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COMMENTARY

Significance of *Staphylococcus epidermidis* in Health Care-Associated Infections, from Contaminant to Clinically Relevant Pathogen: This Is a Wake-Up Call!

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Coagulase-negative staphylococci, particularly *Staphylococcus epidermidis*, have been recognized as an important cause of health care-associated infections. Concurrently, *S. epidermidis* is a common contaminant in clinical cultures, which poses a diagnostic challenge. An article in this issue of *Journal of Clinical Microbiology* (I. Tolo, J. C. Thomas, R. S. B. Fischer, E. L. Brown, B. M. Gray, and D. A. Robinson, J Clin Microbiol 54:1711–1719, 2015, http://dx.doi.org/10.1128/JCM.03345-15) describes a rapid single nucleotide polymorphism-based assay for distinguishing between *S. epidermidis* isolates from hospital and nonhospital sources, which represents an important contribution to the characterization and understanding of *S. epidermidis* health care-associated infections.

Coagulase-negative staphylococci (CoNS) constitute an indigenous part of the microbiota of human and animal skin and mucosa (1). Over a period of several decades, CoNS and particularly *Staphylococcus epidermidis* have evolved as important opportunistic pathogens, primarily causing health care-associated infections in patients with indwelling medical devices (2, 3). These infections were previously predominantly regarded as being of endogenous origin, but considerable evidence has been accumulated confirming that nosocomial genotypes of *S. epidermidis* colonize patients and health care personnel and cause a substantial proportion of health care-associated infections (4–11). *S. epidermidis* is currently the main pathogen in catheter-related bloodstream infections and early-onset neonatal sepsis and is also a frequent cause of prosthetic joint infections, prosthetic valve endocarditis, and other biomedical device-related infections (12–15). A major clinical challenge is that these infections are often caused by multidrug-resistant *S. epidermidis* phenotypes and that the infections are chronic in nature due to adherence and biofilm formation on indwelling medical devices. These factors impede antimicrobial therapy and may ultimately necessitate removal of biomedical devices to clear infections (2).

Compared to what has been observed for methicillin-resistant *Staphylococcus aureus* (MRSA), much less is known about the epidemiology and transmission of *S. epidermidis* in health care settings, even though strains of *S. epidermidis* have been recognized as significant nosocomial pathogens for more than 30 years (2, 16). This negligence may be attributable to ignorance of the actual extent of the impact of *S. epidermidis* on health care-associated infections. Notably, estimates of such clinical importance of CoNS in the health care setting differ even between countries in Northern Europe (17, 18). The significance of *S. epidermidis* as a cause of livestock-associated infections has recently been a subject of investigation (19).

Over a number of years, there has been a lack of simple and reliable methods for species identification, which has hampered the assessment and understanding of the epidemiology of *S. epidermidis* and the evaluation of bacteria of this species in clinical cultures. Several inherent features of *S. epidermidis* infections add to the difficulties in making a correct microbial diagnosis and distinguishing between contamination, colonization, and true infection. Such characteristics consist of phenotypic morphological variation, including small colony variants (SCVs) and different antibiograms (clonal variability), as well as polyclonal infections and multispecies CoNS infections (12, 20–22). Unfortunately, all these characteristics of *S. epidermidis* infection can add to the difficulty of assessing culture findings and hence increase the risk that the results will be dismissed as being due to contamination, preventing proper microbial diagnosis and treatment. These problems occur primarily when *S. epidermidis* is assessed in biofilms and in device-related infections. In recent years, matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) has revolutionized routine microbial diagnostics, because this long-awaited method enables fast and reliable high-throughput species-level identification of clinical isolates (23). MALDI-TOF MS will significantly contribute to improving the assessment and diagnosis of infections caused by CoNS (24).

Another factor that has limited investigations of *S. epidermidis* epidemiology is the lack of rapid, non-labor-intensive, and highly discriminatory and reproducible genotyping methods. Pulsed-field gel electrophoresis has been used in short-term epidemiological studies, and multilocus sequence typing (MLST) has contributed unambiguous and highly reproducible data reflecting long-term evolutionary relationships between isolates (6, 25, 26). However, both of those methods are labor-intensive and time-consuming, and the discriminatory power of MLST is insufficient for routine use in outbreak investigations of health care-associ-

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ated *S. epidermidis* genotypes due to the large proportion of sequence type 2 isolates (6, 11).

In light of the current challenges facing clinical microbiology and professionals addressing control of infectious diseases, the comprehensive article by Tolo and colleagues included in this issue of *Journal of Clinical Microbiology* presents an interesting method for simplifying the identification of *S. epidermidis* genotypes in the clinical setting (27). By analyzing seven single nucleotide polymorphisms (SNPs), these researchers were able to accurately assign 545 (94%) of 578 sequence types to six genetic clusters (GCs), which were hypothesized to reflect three different sources of isolates: blood isolates representing true infection, blood isolates representing contaminants, and carriage isolates from nonhospital sources. Equivalent to the use of a panel of five well-studied genetic markers (*icaA*, IS*256*, *sesD* [*bhp*], *mecA*, and arginine catabolic mobile element [ACME]), GC typing could differentiate hospital from nonhospital isolates with 80% accuracy. However, and not surprisingly, neither of these methods could adequately discriminate between *S. epidermidis* isolates from infection and contaminant sources. This can be attributed to the finding that colonization often precedes infection, which renders a method based on MLST data unable to distinguish between hospital isolates that cause infections and those identified solely as contaminants (26, 28).

Another important and explanatory result reported by Tolo et al. is that using colony morphology is insufficient as a basis for distinguishing contaminants from infection isolates from the same patient, as is common practice in some microbiology laboratories. It is also imperative to analyze genomes from several CoNS isolates from a clinical culture to more fully comprehend and evaluate the above-mentioned challenges associated with clinical assessment of CoNS findings (including but not restricted to SCVs, polyclonal infection, and multispecies CoNS infections). Furthermore, to elucidate genome evolution within a host and to reconstruct transmission events, it will be essential to analyze several isolates from each patient by use of whole-genome sequencing (WGS) (29). In the future, WGS will no doubt be used as a first-line genotyping method that can provide fast and completely unambiguous data with ultimate resolution as well as information regarding chain of transmission and presence of virulence factors, antimicrobial genotypic resistance, and mobile genetic elements (30).

At present, the next-generation sequencing (NGS) methods are still too complex for implementation in routine daily practice at clinical microbiology laboratories for wide-scale use in outbreak investigations and surveillance (26). The current rapid development of NGS analysis will likely lead to increased awareness of *S. epidermidis* as a clinically relevant and resilient pathogen. NGS methods can also help explain the dissemination of *S. epidermidis* strains and their function as a reservoir of transferable genes that can enhance the virulence and resistance of other pathogens in health care settings as well as in livestock production.

The study by Tolo et al. represents an important step toward improving the culture assessment of *S. epidermidis* in clinical microbiology laboratories, which can provide better information to physicians and thereby give them a framework for more-comprehensive understanding of the clinical picture of health care-associated *S. epidermidis* infections. Such knowledge will also facilitate the drawing of conclusions from epidemiological studies and outbreak investigations and aid in evaluating the impact of measures aimed at reducing the spread of multidrug-resistant *S. epidermidis* and resultant infections in the health care setting.

REFERENCES

1. **Otto M.** 2009. *Staphylococcus epidermidis*–the 'accidental' pathogen. Nat Rev Microbiol **7:**555–567. http://dx.doi.org/10.1038/nrmicro2182.
2. **Becker K, Heilmann C, Peters G.** 2014. Coagulase-negative staphylococci. Clin Microbiol Rev **27:**870–926. http://dx.doi.org/10.1128/CMR.00109-13.
3. **Widerström M, Wiström J, Sjöstedt A, Monsen T.** 2012. Coagulase-negative staphylococci: update on the molecular epidemiology and clinical presentation, with a focus on *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*. Eur J Clin Microbiol Infect Dis **31:**7–20. http://dx.doi.org/10.1007/s10096-011-1270-6.
4. **Becker K, Bierbaum G, von Eiff C, Engelmann S, Gotz F, Hacker J, Hecker M, Peters G, Rosenstein R, Ziebuhr W.** 2007. Understanding the physiology and adaptation of staphylococci: a post-genomic approach. Int J Med Microbiol **297:**483–501. http://dx.doi.org/10.1016/j.ijmm.2007.04.004.
5. **Conlan S, Mijares LA, Program NCS, Becker J, Blakesley RW, Bouffard GG, Brooks S, Coleman H, Gupta J, Gurson N, Park M, Schmidt B, Thomas PJ, Otto M, Kong HH, Murray PR, Segre JA.** 2012. *Staphylococcus epidermidis* pan-genome sequence analysis reveals diversity of skin commensal and hospital infection-associated isolates. Genome Biol **13:**R64. http://dx.doi.org/10.1186/gb-2012-13-7-r64.
6. **Miragaia M, Thomas JC, Couto I, Enright MC, de Lencastre H.** 2007. Inferring a population structure for *Staphylococcus epidermidis* from multilocus sequence typing data. J Bacteriol **189:**2540–2552. http://dx.doi.org/10.1128/JB.01484-06.
7. **Hira V, Sluijter M, Goessens WH, Ott A, de Groot R, Hermans PW, Kornelisse RF.** 2010. Coagulase-negative staphylococcal skin carriage among neonatal intensive care unit personnel: from population to infection. J Clin Microbiol **48:**3876–3881. http://dx.doi.org/10.1128/JCM.00967-10.
8. **Rolo J, de Lencastre H, Miragaia M.** 2012. Strategies of adaptation of *Staphylococcus epidermidis* to hospital and community: amplification and diversification of SCC*mec*. J Antimicrob Chemother **67:**1333–1341. http://dx.doi.org/10.1093/jac/dks068.
9. **Mendes RE, Deshpande LM, Costello AJ, Farrell DJ.** 2012. Molecular epidemiology of *Staphylococcus epidermidis* clinical isolates from U.S. hospitals. Antimicrob Agents Chemother **56:**4656–4661. http://dx.doi.org/10.1128/AAC.00279-12.
10. **Saffari F, Widerström M, Gurram BK, Edebro H, Hojabri Z, Monsen T.** 16 March 2016. Molecular and phenotypic characterization of multidrug-resistant clones of *Staphylococcus epidermidis* in Iranian hospitals: clonal relatedness to healthcare-associated methicillin-resistant isolates in Northern Europe. Microb Drug Resist http://dx.doi.org/10.1089/mdr.2015.0283.
11. **Widerström M, McCullough CA, Coombs GW, Monsen T, Christiansen KJ.** 2012. A multidrug-resistant *Staphylococcus epidermidis* clone (ST2) is an ongoing cause of hospital-acquired infection in a Western Australian hospital. J Clin Microbiol **50:**2147–2151. http://dx.doi.org/10.1128/JCM.06456-11.
12. **Kahl BC, Becker K, Loffler B.** 2016. Clinical significance and pathogenesis of staphylococcal small colony variants in persistent infections. Clin Microbiol Rev **29:**401–427. http://dx.doi.org/10.1128/CMR.00069-15.
13. **Baddour LM, Wilson WR, Bayer AS, Fowler VG, Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA, American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, Stroke Council.** 2015. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation **132:**1435–1486. http://dx.doi.org/10.1161/CIR.0000000000000296.
14. **Sgro M, Shah PS, Campbell D, Tenuta A, Shivananda S, Lee SK, Canadian Neonatal Network.** 2011. Early-onset neonatal sepsis: rate and organism pattern between 2003 and 2008. J Perinatol **31:**794–798. http://dx.doi.org/10.1038/jp.2011.40.
15. **Rosenthal VD, Maki DG, Mehta Y, Leblebicioglu H, Memish ZA,**

Al-Mousa HH, Balkhy H, Hu B, Alvarez-Moreno C, Medeiros EA, Apisarnthanarak A, Raka L, Cuellar LE, Ahmed A, Navoa-Ng JA, El-Kholy AA, Kanj SS, Bat-Erdene I, Duszynska W, Van Truong N, Pazmino LN, See-Lum LC, Fernandez-Hidalgo R, Di-Silvestre G, Zand F, Hlinkova S, Belskiy V, Al-Rahma H, Luque-Torres MT, Bayraktar N, Mitrev Z, Gurskis V, Fisher D, Abu-Khader IB, Berechid K, Rodriguez-Sanchez A, Horhat FG, Requejo-Pino O, Hadjieva N, Ben-Jaballah N, Garcia-Mayorca E, Kushner-Davalos L, Pasic S, Pedrozo-Ortiz LE, Apostolopoulou E, Mejia N, Gamar-Elanbya MO, Jayatilleke K, de Lourdes-Duenas M, Aguirre-Avalos G, International Nosocomial Infection Control Consortium. 2014. International Nosocomial Infection Control Consortium (INICC) report, data summary of 43 countries for 2007–2012. Device-associated module. Am J Infect Control **42:**942–956. http://dx.doi.org/10.1016/j.ajic.2014.05.029.

16. **Archer GL.** 1988. Molecular epidemiology of multiresistant *Staphylococcus epidermidis*. J Antimicrob Chemother **21**(Suppl C)**:**133–138. http://dx.doi.org/10.1093/jac/21.suppl_C.133.
17. **Dahl V, Tegnell A, Wallensten A.** 2015. Communicable diseases prioritized according to their public health relevance, Sweden, 2013. PLoS One **10:**e0136353. http://dx.doi.org/10.1371/journal.pone.0136353.
18. **Balabanova Y, Gilsdorf A, Buda S, Burger R, Eckmanns T, Gartner B, Gross U, Haas W, Hamouda O, Hubner J, Janisch T, Kist M, Kramer MH, Ledig T, Mielke M, Pulz M, Stark K, Suttorp N, Ulbrich U, Wichmann O, Krause G.** 2011. Communicable diseases prioritized for surveillance and epidemiological research: results of a standardized prioritization procedure in Germany, 2011. PLoS One **6:**e25691. http://dx.doi.org/10.1371/journal.pone.0025691.
19. **Cuny C, Arnold P, Hermes J, Eckmanns T, Mehraj J, Schoenfelder S, Ziebuhr W, Zhao Q, Wang Y, Fessler AT, Krause G, Schwarz S, Witte W.** 6 April 2016. Occurrence of *cfr*-mediated multiresistance in staphylococci from veal calves and pigs, from humans at the corresponding farms, and from veterinarians and their family members. Vet Microbiol http://dx.doi.org/10.1016/j.vetmic.2016.04.002.
20. **Harris LG, Murray S, Pascoe B, Bray J, Meric G, Magerios L, Wilkinson TS, Jeeves R, Rohde H, Schwarz S, de Lencastre H, Miragaia M, Rolo J, Bowden R, Jolley KA, Maiden MC, Mack D, Sheppard SK.** 2016. Biofilm morphotypes and population structure among *Staphylococcus epidermidis* from commensal and clinical samples. PLoS One **11:**e0151240. http://dx.doi.org/10.1371/journal.pone.0151240.
21. **Van Eldere J, Peetermans WE, Struelens M, Deplano A, Bobbaers H.** 2000. Polyclonal staphylococcal endocarditis caused by genetic variability. Clin Infect Dis **31:**24–30. http://dx.doi.org/10.1086/313915.
22. **Nilsdotter-Augustinsson A, Koskela A, Ohman L, Soderquist B.** 2007. Characterization of coagulase-negative staphylococci isolated from patients with infected hip prostheses: use of phenotypic and genotypic analyses, including tests for the presence of the *ica* operon. Eur J Clin Microbiol Infect Dis **26:**255–265. http://dx.doi.org/10.1007/s10096-007-0281-9.
23. **Szabados F, Woloszyn J, Richter C, Kaase M, Gatermann S.** 2010. Identification of molecularly defined Staphylococcus aureus strains using matrix-assisted laser desorption/ionization time of flight mass spectrometry and the Biotyper 2.0 database. J Med Microbiol **59:**787–790. http://dx.doi.org/10.1099/jmm.0.016733-0.
24. **Spinali S, van Belkum A, Goering RV, Girard V, Welker M, Van Nuenen M, Pincus DH, Arsac M, Durand G.** 2015. Microbial typing by matrix-assisted laser desorption ionization–time of flight mass spectrometry: do we need guidance for data interpretation? J Clin Microbiol **53:**760–765. http://dx.doi.org/10.1128/JCM.01635-14.
25. **Goering RV, Fey PD.** 2014. Pulsed field gel electrophoresis of *Staphylococcus epidermidis*. Methods Mol Biol **1106:**55–60. http://dx.doi.org/10.1007/978-1-62703-736-5_4.
26. **Sabat AJ, Budimir A, Nashev D, Sa-Leao R, van Dijl J, Laurent F, Grundmann H, Friedrich AW, ESCMID Study Group of Epidemiological Markers (ESGEM).** 2013. Overview of molecular typing methods for outbreak detection and epidemiological surveillance. Euro Surveill **18:**20380. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20380.
27. **Tolo I, Thomas JC, Fischer RSB, Brown EL, Gray BM, Robinson DA.** 2016. Do *Staphylococcus epidermidis* genetic clusters predict isolation sources? J Clin Microbiol **54:**1711–1719. http://dx.doi.org/10.1128/JCM.03345-15.
28. **Datta R, Shah A, Huang SS, Cui E, Nguyen V, Welbourne SJ, Quan KA, Thrupp L.** 2014. High nasal burden of methicillin-resistant *Staphylococcus aureus* increases risk of invasive disease. J Clin Microbiol **52:**312–314. http://dx.doi.org/10.1128/JCM.01606-13.
29. **Didelot X, Walker AS, Peto TE, Crook DW, Wilson DJ.** 2016. Within-host evolution of bacterial pathogens. Nat Rev Microbiol **14:**150–162. http://dx.doi.org/10.1038/nrmicro.2015.13.
30. **Leopold SR, Goering RV, Witten A, Harmsen D, Mellmann A.** 2014. Bacterial whole-genome sequencing revisited: portable, scalable, and standardized analysis for typing and detection of virulence and antibiotic resistance genes. J Clin Microbiol **52:**2365–2370. http://dx.doi.org/10.1128/JCM.00262-14.