Are Antimicrobial-Impregnated Catheters Effective? When Does Repetition Reach the Point of Exhaustion?

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We read with interest the reply by McConnell et al. [1], recently published in Clinical Infectious Diseases, to our earlier commentary [2]. We believe our colleagues fail to truly address the points we raised in their enthusiasm to refute a large body of scientific data supporting the efficacy of antimicrobial-impregnated central venous catheters (CVCs). Although their response focused on a number of issues, their arguments can be summed up as follows: 1) most primary bacteremias derive from enteromucosal, rather than cutaneous, sources; 2) even if most primary bacteremias are catheter-related, they are not associated with significant adverse consequences; and 3) even if CVC-related bloodstream infections (BSIs) are not associated with significant adverse consequences; and 3) even if CVC-related bloodstream infections (BSIs) are worth preventing, antimicrobial-impregnated CVCs have not been shown to be effective.

McConnell et al. [1] first obfuscate the discussion over the efficacy of antimicrobial-impregnated CVCs by raising a scientific theory of ambiguous foundation, when they state that most primary bacteremias are catheter-related, rather than enteromucosal, origin, although limited published data weakly support an enteromucosal theory [3, 4]. McConnell et al. [1] ignore a large volume of studies documenting the cutaneous origin of bacteremia associated with the use of short-term CVCs, the subject of our discourse [5–9]. How are we to reconcile the enteromucosal theory with the results of studies demonstrating marked reductions in rates of CVC-related bacteremia associated with educational programs that stress the proper insertion and maintenance of CVCs [10, 11], reduced rates of bacteremia associated with the use of an enhanced cutaneous antiseptic at CVC insertion [12, 13], the marked differences in rates of bacteremia associated with different types of intravascular devices [14], the 60% reduction in rates of bacteremia associated with use of a chlorhexidine-impregnated sponge dressing at catheter insertion sites [15], and the 7-fold reduction in rates of bacteremia in patients receiving hemodialysis when mupirocin ointment is applied to their catheter insertion site [16]?

In point of fact, we are confident that McConnell et al. [1] do not treat primary bacteremia as an “important clinical event” [1, p. 1830]. Arguing that a preventative intervention is based on studies that, although inconclusive with regard to an impact on attributable mortality, have universally shown that catheter-related BSIs are associated with prolonged hospital stays and increased utilization of health care [41–48]. By focusing on an absence of conclusive evidence demonstrating excess mortality associated with catheter-related BSI [49], McConnell et al. [1] imply that CVC-related BSI is not a clinically relevant event. This argument would suggest that McConnell et al. [1] do not consider bacteremia a serious outcome, because they contradict themselves later on when they describe catheter-related BSI as an “important clinical event” [1, p. 1830].

Arguments about the source of primary bacteremias and their consequences aside, the heart of the matter is whether antimicrobial-impregnated CVCs in selected clinical situations on the basis of the position that CVC-related BSI is clearly worth preventing. This recommendation is based on studies that, although inconclusive with regard to an impact on attributable mortality, have universally shown that catheter-related BSIs are associated with prolonged hospital stays and increased utilization of health care [41–48]. By focusing on an absence of conclusive evidence demonstrating excess mortality associated with catheter-related BSI [49], McConnell et al. [1] imply that CVC-related BSI is not a clinically relevant event. This argument would suggest that McConnell et al. [1] do not treat primary bacteremia as an “important clinical event” [1, p. 1830].

The Centers for Disease Control and Prevention (CDC)/Healthcare Infection Control Practices Advisory Committee (HICPAC) Guideline for the Prevention of Intravascular Catheter-Related Infections [40] recommends the use of antimicrobial-impregnated CVCs in selected clinical situations on the basis of...
a study endpoint found major reductions in the numbers of bacteria found on impregnated CVCs, compared with control catheters. Moreover, 13 of the 17 published studies that examined the effect of antimicrobial-impregnated CVCs on rates of CVC-related BSI found either a statistically significant reduction [26, 27, 31, 35] or a strong trend toward a reduction in rates of BSI [17, 19, 20, 24, 25, 28, 30, 32, 34]. Aggregate analysis of these trials suggests that 40% of intravascular device-related BSIs are preventable with the use of antimicrobial-impregnated CVCs [36, 37]. Despite this powerful consistency of effect, McConnell et al. [1] argue that many of the methodological flaws in these studies are “fatal” and therefore should invalidate the study’s findings. We respectfully disagree.

We agree that the CDC’s definitions for CVC-associated bacteremia are inadequate for the purposes of research [50]. However, we fear that McConnell et al. [1] have overlooked the fact that none of the 11 studies that they critiqued [49] used the CDC surveillance definition of CVC-associated bacteremia [51]; rather, all used acceptable criteria for defining CVC-related BSI [50]. Seven of the 11 studies that they reviewed required recovery of the same species from a culture of the removed catheter and from ≥1 peripheral blood culture [21, 22, 25, 28–30, 32], 1 study employed paired quantitative blood cultures [25], and the 3 most rigorous studies required concordance by DNA subtyping between isolates from blood cultures and colonized catheters [20, 26, 27]. We would suggest that the outcome criteria used in these studies are more rigorous than the composite outcome score used to determine the clinical efficacy of antifungal therapies [52, 53]. Moreover, even if the use of methods for defining CVC-related BSI in the studies McConnell et al. [1] criticized had resulted in nondifferential misclassification bias, this would bias study results toward the null hypothesis, not toward the alternative hypothesis [54].

Intention-to-treat (ITT) analyses—“analyze as randomized”—serve a number of purposes, including reducing bias caused by exclusion of odd outcomes, reducing informative dropouts when dropping out is related to the outcome, maintaining the comparability between the study groups, and maintaining the generalizability (i.e., external validity) of the study results. McConnell et al. [1] state that failing to do an ITT analysis is a fatal flaw of a clinical study—that is to say, any result from such a study is presumably invalid and useless. However, it is interesting that our colleagues have participated in a number of studies that did not include ITT analyses [53, 55]. The exclusions found in most studies on antimicrobial-impregnated CVCs occurred because of a very short duration of CVC use (<48 h) or because the study catheter was lost, making a determination of catheter segment colonization impossible. Exclusion of these catheters from the final analysis is similar to the modified ITT analysis considered acceptable in many clinical trials [56, 57]. If we were to subscribe to the dogmatic approach proposed by McConnell et al. [1], we would be forced to disregard the findings of many important studies in the medical literature that have had a positive effect on patient care.

McConnell et al. [1] argue that failing to measure a number of confounders (including severity of illness and degree of immunosuppression) invalidates the findings of the studies of antimicrobial-impregnated CVCs. As pointed out in our previous commentary [2], all of the studies examining antimicrobial-impregnated CVCs employed acceptable randomization schemes that greatly reduce the risk of bias that can arise as a result of imbalances in unmeasured confounders. The possibility that bias could have occurred in a given trial can never be ruled out, no matter how rigorous the randomization scheme; however, to assume that such bias occurred in every study examining the efficacy of antimicrobial-impregnated CVCs seems remote, especially because the detailed comparisons of the study populations in every trial showed very few differences.

McConnell et al. [1] argue that the ideal study of antimicrobial-impregnated CVCs should be restricted to patients without other forms of vascular access who have not undergone placement of a CVC by guidewire exchange. We strongly disagree. Patients with multiple types of intravascular devices tend to have a higher severity of illness, and the risk of catheter-related BSI posed by other types of intravascular devices is not inconsequential [8, 58, 59]. Moreover, CVCs placed by guidewire exchange have a higher risk of CVC-related BSI [8, 60]. McConnell et al. [1] fail to realize that inclusion of patients with these characteristics would most likely bias study results toward the null hypothesis, not toward the alternative hypothesis. Moreover, the process of excluding patients with these characteristics would seriously compromise the external validity of the study, because the patient population at the highest risk of CVC-related BSI would not be able to participate in such a study because of the ubiquity of these characteristics in many patients in intensive care units. As pointed out in our previous commentary [2], we feel very strongly that trials of technologies to prevent CVC-related BSI should have as few exclusions as possible and should include patients at the highest possible risk to allow for generalization to the populations most likely to derive benefit from advances in medical technologies.

McConnell et al. [1] state that there is simply no substitute for evidence-based medicine. We could not agree more, yet we remain perplexed by what they require as evidence, when they argue that most primary bacteremias arise from entero-mucosal surfaces and ardently argue for aggressive protective isolation for immunocompromised patients in the absence of large-scale studies of any quality [61, 62]. In contrast, multiple independent studies of antimicrobial-impregnated CVCs have shown a powerfully consistent reduction in catheter colonization [17–21, 23, 24,
26–34), and the most rigorous and well-designed studies have demonstrated a highly significant reduction in rates of CVC-related BSI [20, 26, 27, 35].

Finally, McConnell and colleagues argue that our support for a large comparative trial of antiseptic-impregnated and antimicrobial-coated CVCs is proof that evidence in support of the use of antimicrobial-impregnated CVCs is inconclusive. The primary goal of the National Institutes of Health Bacterial and Mycological Study Group (BAMSG) study protocol, proposed and coauthored by one of us (D.G.M.), is to determine whether the benefit found in previous studies of antimicrobial-impregnated CVCs would be maintained now that chlorhexidine (which was not routinely available in earlier studies) has become the cutaneous antiseptic of choice in most US hospitals. Unfortunately, although the BAMSG made enormous progress in studies of fungal infections (primarily because industry generously supported their studies of antifungal drugs), manufacturers of intravascular devices have not been willing to provide the funding necessary to undertake the study we proposed, and it has languished for 3 years because of a lack of finances. We believe that BAMSG needs much more funding from the federal government if it is to undertake large-scale studies of this kind to reverse the rising tide of antimicrobial-resistant nosocomial infections in hospitals and nursing homes, which is one of the reasons it was founded [63].

McConnell and colleagues have sufficient experience in clinical investigation to realize that a scientific theory cannot be proven; it can simply be accepted or discarded through the repetitious accumulation of sound scientific data [64]. Readily admitting that earlier studies of the efficacy of antimicrobial-impregnated CVCs possessed methodological flaws, we believe that the cumulative data generated from 19 randomized, controlled trials [17–35], 3 meta-analyses [7, 36, 37], and 2 cost-benefit analyses [38, 39] suggest strongly that antimicrobial-impregnated CVCs are effective for the prevention of CVC-related BSI. Despite the limitations of these studies, we fear that McConnell et al. [1] would pursue the quixotic goal of the perfect clinical trial, not realizing that, even if that goal were achieved, such a trial would still not prove the efficacy of this technology beyond a shadow of a doubt.

A recent study [65] has demonstrated that marked reductions in the prevalence of CVC-related BSI can be achieved without introducing novel technology. By implementing 5 simple procedures—1) educating caregivers, 2) creating catheter-insertion carts, 3) asking clinicians on a daily basis if the CVC can be removed, 4) empowering nurses to stop a catheter insertion when breaches in antisepsis are observed, and 5) using a checklist to ensure adherence to evidence-based guidelines [40]—the authors claim to have prevented >40 CVC-related cases of BSI over a 4-year period [65]. As a result, we are not arguing that antimicrobial-impregnated CVCs should be routinely employed in hospitals for the prevention of CVC-related BSI (although we support their selective use in situations in which rates of CVC-related BSI remain unacceptably high despite adherence to standard infection-control practices) [40]. The goal of our continued discourse on this matter is simply to inform clinicians that antimicrobial-impregnated CVCs are effective and that we believe that resources are better spent on other areas of inquiry. When does repetition reach a point of diminishing returns (and exhaustion)?

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