Are Antimicrobial-Impregnated Catheters Effective? Don’t Throw Out the Baby with the Bathwater

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The antimicrobial-impregnated central venous catheter (CVC) has been the most intensively studied technology for the prevention of CVC-related bloodstream infections (BSIs) over the past 30 years. Although more than a dozen randomized trials have shown significant benefit, authors of an analysis published in a recent issue of Clinical Infectious Diseases have raised questions about the efficacy of antimicrobial-impregnated CVCs because of perceived defects in the experimental design of the studies and statistical analyses of the data. They have further argued that even if this technology might be effective in preventing CVC-related BSI, its cost-effectiveness is questionable. Although most of the studies scrutinized by the authors of this analysis indeed had shortcomings, we believe that their analysis unjustifiably downplays a large body of research that has demonstrated a consistent reduction in CVC-related BSI and a clear-cut cost-effectiveness associated with the use of antimicrobial-impregnated CVCs.

Eighteen randomized trials evaluating the efficacy of chlorhexidine-silver sulfadiazine– or minocycline-rifampin–impregnated central venous catheters (CVCs) have been published as articles or abstracts since 1994 [1–18]. Thirteen of 15 studies that evaluated catheter colonization—defined as positive results of semiquantitative or quantitative cultures of catheter segments [5, 17]—found substantially fewer colonized antimicrobial-impregnated CVCs [1–4, 7, 8, 10–16, 18]. Catheter colonization is a surrogate end point that has been shown to correlate powerfully with the subsequent development of catheter-related bloodstream infection (BSI) [19]. In aggregate, antimicrobial-impregnated CVCs were associated with a 46% reduction in the number of colonized CVCs when compared with control nonimpregnated CVCs (269 of 1723 vs. 492 of 1716; OR, 0.54; 95% CI, 0.48–0.62; \( P < .0001 \)).

But of even more importance, 11 of the 15 published studies that examined the effect of antimicrobial-impregnated CVCs on rates of CVC-related BSI found either a statistically significant reduction [10, 11, 15] or a strong trend towards a reduction in rates of CVC-related BSI [1, 3, 4, 8, 9, 12, 14, 16, 18]. Aggregate analysis of the 15 studies that compared antimicrobial-impregnated CVCs with nonimpregnated CVCs [1, 3–6, 8–14, 16–18], encompassing a total of 4250 CVCs, show that antimicrobial-impregnated CVCs are associated with a 40% reduction in CVC-related BSI (61 of 2129 vs. 101 of 2118 CVCs; OR, 0.60; 95% CI, 0.44–0.82; \( P = .001 \)), a result remarkably similar to the findings of 3 published meta-analyses [20–22].

Finally, 2 rigorous and sophisticated economic analyses have found that antimicrobial-impregnated CVCs are cost-effective [23, 24]. Veenstra et al. [23] showed that antimicrobial-impregnated CVCs remained cost-effective, even if the cost of a CVC-related BSI was as low as $687 per case; cost savings were $196 per antimicrobial-impregnated CVC when a more realistic cost of a CVC-related BSI of $9738 was used in the analysis. Shorr et al. [24] showed that use of antimicrobial-impregnated CVCs was associated with a cost-savings of $9600 per CVC-related BSI prevented and that $165 to $280 would be saved for every patient who received an antimicrobial-impregnated CVC. On the basis of this large body of data, 2 national advisory panels have recommended the use of antimicrobial-impregnated CVCs in selected clinical settings [25, 26].

McConnell et al. [27] have called into
question the efficacy and cost-effectiveness of antimicrobial-impregnated CVCs in a paper recently published in *Clinical Infectious Diseases* [27]. We believe that a careful examination of their arguments supports the conclusions they seek to refute.

**VIEWPOINTS**

- McConnell et al. [27] argue that none of the studies of antimicrobial-impregnated CVCs demonstrated an improvement in CVC retention, antimicrobial use, duration of hospitalization, or patient mortality.

We agree, but this criticism ignores the fact that these studies were not designed or powered to answer these questions. In point of fact, to determine whether antimicrobial-impregnated CVCs reduce patient mortality would require a trial with 8000–17,000 subjects randomized to each arm of the study, assuming an attributable mortality as high as 20% and a power of 0.80. Asking the reader to dismiss the results of the published trials because investigators did not address these outcomes is akin to dismissing the benefit of antiretroviral therapy in the treatment of patients with AIDS because, individually, the trials examining drug efficacy were not designed or powered to assess their impact on AIDS-related mortality [28]. In the absence of monetary support for a trial large enough to answer such end points, clinicians must be guided by the best available data, which shows an unequivocal protective effect with the use of antimicrobial-impregnated CVCs.

- McConnell et al. [27] criticize the use of different criteria for CVC-related BSI in the published trials. All 11 of the trials they scrutinized employed accepted published criteria for diagnosing and defining CVC-related BSI [29–31]. Recovery of the same species from a culture of the removed catheter and ≥1 peripheral blood culture was used as criteria in 7 of the 11 studies reviewed by McConnell et al. [5, 6, 9, 12–14, 16]; 1 study employed paired quantitative blood cultures [9]; and 3 also required concordant results of DNA subtyping for isolates from blood cultures and colonized catheters [4, 10, 11].

We should point out that failure to use molecular subtyping in most of the published trials actually strengthens the conclusions of the pooled analysis, because one would expect a dilution of outcome effect with a less rigorous case definition. This appears to be the case, because the studies that employed the most rigorous clinical and laboratory criteria for defining CVC-related BSI—concordant PFGE results for isolates from peripheral blood cultures and semiquantitative subcutaneous catheter segment cultures—showed the greatest risk reduction with antimicrobial-impregnated CVCs (risk ratio, 0.10; 95% CI, 0.02–0.44; P < .001) [4, 10, 11].

- McConnell et al. [27] argue that confounding variables, such as severity of illness or degree of immunosuppression, were not adequately addressed in the published studies.

Ten of the 11 studies they scrutinized used acceptable randomization schemes when allocating subjects to treatment and control groups, making it unlikely that there were major imbalances in unreported variables between the 2 study groups. Furthermore, in the 8 studies that provided the greatest detail on baseline features of the study populations [4–6, 9–11, 13, 14], there were no material differences between subjects randomized to receive antimicrobial-impregnated CVCs and those randomized to receive control CVCs. Moreover, when small imbalances were found, such as more CVCs exchanged over a guidewire [10] or a longer duration of catheterization [14], the imbalances favored the control group rather than patients receiving an antimicrobial-impregnated CVC.

- McConnell et al. [27] criticize the trials that allowed enrollment of patients with arterial catheters or patients who had a second catheter placed in an old insertion site by guidewire exchange.

We believe this criticism is specious. Many of these studies were performed in the intensive care unit setting, where arterial catheters are ubiquitous. Moreover, for better or worse, guidewire catheter exchanges are also a fact of life in modern day intensive care. We believe it is a mistake to arbitrarily exclude large numbers of patients in a clinical trial of an important new preventative technology, because it then becomes difficult to infer wide applicability if the technology has only been studied in a very narrowly defined patient population. Furthermore, allowing for the use of other forms of vascular access and guidewire-exchanged catheters again most likely dilutes the protective effect seen with antimicrobial-impregnated CVCs, which, in essence, strengthens the conclusions found in the aggregate analyses [20–22].

- McConnell et al. [27] criticize the statistical methodology of most of the trials, pointing to the failure to report 95% CIs or provide infection rates per 1000 CVC-days and to a paucity of classic intent-to-treat analyses.

95% CIs are easily calculable from most of the published trials, and the omission of infection rates per 1000 CVC-days does not change the findings of any individual study or of the aggregate analyses. The absence of intent-to-treat analysis in individual studies is a valid criticism. However, only 8% of the CVCs examined in the 11 studies cited by McConnell et al. [27] were lost to follow-up. Moreover, three-fourths of the study CVCs lost to follow-up were excluded because cultures of the CVC segments could not be performed or because the CVC was in place for periods ranging from <48 h up to 96 h. In the 5 studies that provided the most complete data, follow-up losses of enrolled CVCs were comparable in both treatment groups [5, 6, 10, 11, 14].

It must be pointed out that all of the studies cited employed a prospective ran-
domination design, and, in 10 of 11 studies that reported baseline demographic features of patients in both arms of the study, no differences were found, making selection bias highly unlikely. None of these shortcomings invalidate the findings of a large body of data that demonstrates a powerful reduction in risk of infection and a remarkable consistency of effect across multiple studies, characteristics that are very important from an epidemiologic standpoint [32].

- McConnell et al. [27] go out of their way to downplay the morbidity of CVC-related BSIs.

In other words, even if antimicrobial-impregnated CVCs might prevent CVC-related infection, CVC-related BSI is really not that big a deal. McConnell et al. [27] contend that, because coagulase-negative staphylococci caused the majority of CVC-related BSIs in the published studies, the benefit seen with antimicrobial-impregnated CVCs is somehow diminished. We doubt that McConnell et al. [27] no longer treat the coagulase-negative staphylococci bacteremias they encounter at their institution. Although some investigators have reported a 14%–16% attributable mortality with coagulase-negative staphylococci bacteremia [33–35], we are willing to accept that coagulase-negative staphylococci bacteremias may not be associated with excess mortality [36, 37]. However, we challenge the inference of McConnell et al. [27] that CVC-related BSIs in general are not associated with significant attributable mortality—a conclusion that they base primarily on the results of 3 recent studies [38–40].

Coagulase-negative staphylococci and enterococci accounted for >60% of the isolates in 2 of these 3 studies [39, 40], diluting the far greater attributable mortality of CVC-related BSIs caused by more pathogenic organisms, such as *Staphylococcus aureus* [41–48] and *Candida* species [49–54]. Furthermore, we believe that, although all 3 of these case-control studies were laudable in their attempts to adjust for the presence of confounding variables in their patient populations, 2 had problems matching case patients to control subjects, as witnessed by the divergence of severity-of-illness scores among study participants after matching but well before onset of CVC-related BSI [38] and a paradoxically increased mortality among control patients [40]. Moreover, all 3 of these studies were quite small, consisting of 98 [40], 114 [39], and 136 [38] patients. Studies of this size would only have a power of 19%–50% to detect a 12%–25% attributable mortality of CVC-related BSI, assuming a 30% baseline mortality among uninfected patients.

Focusing solely on the results of these studies ignores the fact that at least 5 studies published since 1991 have shown that CVC-related BSIs are associated with significant attributable mortality, ranging from 4% to 37% [55–59]. Until larger, better designed trials are performed, the excess mortality associated with CVC-related BSI remains an unresolved issue; however, it must be pointed out that a useful public health intervention does not have to save lives to be worthwhile if it reduces morbidity and health care costs.

The impact of CVC-related BSIs on other outcomes is far less controversial, because every published study examining the clinical sequelae of CVC-related BSI—even the studies cited by McConnell et al. [27], which infer an absence of attributable mortality from CVC-related BSI [38–40]—found that these infections are associated with substantially increased length of hospitalization and incremental health care costs, ranging from $3700 to $56,000 per case [38–40, 55–58]. These findings, coupled with the results of formal economic analyses [23, 24], strongly support the use of antimicrobial-impregnated CVCs on the basis of a cost-effectiveness standpoint.

**DISCUSSION**

Neither we nor other workers in this field have called for the routine use of antimicrobial-impregnated CVCs, because of their substantial costs. The 2002 Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention recommends the use of antimicrobial-impregnated CVCs only in institutions where rates of CVC-related BSI remain high (>3.3 BSIs per 1000 CVC-days) despite consistent application of appropriate infection-control practices [26]. The growing availability of simpler, less expensive technologies, such as chlorhexidine gluconate for access site cutaneous antisepsis [60] and chlorhexidine-impregnated dressings [61], may further reduce the need for relatively expensive antimicrobial-impregnated CVCs [22].

We welcome the critical scrutiny of this important topic by McConnell et al. [27]. However, we fear that they would throw out the baby with the bathwater. Prospective, randomized trials of strategies for control of nosocomial infection are relatively recent phenomena in clinical research, with the vast majority of studies done and published only within the past decade, in great measure because of as yet limited federal support for this type of research. There have been very few multicenter trials to date [11, 15, 61–65], despite a desperate need for such trials in the field.

We would point out that the early studies of anti-infective agents used for treatment of neutropenic fever [66–68], drugs used for the prevention and treatment of invasive fungal infections in immunocompromised patients [69, 70], and high-efficiency particulate air–filtered air for protecting granulocytopenic and other immunocompromised patients from filamentous fungal infections [71, 72] are vulnerable to most or all of the criticisms raised by McConnell et al. [27], yet the results of these studies were accepted at the time and were widely applied in clinical practice. Only in the past decade, during which there has been greatly increased federal and industry support, have more rigorous, large-scale, multicenter trials been undertaken in some of these areas.
[73–75], with cutting-edge experimental design and statistical analyses that have permitted more conclusive results and stronger evidence-based guidelines [76–78].

In summary, although most studies to date of antimicrobial-impregnated CVCs have not been perfect in terms of experimental design and statistical analyses, all have been prospective, all have been randomized and have showed excellent balance between the treatment groups, and, in most, relatively few enrolled CVCs were lost to follow-up. Moreover, all studies except 2 have demonstrated with impressive consistency a striking reduction in the number of colonized CVCs, the prelude to CVC-related BSI. Finally, the largest and best-controlled trials, which also utilized molecular subtyping, have not only shown a substantial reduction in colonization, but a very substantial and highly significant reduction in CVC-related BSI [10, 11, 15].

Every published clinical trial has faults, and waiting for the perfect study not only wastes precious resources but delays adoption of needed advances in patient care while we do even more research to try to show what we have already found to be true. Don’t throw out the baby with the bathwater.

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