confirming the generally virulent nature of *S. lugdunensis*.

Adherence Proteins

The ability of *S. lugdunensis* to cause endocarditis and foreign-body-associated infections suggests that the organism is proficient at interacting with host tissues and proteins that may coat foreign surfaces following implantation. Paulsson et al. undertook an investigation to identify cell surface factors of *S. lugdunensis* that facilitate binding to proteins commonly encountered in host tissues (135). Of the soluble proteins tested, *S. lugdunensis* strains exhibited the highest percentage of binding to purified collagen types I and IV and immunoglobulin G, although less than 40% of the total protein was bound in each case (135). *S. lugdunensis* strains bound fibrinogen, laminin, vitronectin, fibronectin, thrombospondin, and plasminogen at lower levels (~8 to 19% bound protein). Strains variably bound to immobilized forms of collagen type I, fibrinogen, and vitronectin. Primers designed to anneal to the *S. aureus* fibronectin-binding protein gene (*fbn*) were used to successfully amplify products of the expected size, based on the *S. aureus fbn* sequence, in three clinical isolates of *S. lugdunensis*, thereby suggesting the genomic presence of a fibronectin-binding protein gene similar to that found in *S. aureus* (119).

vWf-binding protein. A protein that specifically binds von Willebrand factor (vWf) was identified from the affinity selection of a *S. lugdunensis* phage display library against vWf (Table 4) (125). vWf is a blood plasma glycoprotein produced by platelets and endothelial cells that is involved in several facets of coagulation, including binding to platelets and subendothelial collagen following vascular injury and stabilizing factor VIII of the clotting cascade. The *vwbl* gene, found in all clinical isolates tested, encodes the 2,060-amino-acid *S. lugdunensis* vWf-binding protein (vWbl). The protein sequence contains a predicted N-terminal signal peptide that, upon cleavage, results in a 226-kilodalton, 2,013-amino-acid mature protein (125). The 1,255 amino acids following the signal peptide, termed the A region, contain an arginine-glycine-asparagine (RGD) motif. RGD motifs are most often found in integrin-binding proteins, although the physiological relevance of the motif in this protein is unknown. The A region is followed by a series of 10 67-amino-acid repeats that are similar to one another and house the minimal vWf-binding domain of the protein. The C-terminal portion of vWbl likely anchors the protein in the cell membrane. Although *S. aureus* also possesses a vWf-binding protein (14), vWbl shares no similarity with any other known proteins (125). Interestingly, binding of vWbl to recombinant vWf could be inhibited by the *S. aureus* vWf-binding protein (125), suggesting that both proteins interact with vWf at the same site.

Fibrinogen-binding protein. Two concurrent reports described and characterized a fibrinogen-binding protein called Fbl in *S. lugdunensis* (Table 4) (120, 124). Staphylococcal binding to fibrinogen, the precursor molecule of fibrin, is well documented (62). Fbl is an 881-amino-acid protein encoded by *fbl*, which was found in all 30 *S. lugdunensis* strains screened (120, 124). The full-length polypeptide contains an N-terminal signal sequence followed by the N1, N2, and N3 domains that

share significant homology (about 60% identity) with *S. aureus* clumping factor A (ClfA) (120, 124). The fibrinogen-binding region is located within the N2 and N3 domains between residues 40 and 534 (120). Fbl also contains a repetitive SD repeat region between the N3 domain and the C-terminal cell wall anchoring sequence, indicating that Fbl belongs to the large Sdr (SD repeat) family of structurally related staphylococcal surface-associated proteins (62). *S. lugdunensis* Fbl, whether recombinantly purified from *Escherichia coli* (124) or expressed on the cell surface of *Lactococcus lactis* (120), specifically binds fibrinogen, and this interaction can be disrupted with antibodies raised against *S. aureus* ClfA, confirming the high degree of similarity between ClfA and Fbl and the importance of Fbl in mediating *S. lugdunensis* binding to fibrinogen. Further, Fbl and ClfA interact with the same general region of fibrinogen, although ClfA binds fibrinogen with a 10-fold-greater affinity than Fbl (120).

Taken together, these studies provide evidence that *S. lugdunensis* possesses surface-associated proteins that enable bacterial adherence to a variety of host cells and tissues, as well as foreign body surfaces, a critical step in the process of staphylococcal biofilm formation (75). The ability of *S. lugdunensis* to bind fibrinogen and vWf may contribute to this organism's success in causing endocarditis.

Biofilm Formation

Biofilm formation by CNS, referred to as "slime production" in early reports, has long been associated with virulence (31), although it is now understood that commensal or environmental isolates can also form biofilm. Adherence capabilities of CNS and *S. aureus* can be quickly and easily assessed in the laboratory by evaluating whether organisms produce a stainable film on the walls of the growth chamber following incubation (31, 32). Initial studies revealed "slime production" on polystyrene conical tubes by 8/31 *S. lugdunensis* colonizing, infectious, or environmental isolates (60) and on glass tubes by only 4/38 *S. lugdunensis* clinical isolates (80). Despite the relatively low frequency of in vitro biofilm formation originally observed in these two collections of organisms, these studies indicated that some *S. lugdunensis* isolates have the potential to adhere to inert surfaces. We confirmed that most organisms in a collection of clinical isolates form in vitro biofilm on polystyrene surfaces (66). Scanning electron microscopy of a 24-h biofilm formed by an *S. lugdunensis* folliculitis isolate on a silicone elastomer surface revealed a complex architecture of cells that appeared to be embedded in an extracellular substance (Fig. 2A). When these data are coupled with the known types of infections caused by *S. lugdunensis* and the knowledge that host surface adherence proteins are present in *S. lugdunensis*, it is reasonable to propose that, like for most other pathogenic staphylococci, biofilm formation is one of the virulence mechanisms employed by this organism (Table 4).

Staphylococcal biofilm formation, characterized in detail for *S. epidermidis* and *S. aureus*, proceeds through an ordered series of events in which cells first attach to a surface and begin to form layers as they replicate and accumulate, followed by the production of extracellular matrix components that lead to intercellular adhesion (150). A large number of *S. aureus* and *S. epidermidis* adherence proteins mediate primary surface attachment, which is critical to biofilm formation (150). Once established, the elaboration of a polymeric matrix, often composed of polysaccharides, ensues. The matrix serves to connect cells within the structured architecture of the biofilm, as well as to provide protection from harsh conditions encountered in

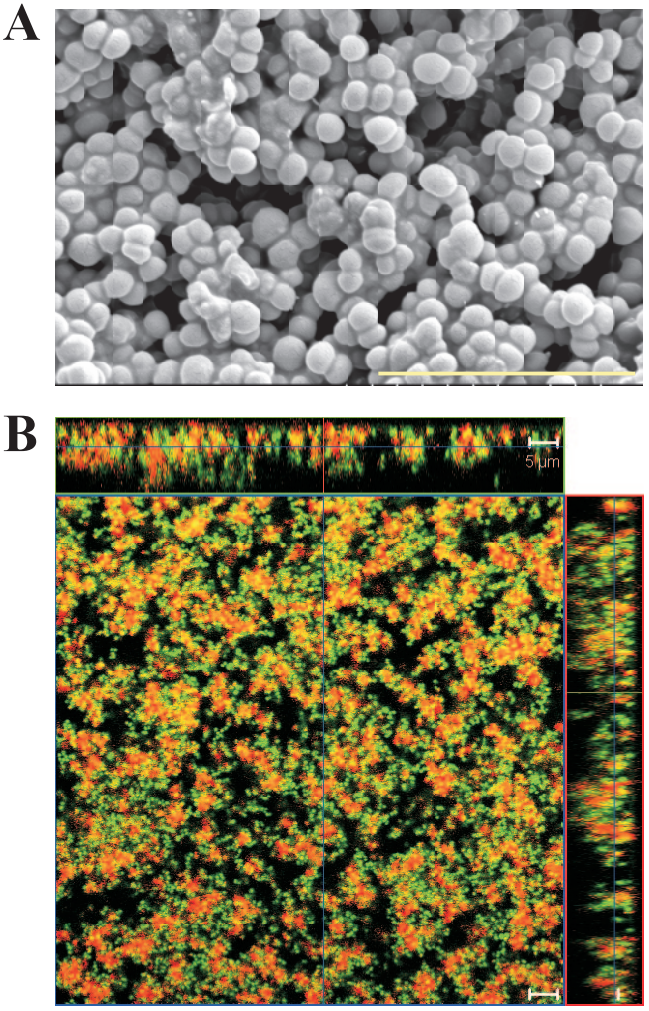

FIG. 2. Microscopic visualization of *S. lugdunensis* biofilms. (A) Scanning electron micrograph (magnification, ×11,000) of *S. lugdunensis* IDRL-2640 biofilm formed on a silicone elastomer disk (Bentec Medical, Woodland, CA) after 24 h. Nonadherent cells were rinsed from the disk following incubation, and the disk was placed in Trumps fixative (4% formaldehyde and 1% glutaraldehyde in phosphate buffer, pH 7.3). Images were acquired on a Hitachi S-4700 instrument (Hitachi Ltd., Tokyo, Japan) by cold-field emission microscopy following critical-point drying and gold-palladium sputter coating. Bar, 5 μm. (B) Confocal scanning laser microscopy image of an *S. lugdunensis* IDRL-2640 biofilm grown in a chambered coverglass well (Lab-Tek II; Nalge Nunc International, Rochester, NY) for 24 h. Cells (green) were stained with the nucleic acid stain Syto-9 (Molecular Probes, Eugene, OR), and extracellular proteins (red) were visualized with Sypro Ruby (Molecular Probes). Fluorophores were excited with an argon laser at 458 nm (Sypro Ruby) and 488 nm (Syto-9). Fluorescence was detected from Sypro Ruby with an LP 650 filter and from Syto-9 with a BP 505-530 filter. Images were collected on an LSM410 unit equipped with an Axiovert 100 M inverted microscope using a Plan-Apochromat 100×/1.4 NA oil immersion objective (Carl Zeiss, Inc., Thornwood, NY). Bar, 5 μm.

the environment, including interfering with attempts of the host immune system to clear the infection.

Soon after the description of *S. lugdunensis*, Lambe et al. showed that a glycocalyx, described as a negatively charged polysaccharide matrix surrounding bacterial microcolonies, could be visualized by transmission electron microscopy when cells were stained with ruthenium red, a stain with affinity for polyanionic structures (102, 103). Various amounts of glycocalyx were produced by different *S. lugdunensis* strains (103). That group further showed that a carbohydrate-containing glycocalyx purified from *S. lugdunensis* strains effectively stimulated monocyte prostaglandin E_2 production, which leads to the inhibition of T-cell proliferation, thus having an immunomodulatory effect on the immune system (173). A later study verified that purified glycocalyx from two distinct *S. lugdunensis* strains stimulated murine peritoneal macrophages to synthesize prostaglandin E_2 and the proinflammatory cytokine interleukin-1. In addition, glycocalyx modulated macrophage production of tumor necrosis factor alpha and nitric oxide (174). This work provides mechanistic evidence that a polymeric carbohydrate-containing material produced by *S. lugdunensis* protects surface-attached cells from host immune defenses by impeding the normal functions of monocytes and macrophages.

***ica* locus.** A polysaccharide polymer of β-1,6-linked *N*-acetylglucosamine residues (PNAG), also referred to as the polysaccharide intercellular adhesin (PIA), is the most well-characterized component comprising the staphylococcal biofilm matrix (75, 129). The genes of the *icaADBC* locus encode the biosynthetic machinery required to assemble (*icaAD*), export (*icaC*), and deacetylate (*icaB*) PNAG/PIA (75, 192). A negative regulatory protein gene, *icaR*, is located upstream and in the opposite direction of *icaA* (35). The genomic organization and the regulation of the *icaADBC* genes have been described in detail for *S. aureus* and *S. epidermidis* (129), and homologues have been detected in several other CNS species, including *S. lugdunensis* (40, 63). PCR amplification and sequencing of *ica* genes in *S. lugdunensis* were first reported by Sandoe and Longshaw in 2001 following characterization of biofilm formation by an isolate causing ventriculoperitoneal shunt infection (157); however, the authors did not submit the sequence to a public sequence repository. We subsequently attempted to amplify *icaA* from *S. lugdunensis* isolates causing prosthetic joint infection but were unable to do so with primers designed from conserved areas in the *S. aureus* and *S. epidermidis icaA* sequences, suggesting a marked difference in the sequence of the *S. lugdunensis ica* locus (63). We eventually amplified an *icaA* homologue using the same primers as Sandoe and Longshaw (157) and used a primer-walking strategy to acquire sequence for the entire region surrounding the *S. lugdunensis ica* locus (66). More recently, Chokr et al. reported PCR amplification of *icaA* and/or *icaD* in only 6/11 *S. lugdunensis* strains from implant-associated infections (30), although we showed that *icaADBC* genes were present in all 15 *S. lugdunensis* isolates that we tested (66). Similar to the case for other staphylococcal *ica* loci, the *S. lugdunensis icaADBC* homologues are 30 to 60% identical to their related genes in *S. aureus*, *S. epidermidis*, and *S. caprae* (Table 4). Unexpectedly, *icaR* was not detected in the genome of *S. lugdunensis*; rather, a novel open reading frame with putative glycosyl hydrolase activity and which shares a high degree of similarity to the biofilm-degrading enzyme dispersin B from *Actinobacillus* species was found upstream of *icaA*. The *S. lugdunensis ica* genes and the adjacent open reading frame span a region of 4.75 kilobases that is flanked on the 5′ and 3′ ends by homologues of the *yycJ* and *yycI* genes, respectively, from other staphylococci.

Composition of the biofilm matrix. Chokr et al. reported that of 11 *S. lugdunensis* isolates, only one *icaA*-positive strain that concomitantly formed biofilm was detected (30). They were unable to detect PIA in biofilm extracts from this strain using an anti-PIA antiserum. PIA was also not detected in static cultures of the remaining five *icaA*-positive, biofilm-negative *S. lugdunensis* strains in their collection. Two other organisms formed biofilm but lacked both PIA and the *icaA* locus, signifying that alternative mechanisms for biofilm formation exist in these strains. In subsequent studies, these investigators showed that biofilms formed by the two *ica*-negative *S. lugdunensis* strains contained proteins and extracellular teichoic acids composed of glycerol, glucose, and glucosamine but lacked prominent levels of PNAG (94, 152). Proteinase K and other proteases, but not the carbohydrate-degrading reagent sodium metaperiodate or the biofilm-degrading enzyme dispersin B (90), released preformed *ica*-negative *S. lugdunensis* biofilms (27, 94, 152), suggesting that protein components stabilize the PNAG-negative biofilms formed by these two strains (Table 4).

In our own studies with 15 *icaADBC*-positive *S. lugdunensis* clinical isolates that form in vitro biofilm to various degrees, we were surprised to find that none of the isolates produced detectable levels of PNAG in biofilms or static-phase cultures (66). Similar to the results described above for the reported *ica*-negative strains, treatment of *ica*-positive *S. lugdunensis* biofilms with proteinase K, trypsin, thermolysin, and chymotrypsin led to the overwhelming detachment of nearly all isolates (66). Visualization of the *S. lugdunensis* extracellular matrix by fluorescence confocal scanning laser microscopy revealed abundant amounts of extracellular protein (Fig. 2B). Despite the presence of an intact *icaADBC* locus in all isolates of *S. lugdunensis* that we examined, the extracellular matrix of in vitro biofilms formed by this species appears to be composed predominantly of proteins (Table 4).

Phenotypic responses of biofilm formation to changing environmental conditions. The presence of exogenous factors in the growth environment directly influences the staphylococcal biofilm formation phenotype (59). Such changes include accentuation of *S. epidermidis* and *S. aureus* biofilm formation in response to increasing glucose concentrations, heightened osmolarity, and ethanol (129). Like for other staphylococci, increasing concentrations of glucose stimulate *S. lugdunensis* biofilms. However, opposite to what is observed for other staphylococci, the presence of sodium chloride and ethanol in the growth medium prevents most *S. lugdunensis* isolates tested from adhering to polystyrene (66).

Intravenously administered catecholamine inotropes and heparin also enhance biofilm formation by *S. epidermidis* (112) and *S. aureus* (163). When *S. lugdunensis* isolates were grown in medium containing epinephrine, biofilm production decreased in 47% (7/15) of isolates (65). Dopamine decreased biofilm formation in some isolates but enhanced biofilm formation in the majority of the *S. lugdunensis* isolates. Dobutamine demonstrated the most pronounced effect on *S.*

lugdunensis biofilms by preventing adherence in 87% of isolates tested. The biofilm phenotype when bacteria were grown in the presence of heparin was identical to the results obtained with dobutamine, which is in direct contrast to the results previously reported for *S. aureus* (163). Further, treatment of preformed biofilms with concentrations of heparin used clinically to flush catheters resulted in biofilm detachment of 73% of *S. lugdunensis* isolates, suggesting a mechanism through which organisms colonizing and infecting intravascular catheter surfaces may metastasize to alternate sites in the host.

In nearly all environmental situations examined for biofilms formed by *S. lugdunensis* isolates thus far, the phenotypic response is opposite to what would be predicted based on prior studies with *S. aureus* or *S. epidermidis*. The phenotypic differences observed for *S. lugdunensis* biofilms under these conditions are likely due to the as-yet-uncharacterized mechanism of PNAG-independent, proteinaceous biofilm formation employed by these isolates.

CONCLUDING REMARKS

Although *S. lugdunensis* does not cause infection at the same frequency as *S. aureus* or *S. epidermidis*, its pathogenic potential should not be underestimated. In 20 years, the plethora of case reports published on *S. lugdunensis* (Table 1) reveal the significance of this organism as a pathogen in a large number of infections, including particularly virulent cases of endocarditis. The relative lack of genomic diversity and the prevalent susceptibility to numerous antimicrobial agents suggest that *S. lugdunensis* has evolved along a different path than the other pathogenic staphylococci. In particular, in comparison with what is known about other staphylococci, the substantial differences in *S. lugdunensis* biofilm formation phenotypes, the composition of the biofilm matrix, and the genomic organization of the *ica* locus serve as examples of the distinctive qualities that this organism has acquired during evolution. Further investigations of *S. lugdunensis* biofilm formation should yield additional insight into other aspects of the properties that contribute to this organism's enhanced virulence. In the present age of readily available genomic sequencing technology, we anticipate that any *S. lugdunensis* genome sequencing projects that may commence in the future will provide more clarity in understanding the exceptional traits that make this organism such a successful pathogen.

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