Significant controversy surrounds the usefulness of central venous catheters (CVCs) impregnated with antimicrobial agents (A-CVCs) for the prevention of catheter-related bloodstream infections (CRBSIs). In a recent issue of *Clinical Infectious Diseases*, we reviewed 11 published trials of A-CVCs versus uncoated CVCs, and we concluded that there is a lack of solid evidence to support a benefit of A-CVCs in reducing the rate of CRBSIs. A response to our review was recently published in *Clinical Infectious Diseases*. In this response, our colleagues assert that there is a large body of evidence that demonstrates a powerful decrease in the risk of infection, and they conclude that we should not waste precious resources while we perform additional research to confirm what we have already found to be true. Although these authors agree with us on the significant shortcomings of the studies used to support the use of A-CVCs, they dismiss the need for additional trials to demonstrate that the use of A-CVCs does reduce infections. This dismissal, however, cannot be justified, because of the existence of an ongoing, federally supported, multicenter, prospective, placebo-controlled trial, led by our colleagues, that compares the rate of CRBSIs among patients randomized to receive either an A-CVC or a “placebo” uncoated CVC. That our colleagues are leading a trial that assesses the efficacy of A-CVCs versus placebo uncoated CVCs supports our viewpoint that the truth regarding the protective role of A-CVCs has yet to be determined. Because of the significant cost, potential toxicity, and risk of increased antimicrobial resistance associated with the use of A-CVCs, and until the results of the important trial conducted by our colleagues convincingly demonstrate that A-CVCs reduce the rate of clinically significant events (not just catheter colonization), we recommend that the use of A-CVCs be limited to investigational settings.

We are pleased that our viewpoint on the use of central venous catheters impregnated with antimicrobial agents (A-CVCs) [1] has prompted response in the form of a full-length article [2] as well as personal communications, most of which have been supportive, from colleagues. The purpose of our review [1] was, indeed, to engage the medical community in a healthy debate regarding the need for evidence-based medicine (EBM) in the field of research involving central venous catheters (CVCs) and catheter-related bloodstream infections (CRBSIs). It is in this spirit that we strongly endorse the trial recently proposed by Dr. Maki and Dr. L. Siman and conducted through the Bacteriology and Mycology Study Group (BAMSG), which is fully supported by the National Institutes of Health (NIH; Bethesda, MD). The trial is a randomized, multicenter, comparative trial of CVCs impregnated with silver sulfadiazine and chlorhexidine (S/C CVCs) versus CVCs coated with minocycline and rifampin (M/R CVCs) versus uncoated CVCs (placebos) for patients in the intensive care unit. The trial seeks to determine whether CRBSI can be prevented by the use of an A-CVC versus a placebo, and, if so, which A-CVC (an S/C CVC or an M/R CVC) is most effective and is least likely to induce antimicrobial resistance. The latter question is important to ask, because independent confirmation of the positive findings of the inventors of the M/R CVC is still lacking [3, 4]. The BAMSG trial will address these and other controversies surrounding the A-CVC. In their response to our published viewpoint, our colleagues Dr. Crnich and Dr. Maki agree that studies of A-CVCs have suffered from method-
the in vitro activity of the antimicrobial agents that the CVCs were coated with and that eventually leached into the culture media [6–8]. Furthermore, mucosal sites—not skin—are the source of the most common cause of CRBSI: coagulase-negative staphylococci (CONS). This conclusion is supported by the significant colonization of mucosal sites by CONS in various patient populations, by the clinical and experimental evidence of CONS mucosal translocation leading to CONS bloodstream infection, and by the molecular relatedness of mucosal and blood isolates [9]. Supporting evidence for the skin as a primary source of CONS bacteremia could not be found [9].

- Crnich and Maki argue that the studies “were not designed or powered” [2, p. 1288] to demonstrate the clinical benefit of A-CVCs.

Although Crnich and Maki now agree that A-CVCs have not been shown to decrease clinically relevant end points (such as catheter retention rate, antimicrobial use, antimicrobial resistance, duration of hospitalization, or patient mortality), they contend that the studies of A-CVCs “were not designed or powered” [2, p. 1288] to show such a benefit. This latter statement stands in contrast to their (and most other experts’) advocacy of the adoption of the use of A-CVCs to enjoy “the benefit gained in reduction of mortality rates” [10, p. 1366].

In support of their point, the authors make an analogy between A-CVCs and antiretroviral therapy because, individually, the trials were not powered to assess survival [2]. This analogy is misguided because trials have shown a significant benefit of antiretrovirals in reducing AIDS-associated morbidity and mortality [11, 12]. A better analogy might be made between A-CVCs and the use of hormone replacement therapy (HRT) for postmenopausal women. On the basis of expert opinion and suboptimal trials that have suggested that cardioprotection is a benefit of HRT, millions of women worldwide have received HRT. However, HRT has now been mostly abandoned for cardioprotection on the basis of the results of well-conducted trials that have demonstrated an associated increased risk of coronary heart disease, venous thromboembolism, stroke, and breast cancer [13–15]. There is simply no substitute for EBM—not even the strongest opinion of the leading experts in the field.

- Crnich and Maki [2] state that all reviewed trials had used accepted published criteria for the diagnosis and definition of CRBSI.

This point clearly highlights one of the most glaring problems associated with the interpretation of the literature on CRBSI—namely, either that the “accepted published criteria” [2, p. 1288] are subjective and, thus, nonreproducible or that they lack supporting evidence. A case in point involves the use of a definition of infection at the CVC exit site that is based on the appearance of the CVC site (erythema or induration) [16]. In a trial of 1263 CVCs that was conducted by Dr. N. Safdar and Dr. Maki, the use of such a definition of infection was discouraged by the investigators’ conclusion that “site appearance cannot be relied on to identify catheter colonization or CRBSI” [17, pp. 1 and 3]. Another example of the problems associated with the accepted published criteria is the definition of CRBSI as “bacteremia/fungemia in a patient with an intravenous catheter with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infection (i.e., fever, chills, and/or hypotension) and no apparent source for the BSI except the catheter” [16, p. 1298]. We wonder why the definition of such an important clinical event should depend on a clinician’s willingness and ability to conduct and appropriately interpret the extensive workup often needed to detect a source of a bloodstream infection. Even more troubling is the definition of the most common cause of CRBSI (i.e.,

If the evidence demonstrating that A-CVC use is associated with a powerful reduction in infection is so convincing that it constitutes an unchallengeable truth, then it would be difficult to ethically justify the use of a placebo for the high-risk intensive care unit patients who our colleagues are enrolling in the BAMSG trial or to justify the significant resources needed to conduct the BAMSG trial. In addition, our recent review shows that 9 of the 11 published studies failed to demonstrate a reduction in the rate of CRBSI [1]. In the largest of these 11 trials (a trial that involved 680 CVCs), no difference could be identified between the A-CVC and the uncoated catheter, with regard to the rate of CRBSI (5% vs. 4.4%, respectively), antibiotic use, or CVC retention (duration of CVC retention in both study arms, 20 days) [5].

Crnich and Maki state that “all studies except 2 have demonstrated with impressive consistency a striking reduction in the number of colonized CVCs” [2, p. 1290], a prelude to CRBSI. The assertion that CVC colonization (presumably resulting from contaminated skin) is a prelude to CRBSI remains to be convincingly demonstrated, because the reduced rate of CVC colonization may simply represent the in vitro activity of the antimicrobial and the uncoated catheter, with regard to antibiotic use, antimicrobial resistance, duration of hospitalization, or patient mortality), they contend that the studies of A-CVCs “were not designed or powered” [2, p. 1288] to show such a benefit. This latter statement stands in contrast to their (and most other experts’) advocacy of the adoption of the use of A-CVCs to enjoy “the benefit gained in reduction of mortality rates” [10, p. 1366].

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CONS, a common skin contaminant). This definition now allows a single blood culture result as evidence of CRBSI, provided “the physician institutes appropriate therapy” [16, p. 1299]. However, and given the concerns about serious gram-positive bacterial infections other than those due to CONS, it would be difficult to imagine a scenario in which a patient with signs and symptoms of infection and with 1 of 4 blood cultures yielding gram-positive cocci (identification pending) would be denied antimicrobial therapy for gram-positive bacterial infection while awaiting identification of the organism. Such a common clinical presentation would thus be considered to denote CRBSI due to CONS, despite evidence indicating that the likelihood of this blood isolate causing infection is only 2% [18] and that the overwhelming majority of such CONS blood isolates represent contamination [18–31]. In view of these concerns, we respectfully urge the Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention panel (Atlanta, GA) [16] to revise the guidelines for the prevention of CRBSI so that only objective, EBM-supported definitions of CRBSI are used.

- Crnich and Maki [2] criticize our concerns about the statistical methodology used in most of the trials.

Crnich and Maki [2] agree that the lack of intent-to-treat analysis (a technique intended to prevent investigator bias) is a valid criticism and, we might add, a fatal flaw of most trials [2, 32, 33]. They also assume (without providing supporting evidence) that the imbalance in the severity of illness and immunosuppression noted between study arms is unlikely because the studies used acceptable randomization schemes; however, imbalances in the key variables between study groups do occur, even when acceptable randomization schemes are used [33, 34], and clinical investigators are encouraged not only to report key patient characteristics (such as illness severity and immunosuppression) but, also, to resort to stratification, which, in contrast to randomization, ensures balance with respect to important prognostic factors [33, 34].

- Crnich and Maki [2] state that our criticism of allowing enrollment of patients with major confounding variables (e.g., arterial catheters and guidewire exchange) is “specious” [2, p. 1288] (i.e., having a deceptive ring of truth or plausibility). They contend that not including such patients would result in the exclusion of a large number of patients from trials.

That 7 of the 11 published trials [5, 35–40], including the largest trial (which involved 680 CVCs) [5], were able to enroll a large number of patients without including these confounding variables demonstrates the feasibility of this approach.

- Crnich and Maki [2] raise concerns that we go out of our way to downplay the morbidity associated with CRBSI [2].

We are pleased that our colleagues acknowledge that the issue regarding the excess mortality associated with CRBSI remains unresolved [2]. Dismissing the morbidity associated with CRBSI in general was never our intention. Our point was to emphasize issues raised by others—namely, (1) that the morbidity and mortality of CRBSI were grossly exaggerated [41–44] and were related not to CRBSI but, rather, to the severity of illness of the host [41, 42] and (2) that the reduction in the rate of CRBSIs in 1 of the only 2 A-CVC studies with positive findings was almost exclusively related to a decrease in CRBSI due to CONS [39], a common skin contaminant [18–31].


In the absence of EBM supporting the effectiveness of A-CVCs on the basis of clinically relevant end points, cost-effectiveness studies are an exercise in futility, particularly when they are based on invalid clinical assumptions [1].

**DISCUSSION**

Crnich and Maki [2] agree with us that studies of A-CVCs suffer from methodological and statistical flaws, that the use of A-CVCs has not been shown to improve clinically relevant end points, and that the excess mortality associated with CRBSI remains to be demonstrated. We are, however, surprised by their assertion that the reduction in the risk of infection has been so convincingly demonstrated that conducting more studies of this matter “wastes precious resources…while we do even more research to try to show what we have already found to be true” [2, p. 1290]. The BAMS/G trial, the laudable effort led by our colleagues (with federal support) to “do even more research” to demonstrate that A-CVCs reduce the rate of CRBSI, supports our viewpoint that the search for the truth regarding the effectiveness of A-CVCs continues.

Finally, our colleagues fear that we would “throw out the baby with the bathwater” [2, p. 1289]. This adage dates back to the Middle Ages. During the Middle Ages, a large tub was often used for bathing, with the man of the house first in clean water. His wife then bathed, followed by any other women in the household and, then, by the children, with the youngest child bathing last. The joke was that, by the time the youngest child began to bathe, the water had become so murky that one could not tell whether there was anyone in it; therefore, when the foul bathwater was thrown out, there was a risk of discarding the baby with the bathwater. This saying has become a metaphor for throwing away something valuable along with something unwanted. Dr. Crnich and Dr. Maki could not have employed a better proverb to describe the
current state of the research involving CVCs. We are not suggesting discarding the baby (the A-CVC)—only the contaminated bathwater (current data), which we want to replace with clean water (new data) so that we can see whether the bathwater indeed has a baby in it. By conducting the placebo-controlled A-CVC BAMSG trial, our colleagues are leading this effort, which is a testimony to their huge contributions to this field of research. The best credit that we can give them is to participate in their quest for the truth. So let us all join them, replace the water, and grab our washcloth. We have a baby to wash.

Acknowledgment

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