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The Pros & Cons of the CoNS:

An Update

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Disclosures:

- Currently involved in compensated research projects with Attostar LLC

Objectives:

- 1: Develop familiarity with current CoNS* species, and emerging disease associations
- 2: Examine why *S lugdunensis* is **special**
- 3: Consider why reporting CoNS by species may be clinically impactful

*Coagulase-negative Staphylococci

Guidepost:

- 1. *Staphylococcus*, in general
- 2. **CoNS**, specifically
  - Biofilm
  - Molecular Armamentarium
- 3. Laboratory Considerations
- 4. Antimicrobial Considerations

Staphylococcus en generale

Becker et al.

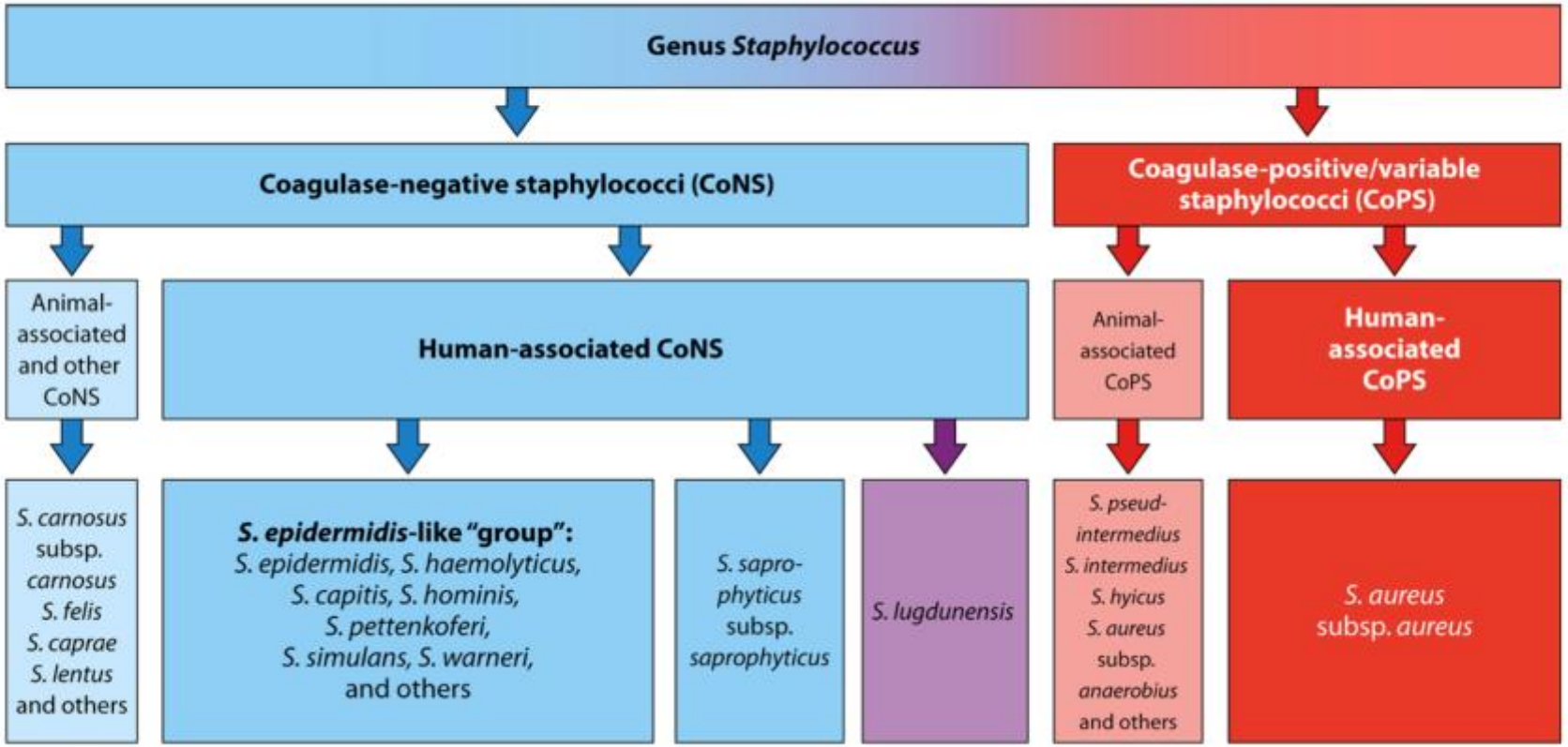

FIG 2 Clinical and epidemiological schema of staphylococcal species, based on the categorization of coagulase as a major virulence factor and its resulting impact on human health.

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Coagulase-Negative Staphylococci

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Are coagulase-negative staphylococci virulent?

Heilmann C[1], Ziebuhr W[2], Becker K[3].

Author information

Abstract

BACKGROUND: Progress in contemporary medicine is associated with an increasing number of immunocompromised individuals. In this vulnerable group, the underlying disease together with long-term hospitalization and the use of medical devices facilitate infections by opportunistic pathogens, of which coagulase-negative staphylococci (CoNS) represent a prime example.

OBJECTIVES: The diversity of CoNS with species- and strain-specific differences concerning virulence and clinical impact is highlighted. A focus is on the ability of CoNS to generate biofilms on biotic and abiotic surfaces, which enables skin and mucosa colonization as well as establishment of CoNS on indwelling foreign bodies.

SOURCES: Literature about the virulence of CoNS listed in PubMed was reviewed.

CONTENT: Most catheter-related and prosthetic joint infections as well as most other device-related infections are caused by CoNS, specifically by Staphylococcus epidermidis and Staphylococcus haemolyticus. A common theme of CoNS infections is a high antibiotic resistance rate, which often limits treatment options and contributes to the significant health and economic burden imposed by CoNS.

IMPLICATIONS: Breaching the skin barrier along with the insertion of medical devices offers CoNS opportunities to gain access to host tissues and to sustain there by forming biofilms on foreign body surfaces. Biofilms represent the perfect niche to protect CoNS from both the host immune response and the action of antibiotics. Their particular lifestyle, combined with conditions that facilitate host colonization and infection, has led to the growing impact of CoNS as pathogens. Moreover, CoNS may serve as hidden reservoirs for antibiotic resistance and virulence traits.

KEYWORDS: Biofilm; Catheter-related infection; Coagulase-negative staphylococci; Foreign body–related infection; Multiresistance; Pathogenicity; Staphylococcus epidermidis; Staphylococcus haemolyticus; Staphylococcus lugdunensis; Virulence

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

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

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

The CoNS

- CoNS are mostly skin microbiota
  - Skin is a very diverse microenvironment
    - A jungle warzone of intense competition
    - Survival depends on precisely tuned “niches”
  - Jungle = Humidity
- Beneficial commensals, or not?
  - Compete with *S aureus* in nares, and elsewhere

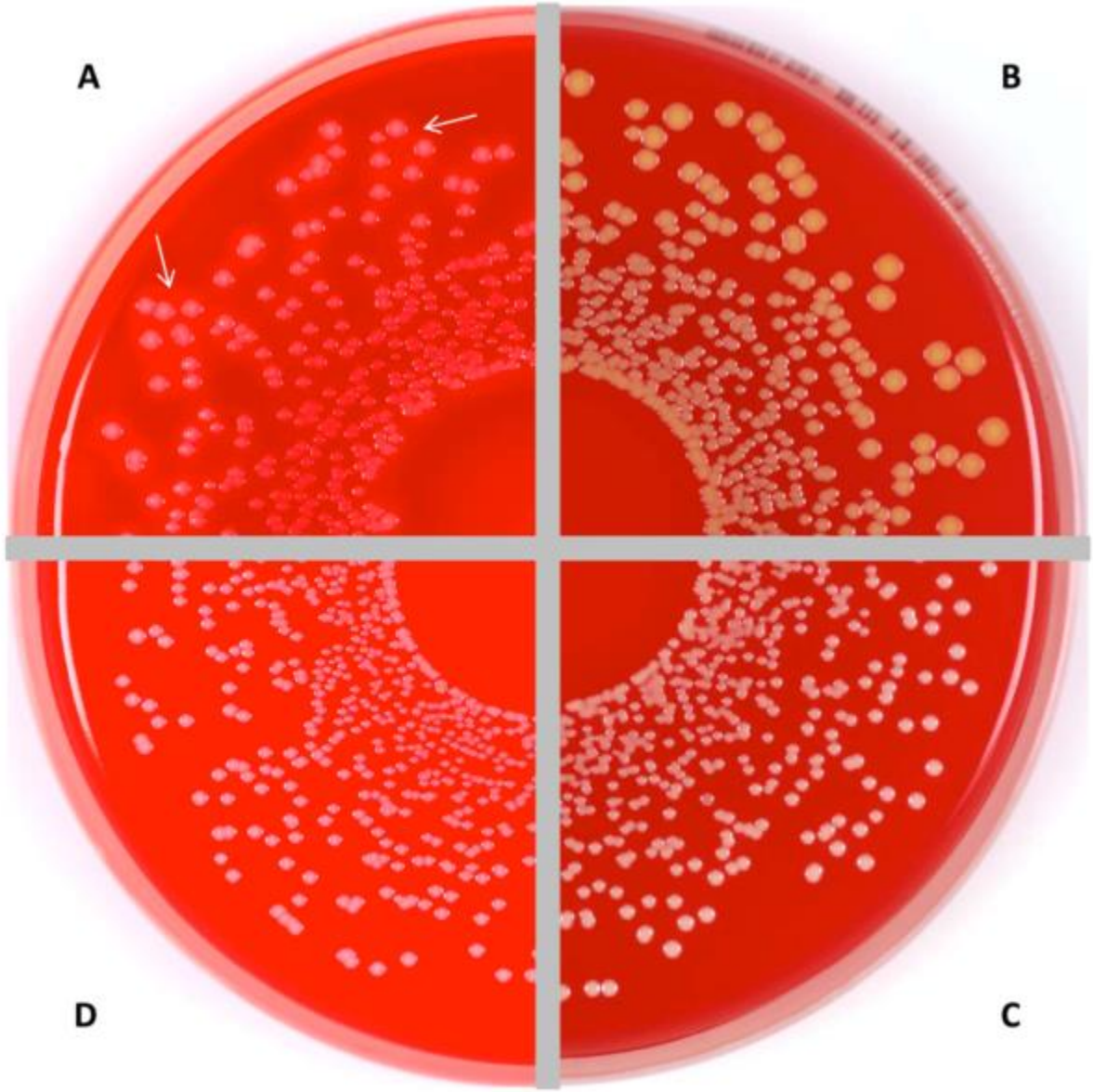


FIG 5 Sections of Columbia blood agar plates showing grayish, hemolytic colonies of *S. haemolyticus* (the color of this photograph was modified to enhance visibility of the weak hemolysis zones [arrows] surrounding the colonies, resulting in a nonnatural reddish tinge) (A); orange, nonhemolytic colonies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

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

CoNS species	Source(s)	SCC*mec* (sub)type(s)[a] [reference(s)]
S. capitis	Humans, dogs	I, IA, II, III, IV, IVa, V, NT
	pigs, sheep	631, 634)
S. warneri	Humans, dogs, pigs, fish food	IV, IV.1, IVb, IVE, NT (629, 632–634, 637)
S. xylosus	Cattle	III, XI[b] (474, 631)

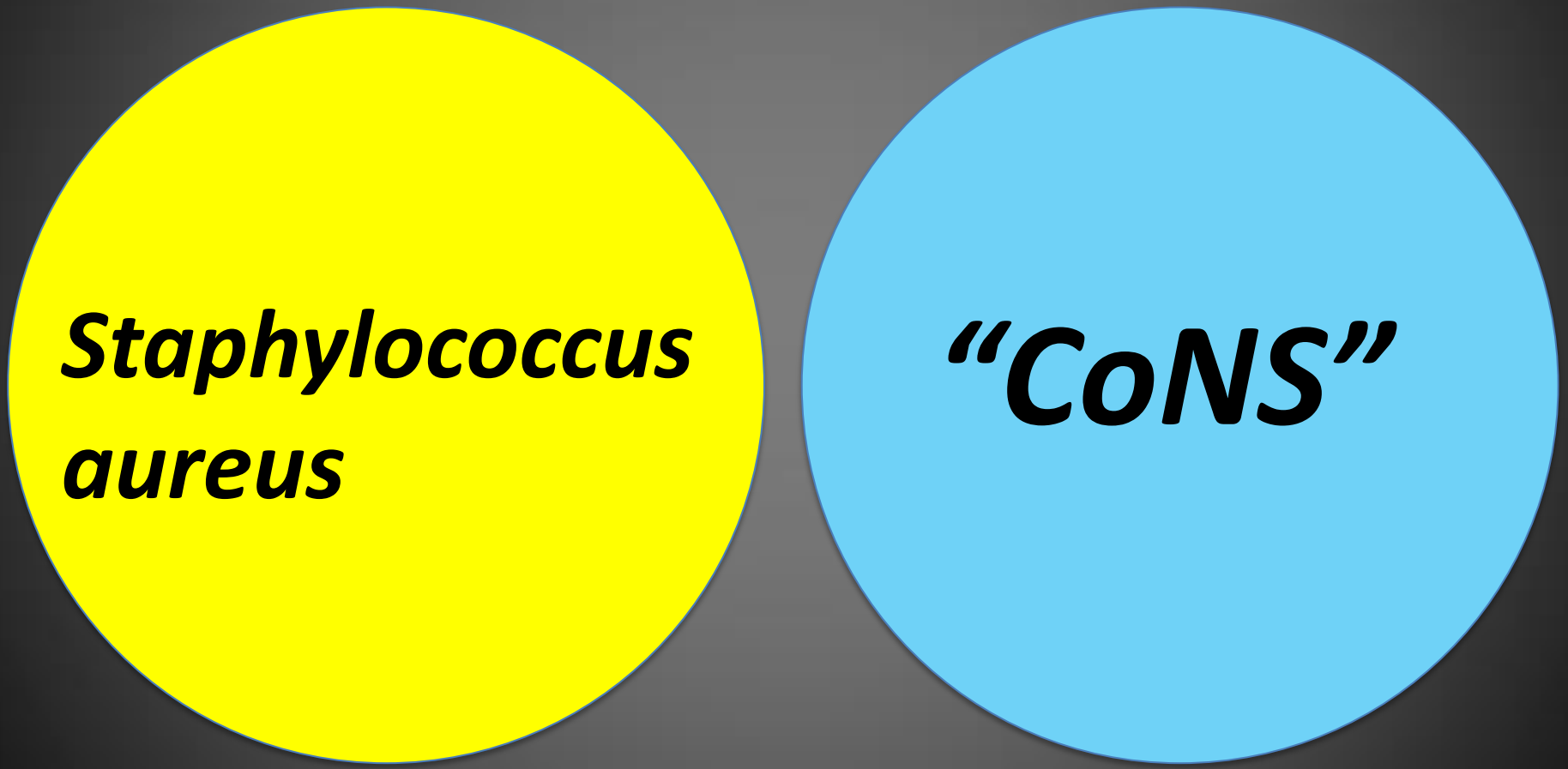
[a] NT, nontypeable and/or novel nondesignated types.
[b] Harbors the *mecC* gene or its allotype (*mecC1*).

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

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

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

The Duality Idea (1980s)

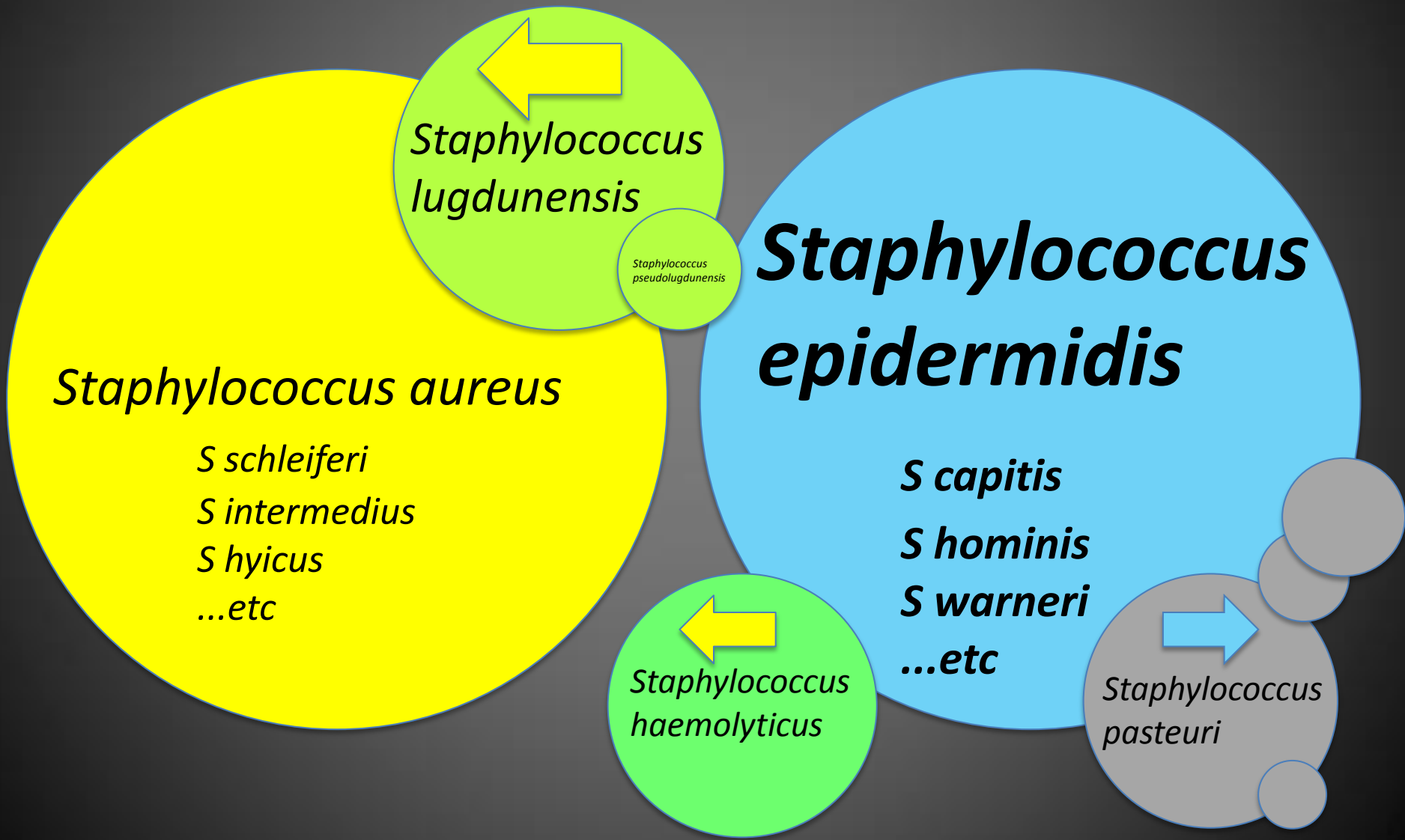


The Price of Dichotomy

- Possibly outdated concept of assigning relative value to the virulence potential between the two "groups"

- Based on epidemiology that is no longer relevant in a post-MALDI or NGS world
  - Disease associations will evolve
  - Mechanistic understanding of virulence will evolve
  - Epidemiology will assuredly evolve

The Duality Idea (2019)



Infection (2017) 45:179–186
DOI 10.1007/s15010-016-0945-4

ORIGINAL PAPER

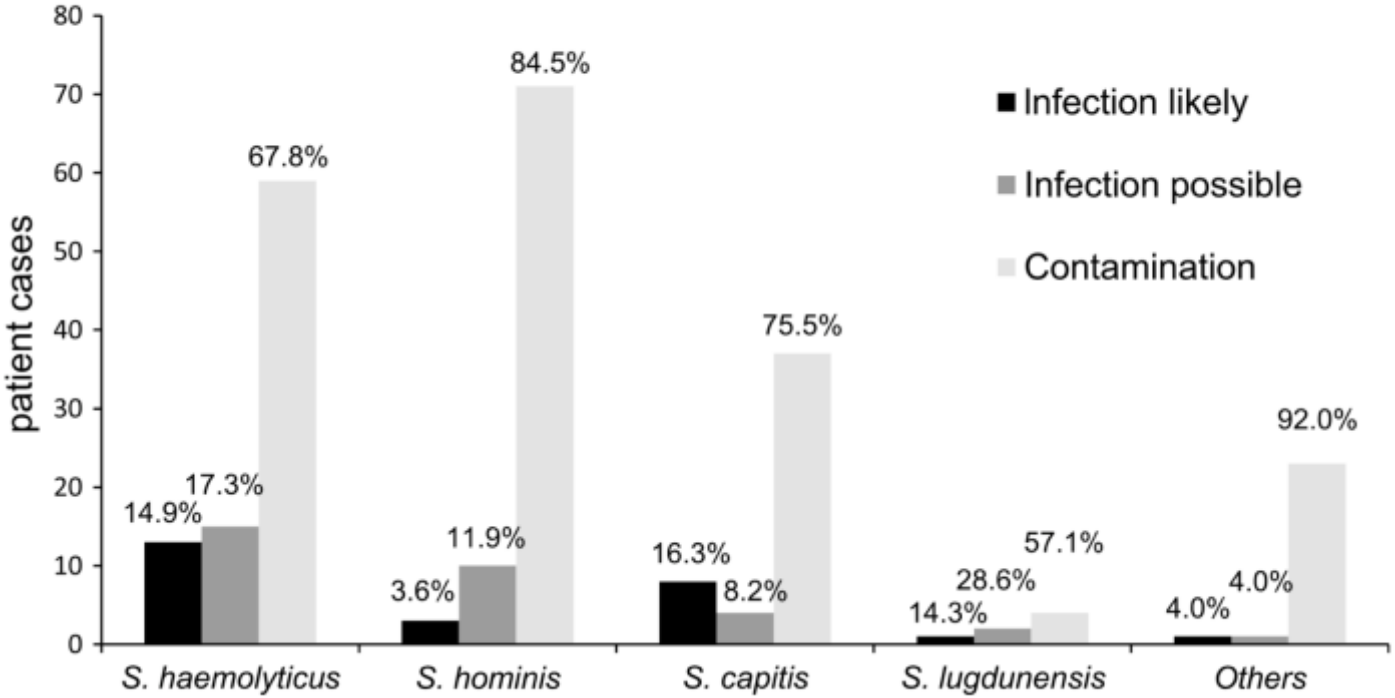


Fig. 2 Patient cases of infection (likely or possible) vs. contamination in all 252 NonSe-CoNS isolates which were include in our study, responsible for infection in "others", were *S. warneri* und *S. cohnii*

A Word on Coagulases:

Free Coagulase

- Prothrombin activation, and conversion of fibrinogen into fibrin

- CoNS:
  - *Staphylococcus pseudointermedius*
  - *Staphylococcus intermedius*
  - *Staphylococcus delphini*
  - *Staphylococcus hyicus*
  - *Staphylococcus lutrae*

Bound Coagulase

- "Clumping Factor"
  - A and B
- Converts fibrinogen into the fibrin directly
- *Staphylococcus aureus*

- CoNS: (different enzyme)
  - *Staphylococcus lugdunensis* (65%)
  - *Staphylococcus schleiferi*
  - *Staphylococcus sciuri*

What Makes a Virulent Staph?

- **Depends on a few factors:**
  - 1. Found in humans
  - 2. Capable of producing infection in humans
  - 3. Produces clinically apparent infection
  - 4. Virulence factors are produced in vitro

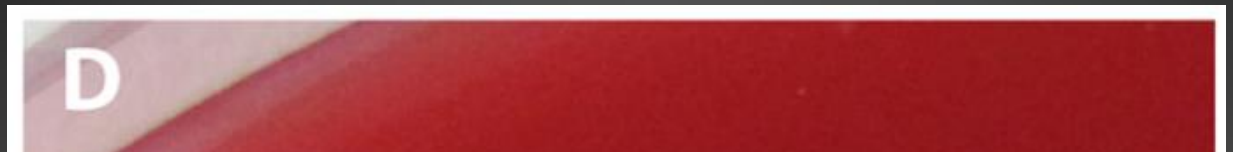


TABLE 2 Reports on staphylococcal SCVs recovered from human and animal clinical specimens since 2000

SCV-associated colonization, infection, or syndrome[a,b]	Species	Clinical details	Reference[c]
Circulatory system infections			
Pacemaker-related bloodstream infection	*S. aureus*	Recurrent (7 mo) bloodstream infection due to infected cardiac pacemaker electrode	34
Sepsis	*S. epidermidis*	Fatal case in a neutropenic patient suffering from acute myeloid leukemia despite catheter removal	19
Pacemaker-related bloodstream infection	*S. lugdunensis*	Recurrent (10 mo) bloodstream infection due to infected ventricular pacemaker lead	26
Bacteremia	*S. aureus*	Recurrent cardiac pacemaker-related bacteremia in a hemodialysis patient	201
Bacteremia, spinal process	*S. aureus*	MRSA-SCV with rifampin resistance and reduced linezolid susceptibility from a spinal aspirate; SCV phenotype as a result of permanent activation of the bacterial stringent response	149
Endocarditis	*S. aureus*	Isolation from blood from a child with subaortic ventricular septal defect	208
Bacteremia	*S. aureus*	No further clinical details	159
Prosthetic valve and pacemaker endocarditis with left ventricular assist device infection	*S. aureus*	Thymidine-dependent SCVs isolated from blood culture and left ventricular assist device infection	38

Kahl et al, CMR 2014

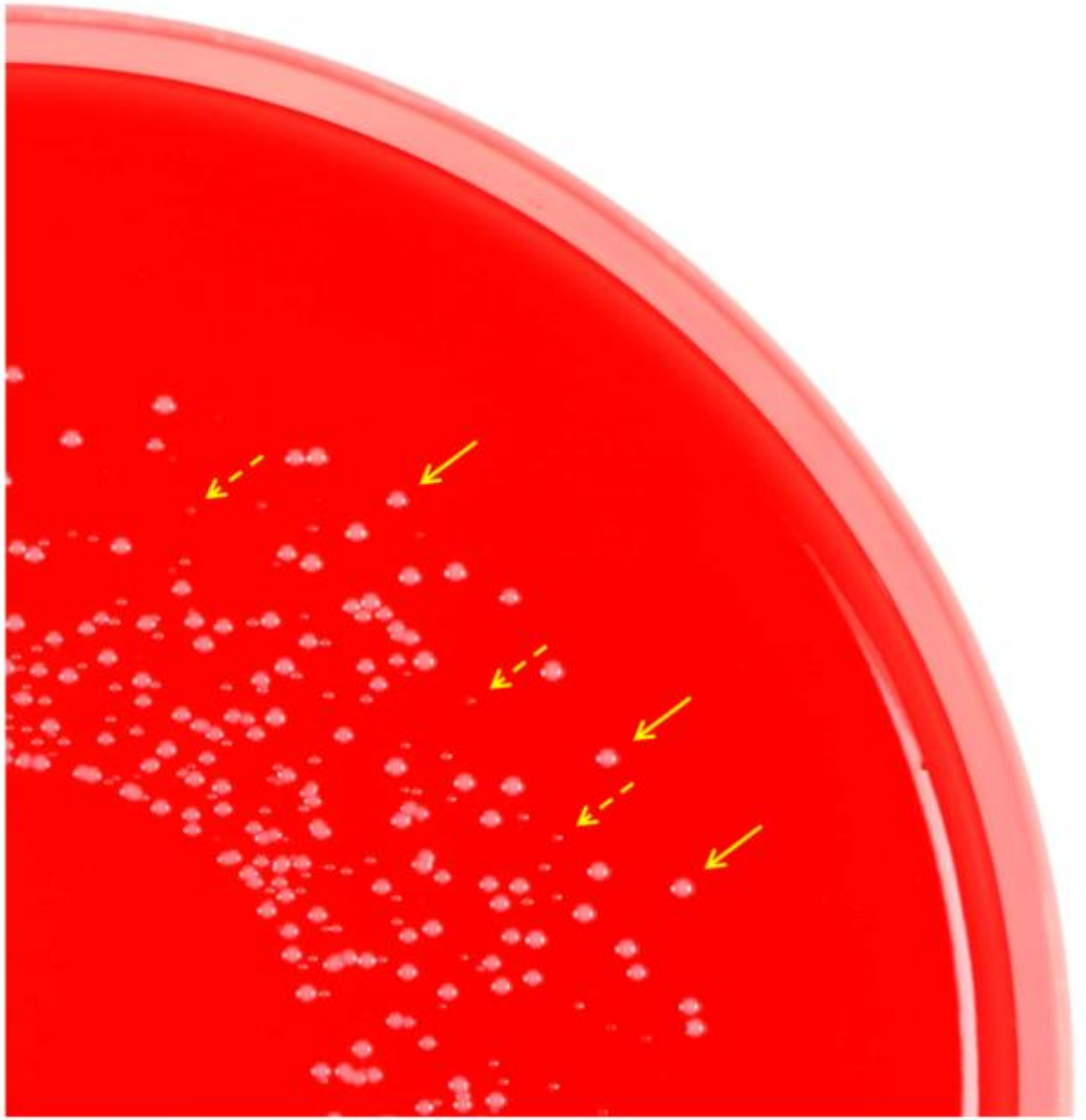


FIG 6 Columbia blood agar plate showing an isogenic *S. epidermidis* strain pair displaying both the normal (arrows) and SCV (dashed arrows) phenotypes. The normal phenotype (NP) on this plate was the result of a spontaneous reversion of the SCV back to the NP.

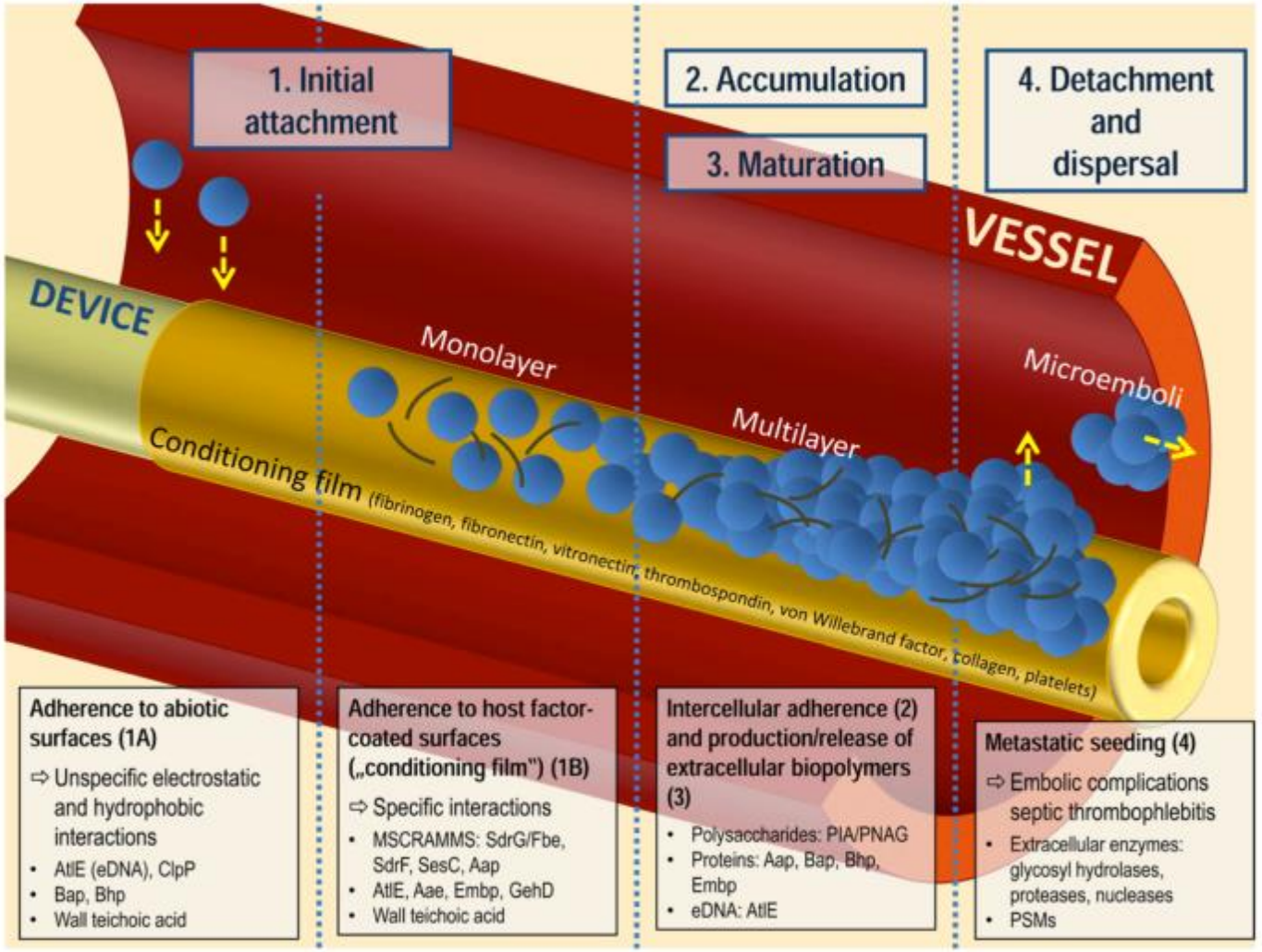


FIG 4 Pathogenesis of catheter-related infections and factors influencing biofilm genesis. The image shows the three-step process of biofilm formation on the surface of an intravascular catheter, with rapid initial adhesion and attachment of CoNS microorganisms to the polymer foreign body surface resulting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

The MALDI-TOF World

Implementation of Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry in Routine Clinical Laboratories Improves Identification of Coagulase-Negative Staphylococci and Reveals the Pathogenic Role of *Staphylococcus lugdunensis*

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Université de Strasbourg, Hôpitaux Universitaires de Strasbourg, Fédération de Médecine Translationnelle de Strasbourg, EA7290 Virulence Bactérienne Précoce, Strasbourg, France[a]; Laboratoire de Microbiologie, Hôpitaux Universitaires, Strasbourg, France[b]; Service des Maladies Infectieuses et Tropicales, Hôpitaux Universitaires, Strasbourg, France[c]

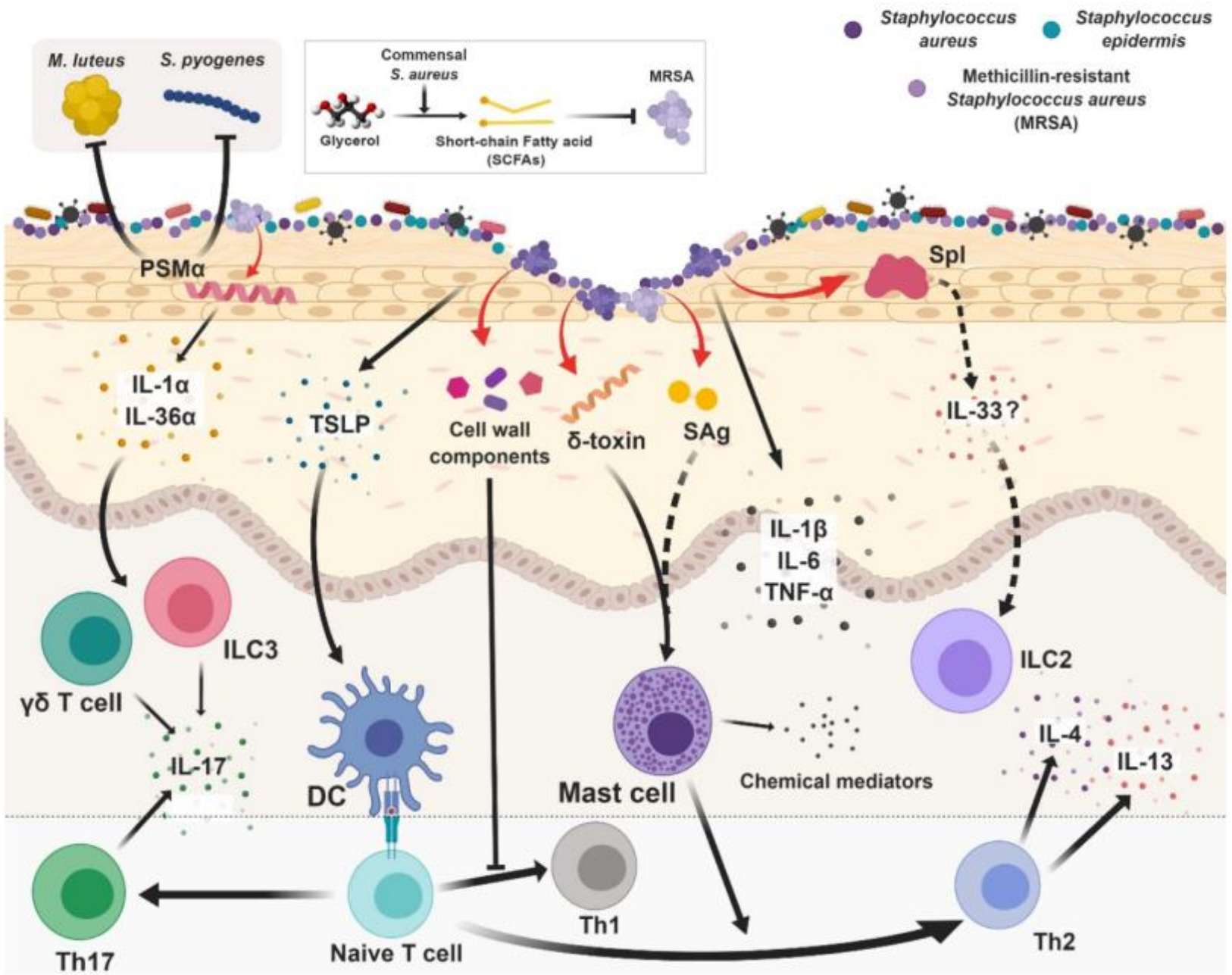
The use of matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) for staphylococcal identification is now considered routine in laboratories compared with the conventional phenotypical methods previously used. We verified its microbiological relevance for identifying the main species of coagulase-negative staphylococci (CoNS) by randomly selecting 50 isolates. From 1 January 2007 to 31 August 2008, 12,479 staphylococci were isolated with phenotypic methods, of which 4,594 were identified as *Staphylococcus aureus* and 7,885 were coagulase negative staphylococci. Using MALDI-TOF MS from 1 January 2011 to 31 August 2012, 14,913 staphylococci were identified, with 5,066 as *S. aureus* and 9,847 as CoNS. MALDI-TOF MS allowed the identification of approximately 85% of the CoNS strains, whereas only 14% of the CoNS strains were identified to the species level with phenotypic methods because they were often considered contaminants. Furthermore, the use of MALDI-TOF MS revealed the occurrence of recently characterized *Staphylococcus* species, such as *S. pettenkoferi*, *S. condimenti*, and *S. pisciferm*entans. Microbiological relevance analysis further revealed that some species displayed a high rate of

TABLE 2 Laboratory identification of staphylococci with phenotypic methods and MALDI-TOF MS in a clinical laboratory

Organism(s)	No. (%) of strains in period:			Comparison of periods 1 and 2 (all staphylococci) (*P* value)
	1, isolated from 2007 to 2008 by phenotypic methods ($n = 12,479$)	2, isolated from 2011 to 2012 by MALDI-TOF MS identification ($n = 14,913$)		
	All staphylococci	All staphylococci	Blood cultures	
S. aureus	4,594 (36.8)	5,066 (34)		<0.001
Nonidentified CoNS	6,781 (54.3)	1,459 (9.8)		
Identified CoNS	1,104 (8.9)	8,388 (56.2)		
S. epidermidis	694 (62.9)	5,259 (62.7)	1,388 (26.4)	0.915
S. hominis	84 (7.6)	698 (8.3)	396 (56.7)	0.418
S. haemolyticus	84 (7.6)	975 (11.6)	150 (15.4)	<0.001
S. capitis	52 (4.7)	552 (6.6)	194 (35.1)	0.017
S. warneri	25 (2.3)	278 (3.3)	62 (22.3)	0.064
S. lugdunensis	25 (2.3)	205 (2.4)	17 (8.3)	0.716
S. simulans	7 (0.6)	78 (0.9)	2 (2.6)	0.330
S. saprophyticus	80 (7.2)	80 (1)	3 (3.8)	<0.001
S. caprae	7 (0.6)	56 (0.7)	1 (1.8)	0.897
S. pettenkoferi	0	54 (0.6)	30 (55.6)	
S. schleiferi	1 (0.1)	30 (0.4)	3 (10)	0.176
S. cohnii	10 (0.9)	35 (0.4)	5 (14.3)	0.030
S. pasteuri	14 (1.3)	25 (0.3)	9 (36)	<0.001
S. intermedius	3 (0.3)	17 (0.2)	0	0.639
S. sciuri	1 (0.1)	14 (0.2)	5 (35.7)	0.555
S. auricularis	3 (0.3)	9 (0.1)		0.163
S. xylosus	6 (0.5)	9 (0.1)		0.002
S. saccharolyticus	5 (0.5)	7 (0.08)		0.004
S. condimenti	0	3 (0.04)		
S. piscifermentans	0	3 (0.04)		
S. carnosus	0	1 (0.01)		
S. vitulinus	1 (0.1)	0		
S. lentus	1 (0.1)	0		
S. chromogenes	1 (0.1)	0		

Staphylococcus epidermidis

- The Big One (*S albus*)
  - #1 contaminant...
  - #1 cause of many infections
    - Increasing instrumentation and use of various medical devices is probably one driver
- Highly clonal in healthcare environments
  - ? Biofilm
  - ? Cell phones (Debnath et al J Microsc Ultrastruct 2018)
  - ?? Chlorhexidine resistance (Addetia et al, AAC 2019)


Staphylococcus aureus
Staphylococcus epidermis
Methicillin-resistant Staphylococcus aureus (MRSA)
M. luteus
S. pyogenes
Commensal S. aureus
MRSA
Glycerol
Short-chain Fatty acid (SCFAs)
PSMα
Spl
IL-1α
IL-36α
TSLP
Cell wall components
δ-toxin
SAg
IL-33?
IL-1β
IL-6
TNF-α
ILC3
γδ T cell
ILC2
IL-17
DC
Mast cell
Chemical mediators
IL-4
IL-13
Th17
Naive T cell
Th1
Th2

Staphylococcus epidermidis (2)

- Possible role in atopic dermatitis
- Increasing number of AMPs
  - Phenol-soluble Modulins (PSMs)
  - MSCRAMMS
- VISE emerging
  - VRSE not (yet) a major player...

Clin Microbiol Infect. 2017 Nov;23(11):839-844. doi: 10.1016/j.cmi.2017.03.022. Epub 2017 Apr 1.

Vancomycin treatment is a risk factor for vancomycin-nonsusceptible Staphylococcus capitis sepsis in preterm neonates.

Butin M[1], Rasigade JP[2], Subtil F[3], Martins-Simões P[4], Pralong C[5], Freydière AM[5], Vandenesch F[2], Tigaud S[5], Picaud JC[6], Laurent F[7].

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Abstract

OBJECTIVES: Multidrug-resistant, vancomycin-nonsusceptible Staphylococcus capitis is an emerging cause worldwide of late-onset sepsis (LOS) in preterm neonates. The pathophysiology and risk factors for S. capitis-related LOS are poorly understood, but we hypothesized that S. capitis LOS follows translocation from the gut microbiota rather than catheter invasion. The objective of this study was to investigate the risk factors of S. capitis LOS and gut colonization.

METHODS: We conducted a prospective single-centre cohort study of patients hospitalized in a tertiary-care unit (Lyon, France) from June 2011 to January 2012. S. capitis gut colonization was determined weekly from stool cultures. The determinants of gut colonization and LOS were established by multivariate Cox proportional hazards models.

RESULTS: Eighty-three (36.2%) of 229 patients had S. capitis-positive stool culture, and 28 (12.2%) developed S. capitis LOS during hospitalization. Independent risk factors for S. capitis LOS included prior administration of vancomycin independent of a previous LOS episode (hazard ratio 6.44, 95% confidence interval 2.15-19.3, p 0.001) and low birth weight (hazard ratio 0.72 per 100 g increase, 95% confidence interval 0.55-0.95, p 0.02). The prior administration of vancomycin was also an independent risk factor for S. capitis colonization (hazard ratio 3.45, 95% confidence interval 2.07-5.76, p <0.001), particularly in the first week of life and in noncolonized neonates.

CONCLUSIONS: Neonates treated with vancomycin are at a higher risk of LOS caused by vancomycin-nonsusceptible S. capitis. The use of vancomycin in neonates must urgently be optimized to limit the selection of vancomycin-nonsusceptible strains, for which alternative antibiotics are lacking.

KEYWORDS: Microbiota; Neonatal intensive care; Sepsis; Staphylococcus capitis; Vancomycin

Staphylococcus lugdunensis

*Image sources = Wikimedia commons

Staphylococcus lugdunensis

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MINIREVIEW

Is *Staphylococcus lugdunensis* Significant in Clinical Samples?

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ABSTRACT The implication of coagulase-negative staphylococci in human diseases is a major issue, particularly in hospital settings wherein these species often act as opportunistic pathogens. In addition, some coagulase-negative staphylococci such as *S. lugdunensis* have emerged as pathogenic bacteria, implicated in severe infections, particularly, osteoarticular infections, foreign-body-associated infections, bacteremia, and endocarditis. *In vitro* studies have shown the presence of several putative virulence factors such as adhesion factors, biofilm production, and proteolytic factors that might explain clinical manifestations. Taken together, the clinical and microbiological data might change the way clinicians and microbiologists look at *S. lugdunensis* in clinical samples.

KEYWORDS virulence, osteoarticular infections, protease, biofilm, endocarditis, *Staphylococcus lugdunensis*

Accepted manuscript posted online 23 August 2017

Citation Argemi X, Hansmann Y, Riegel P, Prévost G. 2017. Is *Staphylococcus lugdunensis* significant in clinical samples? J Clin Microbiol 55:3167–3174. https://doi.org/10.1128/JCM.00846-17.

Editor Colleen Suzanne Kraft, Emory University

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Staphylococcus lugdunensis (2)

- Some basics:
  - Colonizes 30-50% of humans
    - Inguinal, Axillary, Breast, Nasal [apocrine glands]
  - PYR (+)
  - Ornithine Decarboxylase (+)
  - Beta Hemolytic (*slush*, delta-hemolysin*)*
    - Intensifies if refrigerated overnight
  - "*Eikenella*"-like odor of colonies
  - Numerous virulence factors
    - Biofilm, adhesins, proteases

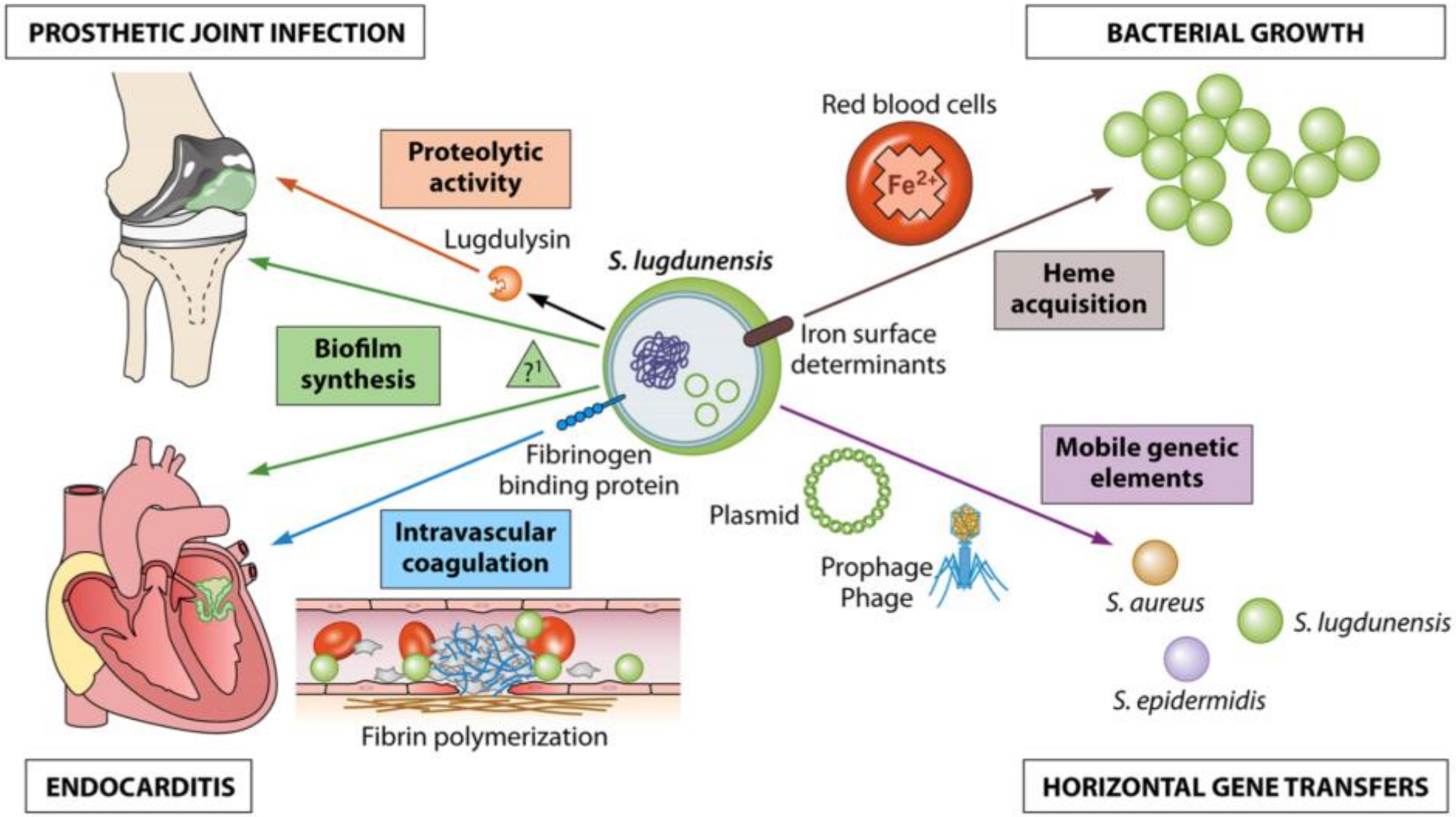


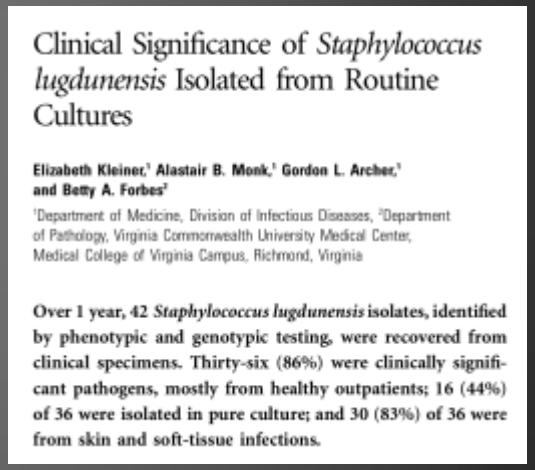
FIG 1 Clinical and bacteriological roles of the main putative virulence factors identified in *S. lugdunensis*.

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

Staphylococcus lugdunensis (3)

- Spectrum of human infections basically identical to *Staphylococcus aureus*:
  - SSTI, surgical site infections
  - Bone / Joint
    - Prosthetic Joint Infections
  - CLABSI
  - Endocarditis (#2 worldwide?)
    - Lower comparable mortality vs. *Staphylococcus aureus*, but not by much (and high risk vs. other CoNS!!)



Clinical Significance of *Staphylococcus lugdunensis* Isolated from Routine Cultures

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Over 1 year, 42 *Staphylococcus lugdunensis* isolates, identified by phenotypic and genotypic testing, were recovered from clinical specimens. Thirty-six (86%) were clinically significant pathogens, mostly from healthy outpatients; 16 (44%) of 36 were isolated in pure culture; and 30 (83%) of 36 were from skin and soft-tissue infections.

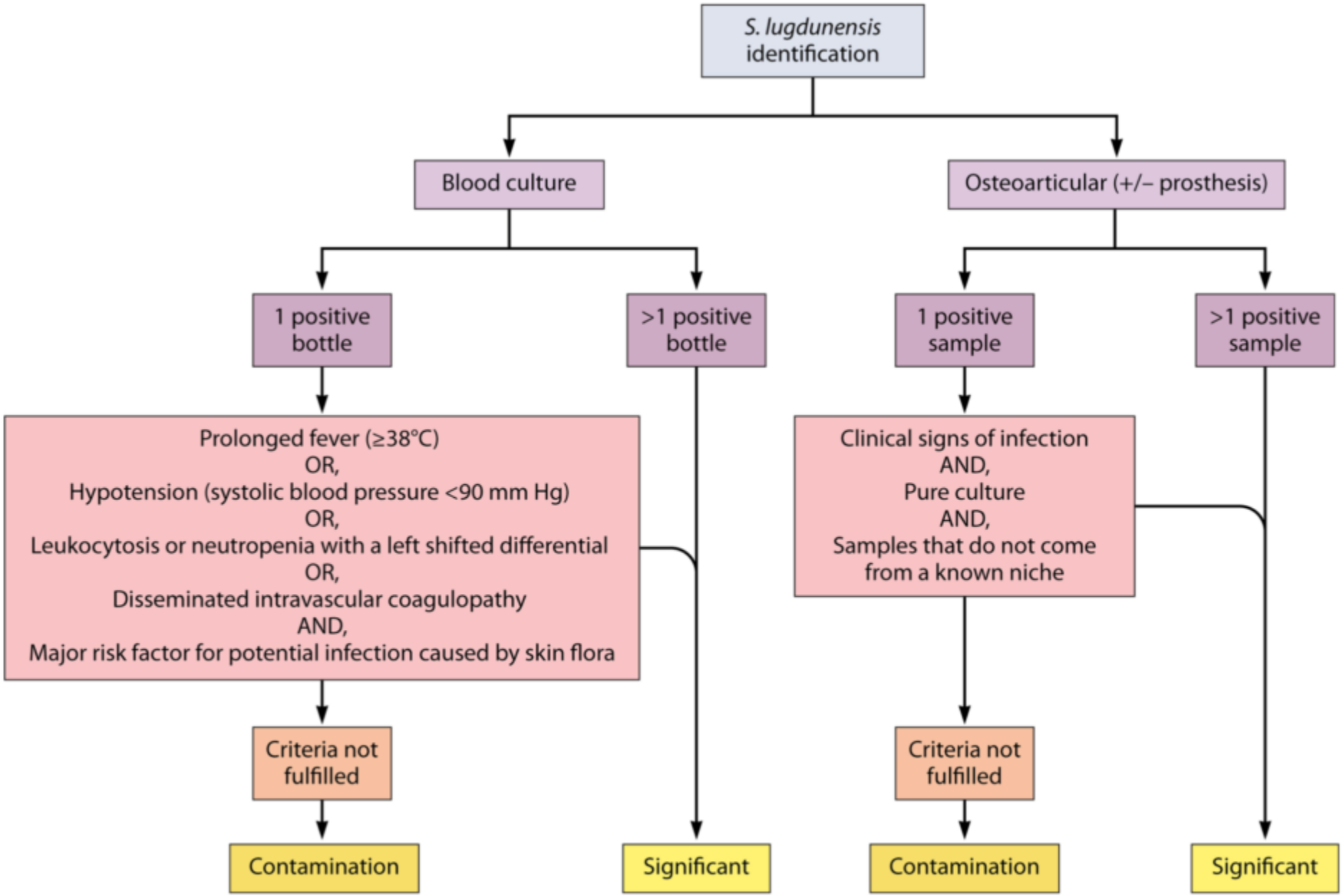

FIG 2 Clinical significance of microbiological samples with *S. lugdunensis* identification in blood cultures and osteoarticular samples. Major risk factors for potential infection caused by skin flora are: long-term intravascular catheterization, peritoneal dialysis, hemodialysis, or extensive postsurgical infections with CoNS. *S. lugdunensis* known niches are inguinal and axillary.

Staphylococcus lugdunensis (4)

- Possibly increasing in incidence?
  - 1.3% up to 7-10% overall?
  - Competing with *Staphylococcus aureus*
- Increasingly drug resistant!
  - Uses the *Staphylococcus aureus* CLSI breakpoints
  - Fosfomycin (R) ~50%
  - *mecA* reported!
    - MRSL

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Staphylococcus lugdunensis, a Common Cause of Skin and Soft Tissue Infections in the Community▽

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***Staphylococcus lugdunensis*, a rare cause of severe infections such as native valve endocarditis, often causes superficial skin infections similar to *Staphylococcus aureus* infections. We initiated a study to optimize the identification methods in the routine laboratory, followed by a population-based epidemiologic analysis of patients infected with *S. lugdunensis* in Viborg County, Denmark. Recognition of a characteristic *Eikenella corrodens*-like odor on Columbia sheep blood agar combined with colony pleomorphism and prominent β-hemolysis after 2 days of incubation, confirmed by API-ID-32 Staph, led to an 11-fold increase in the detection of *S. lugdunensis*. By these methods we found 491 *S. lugdunensis* infections in 4 years, corresponding to an incidence of 53 per 100,000 per year, an increase from 5 infections per 100,000 inhabitants in the preceding years. Seventy-five percent of the cases were found in general practice; these were dominated by skin abscesses (36%), wound infections (25%), and paronychias (13%). Fifty-six percent of the infections occurred below the waist, and toes were the most frequently infected site (21%). Only 3% of the patients suffered from severe invasive infections. The median age was 52 years, and the male/female ratio was 0.69. Our study shows that *S. lugdunensis* is a common cause of skin and soft-tissue infections (SSTI) and is probably underrated by many laboratories. *S. lugdunensis* should be accepted as a significant pathogen in SSTI and should be looked for in all routine bacteriological examinations, and clinicians should be acquainted with the name and the pathology of the bacterium.**

Staphylococcus lugdunensis (5)

- A word on CLSI Breakpoints for *S lugdunensis*
  - 1999 Oxacillin reduction (≥4 to ≥ 0.5)
    - False classification of non-*mecA* 0.5-2.0 as (R)
    - PBP2a instead
  - ...so CoNS breakpoints aren't used
    - Use *Staphylococcus aureus* breakpoints
      - Makes logical sense...
      - Oxacillin ≤ 2 µg/mL = (S)
      - Oxacillin ≥ 4 µg/mL = (R); ~8% MRSL rate

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Clinical Features, Outcomes, and Molecular Characteristics of Community- and Health Care-Associated *Staphylococcus lugdunensis* Infections

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Staphylococcus lugdunensis **is a major cause of aggressive endocarditis, but it is also responsible for a broad spectrum of infections. The differences in clinical and molecular characteristics between community-associated (CA) and health care-associated (HA)** ***S. lugdunensis*** **infections have remained unclear. We performed a retrospective study of** ***S. lugdunensis*** **infections between 2003 and 2014 to compare the clinical and molecular characteristics of CA and HA isolates. We collected 129** ***S. lugdunensis*** **isolates in total: 81 (62.8%) HA isolates and 48 (37.2%) CA isolates. HA infections were more frequent than CA infections in children (16.0% versus 4.2%, respectively;** $P = 0.041$**) and the elderly (38.3% versus 14.6%, respectively;** $P = 0.004$**). The CA isolates were more likely to cause skin and soft tissue infections (85.4% versus 19.8%, respectively;** $P < 0.001$**). HA isolates were more frequently responsible for bacteremia of unknown origin (34.6% versus 4.2%, respectively;** $P < 0.001$**) and for catheter-related bacteremia (12.3% versus 0%, respectively;** $P = 0.011$**) than CA isolates. Fourteen-day mortality was higher for HA infections than for CA infections (11.1% versus 0%, respectively). A higher p[illegible]n of the HA isolates than of the CA isolates were resistant to penicillin (76.5% versus 52.1%, respectively;** $P = 0.004$**) an[illegible]n (32.1% versus 2.1%, respectively;** $P < 0.001$**). Two major clonal complexes (CC1 and CC3) were identified. Sequ[illegible]) was the most common sequence type identified (29.5%). The proportion of ST38 isolates was higher for HA than [illegible]ections (33.3% versus 12.5%, respectively;** $P = 0.009$**). These isolates were of staphylococcal cassette chromosome** ***mec*** **elem[illegible] (SCC*mec*)type IV, V, or Vt. HA and CA** ***S. lugdunensis*** **infections differ in terms of their clinical features, outcome, antibiotic susceptibilities, and molecular characteristics.**

tions 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

Staphylococcus argenteus (2015)

- Capable of carrying PVL
  - SSTI vs Invasive Infections
    - Acquisition of *S aureus* virulence factors?
- *SCCmec* Type IV (MRSArg)
  - Australian Aborigines (~71%)
  - Comparably rare in Europe / USA

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DOI 10.1007/s10096-016-2632-x

ORIGINAL ARTICLE

Low occurrence of the new species *Staphylococcus argenteus* in a *Staphylococcus aureus* collection of human isolates from Belgium

M. A. Argudín[1] · M. Dodémont[1] · S. Vandendriessche[2] · S. Rottiers[1] · C. Tribes[1] · S. Roisin[1] · R. de Mendonça[1] · C. Nonhoff[1] · A. Deplano[1] · O. Denis[1]

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Human infections due to *Staphylococcus pseudintermedius*, an emerging zoonosis of canine origin: report of 24 cases

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ABSTRACT

Background: *Staphylococcus pseudintermedius* has been recently identified as a novel species within the genus *Staphylococcus*, and is commonly associated with infections in dogs. Currently, there are few reports of human infections due to this bacterium.
Objective: To use a population-based approach to describe the characteristics of human *S. pseudintermedius* infections in a large Canadian healthcare region.
Methods: All adult cases aged ≥18 years identified at a large regional laboratory from April 1, 2013 to April 1, 2015 who had at least one positive culture for *S. pseudintermedius* were retrospectively reviewed. A combination of phenotypic methods, mass spectrometry (i.e., MALDI-TOF), and *cpn*60 sequencing were used to identify *S. pseudintermedius*. Chart review was conducted, and cases were analysed descriptively.
Results: Twenty-seven isolates of *S. pseudintermedius* from 24 human cases were included for analysis. 58.3% were male with median age of 61 years (IQR 55–70.5). Most patients [22 (92.1%)] had confirmed contact with dogs at time of infection. *S. pseudintermedius* was isolated in 18 cases (75.0%) of skin and soft tissue infections (SSTI), and 2 invasive cases (8.3%) including a prosthetic joint and bloodstream infection. The other 4 patients were considered to be colonized (skin – 3; lung – 1). Methicillin resistance was identified in 3 cases with 6 total isolates (22.2%); multi-drug resistance was also demonstrated commonly.
Conclusion: *S. pseudintermedius* is most commonly associated with SSTIs in humans. Transmission probably occurs from a pet dog. Species-level identification of *S. pseudintermedius* is important due to the high prevalence of antibiotic resistance, particularly to methicillin.

Staphylococcus pseudointermedius

- Categorically coagulase (+)
- Dog flora (30-60%)
  - Canine Pyoderma, UTI, etc
- MRSP emerging
- SCVs
- Rare human zoonosis in bite wounds
  - Sweden, 2011 hospital outbreak
  - Misidentified as *Staphylococcus aureus*!
    - MICs can be under-called
    - Cefoxitin disks fail!

Eur J Clin Microbiol Infect Dis (2015) 34:839–844
DOI 10.1007/s10096-014-2300-y

ARTICLE

***Staphylococcus pseudintermedius* can be misdiagnosed as *Staphylococcus aureus* in humans with dog bite wounds**

S. Börjesson · E. Gómez-Sanz · K. Ekström · C. Torres · U. Grönlund

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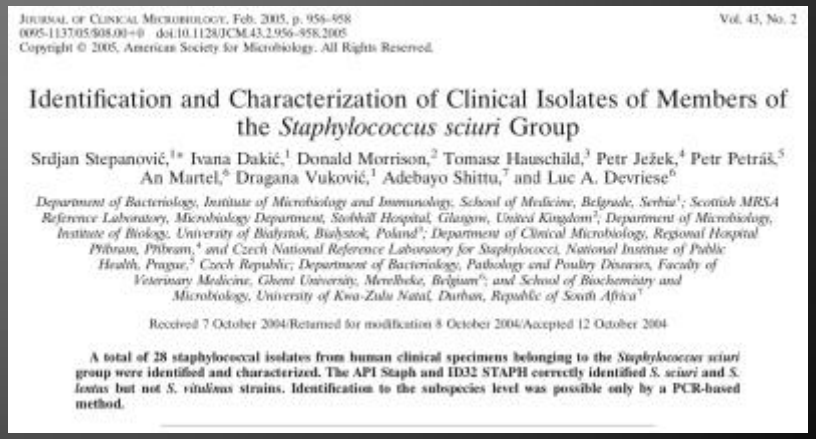
Staphylococcus sciuri Group

- Animal and food sources
  - 1-5% of all human isolates
- Oxidase positive! (*Staphylococcus fleurettii*)
  - Coagulase Negative
  - Novobiocin (R), many *mecA1*
- Emerging association in serious infections
  - Endocarditis
  - Peritonitis
  - Septic Shock



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Identification and Characterization of Clinical Isolates of Members of the *Staphylococcus sciuri* Group

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A total of 28 staphylococcal isolates from human clinical specimens belonging to the *Staphylococcus sciuri* group were identified and characterized. The API Staph and ID32 STAPH correctly identified *S. sciuri* and *S. lentus* but not *S. vitulinus* strains. Identification to the subspecies level was possible only by a PCR-based method.

Available online at www.annclinlabsci.org

Isolation of Rare Coagulase-Negative Isolates in Immunocompromised Patients: *Staphylococcus gallinarum, Staphylococcus pettenkoferi* and *Staphylococcus pasteuri*

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Abstract. Herein, we describe the isolation of *Staphylococcus pasteuri, Staphylococcus pettenkoferi* and *Staphylococcus gallinarum* and summarize the clinical characteristics of five patients. Cases were identified over a 2-year surveillance period that identified the respective strains using microbiologic and molecular methods. These data suggest that rare coagulase-negative staphylococcal infections may be under-diagnosed due to difficulties associated with routine clinical laboratory diagnostic methods.

Key words: Staphylococci, Bacteriaemia, Bacteriology

CoNS Poutpourri

- *Staphylococcus gallinarum* (1983)
  - Birds, immunocompromised humans
- *Staphylococcus pasteuri* (1993)
  - Platelet contamination
- *Staphylococcus pettenkoferi* (2001)
  - Immunocompromised humans
    - Bacteremia
    - Osteomyelitis

Recent Patents on Anti-Infective Drug Discovery, 2009, *4*, 123-129

Epidemiology, Pathogenicity and Emerging Resistances in *Staphylococcus pasteuri*: From Mammals and Lampreys, to Man

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Abstract: *Staphylococcus pasteuri* is a coagulase-negative, Gram positive organism which is emerging as an agent of nosocomial infections and a blood derivatives contaminant, though its role in causing human disease mostly remains controversial. Despite the paucity of isolates recovered, this bacterium has recently appeared to express resistance against several classes of antibiotic compounds, such as methicillin/oxacillin, macrolides, lincosamides, streptogramins, tetracyclines, chloramphenicol, streptomycin, fosfomycin, as well as quaternary ammonium compounds. Also, authors will discuss some essential patents related to the topic reviewed.

Keywords: *Staphylococcus pasteuri*, methicillin, oxacillin, macrolide, lincosamide, streptogramin, tetracyclines, chloramphenicol, fosfomycin, QACs.

Final Words:

- CoNS are increasingly clinically relevant, and increasingly important organisms for the microbiologist
  - Many emerging disease associations
  - Very high burden to our healthcare system
- *S lugdunensis* is emerging as an "equal" to *Staphylococcus aureus* in the clinical space
- Laboratory reporting of CoNS meaningfully informs science and clinical practice

Thank you!

Inquiries?