Making catheter-related bloodstream infections history: From the slogan to the serious strategy*

Central venous catheters (CVC) have become an essential and necessary component of the modern management of critically ill patients. However, the benefits of the CVC are often offset by the fact that such devices have now been recognized as the leading source of bloodstream infections in this critically ill patient population, which is associated with high morbidity and mortality (1).

For years, it has been recognized that catheter-related bloodstream infection (CRBSI) in critically ill patients is a preventable serious complication. In 1988, Maki et al (2) predicted that "binding an antimicrobial to the entire catheter surface may ultimately prove to be the most effective technological innovation for reducing the risk of device-related infections.” Subsequently, Maki et al have demonstrated that CVC impregnated with antimicrobial agents are the “most intensively studied technology for the prevention of CRBSI over the past 30 years” and have also shown that such anti-infective CVC (AI-CVC) are highly cost-effective, safe, and do not appear to select for resistance (3).

In the systematic review and meta-analysis by Hockenhull et al (4) published in this issue of Critical Care Medicine, 38 prospective randomized controlled trials of AI-CVC were evaluated. Meta-analysis data from 27 trials have demonstrated a strong treatment effect in favor of AI-CVC (odds ratio: 0.49; 95% confidence interval: 0.3–0.64). However, further subgroup analysis of different types of AI-CVC showed that the direction of the treatment effect favored the antimicrobial-coated catheters in all subgroups, except for the benzalkonium chloride–treated CVC. Further subanalysis demonstrated that the minocycline/rifampin coating was associated with the most significant treatment effect (odds ratio: 0.26; 95% confidence interval: 0.15–0.47), whereas other antimicrobial coatings varied as far as their efficacy with the second-generation chlorhexidine/silver sulfadiazine (CHSS+) “just failing to achieve statistical significance.”

References

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*See also p. 702.

Key Words: catheter-related bloodstream infection; critically ill patients; anti-infective central venous catheters

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The review and meta-analysis by Hockenhull et al also demonstrated that the AI-CVC is associated with a decrease in medical costs. They have estimated a cost savings in the United Kingdom for every patient who receives an AI-CVC to be equal to £138.2. This cost benefit is consistent with various analyses that have been demonstrated in multiple reviews conducted in the United States (5, 6).

During the last two decades, various infection control interventions have also been shown to be effective in reducing CRBSI, including the use of maximal sterile barrier precautions during insertion of the CVC and applying chlorhexidine at the insertion site (7, 8). More recently, Pronovost et al (9) have shown that when these effective infection control interventions are used concurrently as part of a “bundle” (that includes maximal sterile barrier precautions, hand washing, cleaning the insertion site with chlorhexidine, and avoidance of femoral vein insertion and unnecessary prolonged use of the catheter), a significant decrease in CRBSI is observed in critically ill patients. Despite the fact that the mean rate of CRBSI in the Pronovost et al study was reduced from 7.7 per 1000 catheter days to 1.4 per 1000 catheter days over a 6–18-month study with a reported median of zero, CRBSI continued to occur, despite the implementation of such infection control interventions.

Although the Pronovost et al study included a large number of intensive care unit and critically ill patients, it demonstrated a significant and prolonged reduction in CRBSI that persisted for an 18-month period. However, there were several limitations to the study. Among the limitations are the lack of assessment of compliance as far as the implementation of the infection control bundle, the crossover design of the study, the poor definitions of CRBSI included in the study, and the lack of assessment of confounding variables (such as the introduction of AI-CVC into the units being studied during the study period). Like Pronovost et al, other investigators have demonstrated that infection control interventions (such as the use of maximal sterile barriers) are associated with a decrease in CRBSI (7, 10). However, such measures on their own do not eliminate CRBSI completely. Although it is now well established that the infection control bundle is the mainstay of preventing CRBSI, it is also well recognized that these measures are often associated with high cost and poor compliance, are not very durable, and do not completely eliminate or prevent infections (10).

Hockenhull et al highlight the fact that “it is important to establish whether the strong treatment effect of AI-CVC remains after effective infection control bundles are established.” Two recent prospective randomized trials that are cited by Hockenhull et al could shed light on this issue (11, 12). In a multicenter prospective randomized study by Rupp et al (11), the second-generation CHSS⁺ was compared with uncoated CVC. During the trial, the infection control bundle was implemented into both arms of the study. In the uncoated CVC control arm, where such infection control bundle measures were implemented, the rate of CRBSI was 1.24 per 1000 catheter days. However, in the test arm, whereby the infection control bundles were implemented in addition to the use of AI-CVC (in this case CHSS⁺), the risk of CRBSI was decreased by more than three-fold to a level as low as 0.4 per 1000 catheter days (11). Another prospective randomized trial by Hanna et al (12) compared the use of an AI-CVC coated with minocycline and rifampin with uncoated CVC. Again, in this study, the elements of the infection control bundle were implemented, including the maximal sterile barrier precautions. In the uncoated CVC arm, the rate of CRBSI was 1.28 per 1000 catheter days, which was further reduced significantly with the use of the AI-CVC (coated with minocycline/rifampin) to a low level of 0.25 per 1000 catheter days (12). Hence, the AI-CVC could complement the infection control bundle measures in further bringing the rate of CRBSI to a very low level approaching zero and, therefore, making CRBSI a very rare entity in high-risk patients.

Hockenhull et al also referred to AI-CVC as a “safety net to prevent contaminating microorganisms from developing into CRBSI.” The referral of AI-CVC as a “safety net” is appropriate from several view points. First, it is well recognized that the absolute and complete compliance with all elements of the infection control bundle is never at a 100% level. The fact that the CVC is transformed into an anti-infective device that will prevent the microbial adherence of resistant pathogens represents another major barrier against biofilm colonization and, ultimately, CRBSI independent of human behavior and lack of compliance with infection control measures. Furthermore, the AI-CVC indeed serves as a safety net in that the infection control bundle, including maximal sterile barrier precautions and sterilization of the skin insertion site with chlorhexidine, do prevent contamination of the CVC during insertion. However, the AI-CVC do prevent biofilm colonization of the external and the internal surface not only during insertion but also subsequently during the dwell time of the catheter, where organisms could migrate from the external skin insertion site surface or from the hub into the lumen of the catheter.

In addition, impregnating the CVC with antimicrobial agents is very much similar to the concept of inoculating the patient with a modified attenuated microbial organism through vaccination. Whereas good infection control measures, including good hygiene, are important in preventing the transmission of various infections, such as polio, measles, and mumps, the use of effective vaccines does, indeed, represent an important safety net to further eliminate such infections (13). Appropriate infection control precautions do not substitute, but rather complement, vaccination as an intervention. The same is true for the AI-CVC.

In conclusion, the review and meta-analysis of Hockenhull et al does demonstrate the strong treatment effect that favors AI-CVC in the prevention of CRBSI, particularly in critically ill patients. Furthermore, the review demonstrates the cost effectiveness of such intervention, showing that such antimicrobial technology represents a safety net in the prevention of CRBSI. Given the new directives by the Central Medical Service System in the United States, including Medicare and Medicaid in not reimbursing hospitals for CRBSI, it is important to further press forward toward the elimination of such infections. To achieve such a zero end point and to realistically eliminate CRBSI, the use of AI-CVC in addition to effective infection control bundle should become the standard of care. Slogans such as “zero tolerance” will not achieve a zero end point of CRBSI and could not eliminate such preventable, serious infections unless they are associated with the implementation of a serious strategy that relies on evidence-based medicine. Using the combination of effective infection control measures with highly efficacious tech-
n December 2006, an article in the New England Journal of Medicine showed how a simple intervention virtually eliminated central venous catheter-related bloodstream infections at hospitals participating in the Michigan Keystone ICU Project (1). Lay and medical authors hailed the findings that suggested the OHRP’s action would discourage similar projects (2, 6–8). Leaders of professional organizations protested (6), whereas authors in the lay press labeled the action “bizarre and dangerous” (2). As one ethicist suggested, the government office responsible for protecting human subjects seemed to have taken action that would only increase harm (7).

In this issue of Critical Care Medicine, Savel et al (9) illuminate the factors precipitating the OHRP’s actions, particularly the lack of consensus regarding the relationship between quality improvement (QI) and human subjects research (HuSR). In advance of the project, the IRB at the lead investigator’s institution, Johns Hopkins, had exempted Keystone from review and waived the informed consent requirement (1). The OHRP disagreed with this exemption, believing the study constituted HuSR, thus mandating oversight from each participating hospital and informed consent (4). Months later, the OHRP seemed to modify its findings, indicating that research like Keystone that entailed negligible risk would qualify for expedited review and waiver of consent (10). Projects that were QI only would not need IRB oversight.

Although the OHRP’s final opinion may have closed this particular case, Savel et al (9) argue persuasively for more clarity regarding the oversight needed for work combining QI and HuSR. To prevent future uncertainty, they offer three recommendations. First, they suggest streamlining approval for QI/HuSR and clarifying the rules guiding the use of central IRBs and waiver of informed consent. Second, they suggest developing ways to make IRB approval less onerous. Third, they suggest that hospitals too small to have IRBs could use IRBs from “nearby regional centers of excellence.”

Several others have contributed to this debate (7, 8, 11, 12). Miller and Emanuel (12) believe three questions are key to evaluating projects like Keystone. First, does the project involve HuSR? Second, if yes, is expedited review appropriate? Third, is informed consent needed? At present, there is little controversy regarding questions two and three: expedited review and waived consent.