Small Colony Variants of Staphylococcus aureus and Pacemaker-related Infection

Harald Seifert,* Hilmar Wisplinghoff,*, Petra Schnabel,* and Christof von Eiff†

We describe the first known case of a device-related bloodstream infection caused by *Staphylococcus aureus* small colony variants. Recurrent pacemaker-related bloodstream infection within a 7-month period illustrates the poor clinical and microbiologic response to prolonged antimicrobial therapy in a patient infected with this *S. aureus* subpopulation.

Infections caused by *Staphylococcus aureus* range from mild skin infections to acute life-threatening diseases such as pneumonia, osteomyelitis, and endocarditis. However, *S. aureus* may also cause a chronic disease with persistent and recurrent infections. Skin and soft tissue infections, chronic osteomyelitis, and persistent infections in patients with cystic fibrosis have been associated with small colony variants, a naturally occurring subpopulation of the species *S. aureus* (1–6). *S. aureus* small colony variants are characterized as electron transport deficient bacteria because of their auxotrophism to hemin or menadione or are recognized as thymidine-dependent. These variants produce very small, mostly nonpigmented and non-hemolytic colonies. In addition, they also demonstrate various other features that are atypical for *S. aureus*, including reduced coagulase production, failure to use mannitol, and increased resistance to aminoglycosides and cell-wall active antibiotics (3–10). Furthermore, the ability of these variants to persist intracellularly within nonprofessional phagocytes has been described (3,5,11). Because of their fastidious growth characteristics and unusual morphologic appearance, small colony variants present a challenge both to the microbiologist and the clinician, often resulting in misidentification and misinterpretation (1,2,7,8). Prerequisite for recovering and identifying these variants is the application of extended conventional culture and identification techniques (3,5,8). We report the first case of a pacemaker-related bloodstream infection caused by *S. aureus* small colony variants. This case illustrates the poor clinical and microbiologic response to prolonged antimicrobial therapy in patients infected with these variants.

**Case Report**

A 63-year-old man was transferred to our facility with the presumptive diagnosis of endocarditis related to a pacemaker-lead infection. Past medical history included hypertension, coronary artery disease, and noninsulin-dependent diabetes mellitus. A VVI (ventricular ventricular inhibited) pacemaker had been implanted for treatment of sick sinus syndrome 9 years earlier. Six weeks before admission, this device had been removed because of a pocket infection after blunt trauma with dislocation of the device and perforation of the skin. Specimens for microbiologic culture were not obtained at this time. The pacemaker leads were left in place, a gentamicin-containing sponge was applied to the infection site, and a new pacemaker was implanted on the other side of the chest. Four weeks later, the patient sought treatment at the local hospital for a high fever (39.7°C) and chills and a subcutaneous abscess with oxacillin-susceptible *S. aureus* at the primary insertion site. After surgical drainage, antimicrobial therapy was initiated with intravenous cefuroxime. The remaining pacemaker leads were partially cut but not completely removed. Ten days later, spiking fever and chills unresponsive to the administration of meropenem and vancomycin developed, and the patient was transferred to our medical center for pacemaker ablation. The physical examination did not indicate auscultation abnormalities or stigmata of endocarditis. Laboratory studies were unremarkable except a C-reactive protein (CRP) level of 170 mg/L (normal value ≤8 mg/L) and a blood sedimentation rate of 79 mm/h. Multiple blood cultures taken on admission remained negative. Transeosophageal echocardiography did not show vegetations or other evidence of endocarditis. On hospital day 6, the new pacemaker was completely removed by percutaneous ablation as were the remaining leads of the old device. Only the tip of the pacemaker lead remained fixed in the myocardium, and surgical removal involving extracorporal circulation was not attempted. The patient’s condition improved rapidly, CRP level returned to normal, and on hospital day 32, the patient was transferred to the local hospital to complete a 6-week course of intravenous vancomycin and rifampin as empirical antistaphylococcal therapy. Before transfer, the daily vancomycin dose had been reduced to 250 mg twice a day after an elevated vancomycin serum level. Eight days later, the patient was readmitted with recurrent high fever. Blood cultures taken on readmission were again negative. After the vancomycin dose was increased to 500 mg every 12 hours, the patient promptly became afebrile. Antimicrobial therapy
was discontinued after the patient had completed a 10-week course of vancomycin and rifampin. Three days later, the patient again had spiking fever. After 6 to 48 hours of incubation, four sets of blood cultures obtained on four consecutive days yielded nonpigmented and nonhemolytic staphylococci, initially identified on the basis of a negative tube coagulation test and the API ID 32 Staph system (bioMérieux, Marcy-L’Étoile, France) as coagulase-negative staphylococci, susceptible to oxacillin (MIC 0.5 mg/mL) and vancomycin (MIC 1.0 mg/mL) but resistant to rifampin (MIC >32 mg/mL). However, the colony morphologic findings were suggestive of small colony variants of \textit{S. aureus}, confirmed by polymerase chain reaction amplification of the \textit{nuc} and \textit{coa} genes as well as by determination of the strain’s auxotrophy for hemin. The patient responded promptly to flucloxacinil, 4 g intravenously three times a day. After another 6-week course of parenteral therapy, antimicrobial therapy was discontinued, and the patient was discharged (CRP 7 mg/L, ESR 35 mm/h); he was readmitted after 6 days with chills and high fever. Antimicrobial therapy with intravenous flucloxacinil was resumed and followed by immediate defervescence. Three blood cultures taken on readmission were again positive with \textit{S. aureus} small colony variants. Clonal identity of all isolates was demonstrated by pulsed-field gel electrophoresis of bacterial DNA (data not shown). A transesophageal echocardiogram showed the residual tip of the pacemaker lead fixed in the myocardial septum without vegetations. The remaining device was finally removed by open-heart surgery with use of cardiopulmonary bypass. Microbiologic culture of the pacemaker electrode percutaneously collected at a different institution yielded abundant growth of \textit{S. warneri}, \textit{Acinetobacter} \textit{baumanii}, and \textit{Pseudomonas aeruginosa}, that were attached to fibronectin-coated coverslips were highly resistant to cell-wall–active antimicrobial agents such as oxacillin and vancomycin (13).

In our case, findings suggest that \textit{S. aureus} small colony variants might have been selected from the parent strain population with a normal phenotype after exposure to the locally applied aminoglycoside or to the prolonged administration of vancomycin. Continually positive blood cultures with the same strain as demonstrated by molecular typing and the presumable persistence of these organisms on the pacemaker lead tip may partly be explained by the poor effectiveness of vancomycin and flucloxacinil against these slow-growing organisms that were adhering to the remaining foreign body and the ability of these variants to persist intracellularly (7,8,13).

This case adds to the spectrum of persistent and relapsing infections attributed to \textit{S. aureus} small colony variants and emphasizes that these variants may also play a role in intravascular device–related infections. It also illustrates that complete removal of any foreign body material is essential for the complete cure of prosthetic intravascular device–related \textit{S. aureus} infection. Laboratories should be particularly alert for \textit{S. aureus} small colony variants when samples are submitted from patients who have received long-term antimicrobial therapy, especially if the infection is unusually persistent or recurrent.

Dr. Seifert is professor of clinical microbiology at the Institute for Medical Microbiology, Immunology and Hygiene at the University of Cologne, Köln, Germany. His research interests include the molecular epidemiology of nosocomial pathogens, in particular \textit{Acinetobacter} species and methicillin-resistant \textit{Staphylococcus aureus}, catheter-related infections, and antimicrobial resistance and its mechanisms.

References


Address for correspondence: Harald Seifert, Institut für Medizinische Mikrobiologie, Immunologie und Hygiene, Goldenfelsstr.19-21, 50935 Köln, Germany; fax: 0049 221-4783979; email: harald.seifert@uni-koeln.de

---

**Instructions for Emerging Infectious Diseases Authors**

**Research Studies:** Articles should be 2,000 to 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words) and a brief biographical sketch of first author—both authors if only two.

These articles report laboratory and epidemiologic results within a public health perspective. Although these reports may be written in the style of traditional research articles, they should explain the value of the research in public health terms and place the findings in a larger perspective (e.g., “Here is what we found, and here is what the findings mean”).

**Manuscript Preparation.** For word processing, use MS Word. Begin each of the following sections on a new page and in this order: title page, keywords, abstract, text, acknowledgments, biographical sketch, references, tables, figure legends, appendices, and figures. Each figure should be in a separate file.

**Title Page.** Give complete information about each author (i.e., full name, graduate degree(s), affiliation, and the name of the institution in which the work was done). Clearly identify the corresponding author and provide that author’s mailing address (include phone number, fax number, and e-mail address). Include separate word counts for abstract and text.

**Keywords.** Include up to 10 keywords; use terms listed in Medical Subject Headings Index Medicus.

**Text.** Double-space everything, including the title page, abstract, references, tables, and figure legends. Printed manuscript should be single-sided, beginning with the title page. Indent paragraphs; leave no extra space between paragraphs. After a period, leave only one space before beginning the next sentence. Use 12-point Times New Roman font and format with ragged right margins (left align). Italicize (rather than underline) scientific names when needed.

**Biographical Sketch.** Include a short biographical sketch of the first author—both authors if only two. Include affiliations and the author’s primary research interests.

**References.** Follow Uniform Requirements (www.icmje.org/index.html). Do not use endnotes for references. Place reference numbers in parentheses, not superscripts. Number citations in order of appearance (including in text, figures, and tables). Cite personal communications, unpublished data, and manuscripts in preparation or submitted for publication in parentheses in text. Consult List of Journals Indexed in Index Medicus for accepted journal abbreviations; if a journal is not listed, spell out the journal title. List the first six authors followed by “et al.” Do not cite references in the abstract.

**Tables and Figures.** Create tables within MS Word’s table tool. Do not format tables as columns or tabs. Send graphics in native, high-resolution (200-dpi minimum) .TIF (Tagged Image File), or .EPS (Encapsulated Postscript) format. Graphics should be in a separate electronic file from the text file. For graphic files, use Arial font. Convert Macintosh files into the suggested PC format. Figures, symbols, letters, and numbers should be large enough to remain legible when reduced. Place figure keys within the figure. For more information see EID Style Guide (http://www.cdc.gov/ncidod/EID/style_guide.htm).

**Manuscript Submission.** Include a cover letter indicating the proposed category of the article (e.g., Research, Dispatch) and verifying that the final manuscript has been seen and approved by all authors. Submit an electronic copy (by e-mail) to the Editor, eeditor@cdc.gov.