Editorial

Bloodstream Infection: An Ounce of Prevention Is a Ton of Work

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Bloodstream infection (BSI) remains the most important infectious complication of vascular access and is associated with prolonged hospital stay,[1-4] increased costs,[1,2,4] and, in some studies, attributable mortality.[1-3,5] Prevention of BSI is essential, especially in patients requiring long-term vascular access for chemotherapy, parenteral nutrition, or hemodialysis. This issue of *Infection Control and Hospital Epidemiology* includes several articles about BSI: two evaluate novel anti-infective lock solutions for intravascular device–related BSI,[6,7] one discusses barriers to the implementation of evidence-based recommendations for prevention of intravascular device–related BSI,[8] one describes the outcomes of *Staphylococcus aureus* BSI in patients undergoing hemodialysis,[9] and one evaluates excess mortality and costs associated with candidemia.[10]

Recent advances in our understanding of the pathogenesis of intravascular device–related BSI have led to the development of effective strategies for prevention.[11-13] For long-term devices, it has been shown that the most common route of infection is intraluminal (ie, at the time of insertion or in the days following, microorganisms contaminate the hub [and lumen] of the intravascular device when the intravascular device is inserted over a percutaneous guidewire or later manipulated).[14-16] A promising approach has involved instilling, or locking, an anti-infective solution into the device lumen to prevent colonization of the intraluminal surface by suspended planktonic-phase contaminants.[17-19] In a meta-analysis of seven randomized, controlled trials, a vancomycin–heparin lock or flush solution was found to considerably reduce the risk of intravascular device–related BSI when compared with a heparin solution alone.[20] There remains concern that a vancomycin-containing lock solution may promote the emergence of vancomycin-resistant organisms, although this is unlikely due to the infinitesimal quantities of vancomycin used. A surge in research exploring anti-infective lock solutions for the prevention and treatment of intravascular device–related BSI has led to the development of several new agents. Novel agents that have shown promise in case reports, pilot studies, or small clinical trials include, among others, taurolidine,[21] gentamicin–citrate,[22] minocycline–ethylenediaminetetraacetic acid (EDTA),[23] and ethanol.[24]

In this issue of *Infection Control and Hospital Epidemiology*, Percival et al. report their findings regarding the efficacy of yet another novel lock solution, tetrasodium EDTA, for eradicating biofilms in an in vitro model system.[6] They found that tetrasodium EDTA effectively eradicated (ie, no growth at the lower limit of detection) biofilms of *S. epidermidis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Escherichia coli* after 21 hours of lock treatment with 4 mL of a 40-mg/mL solution; eradication of biofilms of methicillin-resistant *S. aureus* or *Candida albicans* required a further 4 hours of treatment with a fresh lock solution. The study was limited by the fact that the biofilms studied were immature and lacked the complexity of in vivo biofilms and that there are no published data on the microbicidal activity of tetrasodium EDTA to make a strong case for its superiority over other lock solutions being studied. The same group of authors previously published a study of the efficacy of tetrasodium EDTA for eradication of biofilms developed in vivo and recovered from explanted catheters, which more closely approximates the clinical setting.[25] Nonetheless, the results of the current study are intriguing

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and should lead to further assessment of the utility of this novel lock solution.

Bleyer et al. report the results of a pilot double-blind, randomized, controlled trial comparing minocycline–EDTA with a placebo for the prevention of intravascular device–related BSI in 60 patients undergoing hemodialysis with central venous catheters.[7] A single episode of intravascular device–related BSI occurred in the study in the heparin group. As the authors point out, a strong placebo effect was noted, and the study lacked the power to meet the primary endpoint regarding intravascular device–related BSI. Catheter colonization was markedly different in the treatment and placebo groups. However, the study was limited by the fact that cultures were performed at removal for only 14 of 30 catheters in the heparin group and 11 of 30 catheters in the minocycline–EDTA group. Marked improvement in overall catheter survival was found in the minocycline–EDTA group compared with the placebo group (83% and 66%, respectively); however, the incidence of catheter clotting was the same in the two groups. The favorable results from this trial suggest that this agent should be tested in a larger prospective, randomized trial.

In recent years, several randomized, controlled trials of preventive strategies for intravascular device–related BSI have been conducted, and measures such as chlorhexidine for cutaneous antisepsis[26] and maximal barrier precautions for the insertion of intravascular devices[27] have been unequivocally shown to markedly reduce the risk of intravascular device–related BSI. It also has become apparent, however, that such proof of efficacy, although necessary, is not sufficient for these and other efficacious measures to become part of clinical practice.[28,29] Much attention has focused on the factors that hinder the implementation of evidence-based guidelines into practice. Many identified barriers must be removed before evidence-based guidelines can be incorporated into clinical practice with the goal of improving patient care.[30-32] Several guidelines for the prevention of intravascular device–related BSI have been published, the most recent in 2002.[33]

In this issue of *Infection Control and Hospital Epidemiology*, Rubinson et al.[8] report the results of a cross-sectional survey of 1,000 physicians with the goal of identifying and characterizing self-reported barriers to the implementation of two important evidence-based recommendations for prevention of intravascular device–related BSI: maximal barrier precautions and chlorhexidine for cutaneous antisepsis. The authors used the 1996 Centers for Disease Control and Prevention guideline in their 2002 survey. Of a total sample of 1,000, 178 physicians met the criteria for participation (recent CVC insertion) in the entire survey; 42% of these physicians were residency trainees. The a priori sample size required to produce robust models in multivariable modeling as calculated by the authors was not met regarding maximal barrier precautions, and too few respondents used chlorhexidine to permit meaningful comparisons between chlorhexidine and povidone–iodine. These points notwithstanding, the authors' findings are disturbing. High outcome expectancy was associated with high adherence to maximal barrier precautions in a multivariable model. However, awareness of the Centers for Disease Control and Prevention guideline and external factors, such as lack of equipment and inconvenience, failed to reach statistical significance. The complexity of translating evidence into practice suggests that dissemination of guidelines must be supplemented by intensive efforts to ensure adherence. Barriers to adherence may differ from institution to institution, but a multifaceted, systems-based approach with strong institutional commitment has been shown to be effective for the prevention of intravascular device–related BSI.[34] Rubinson et al. found that feedback of BSI rates to intensive care units or physicians was not associated with high adherence; these results are different from those reported elsewhere[35] and may be related to the small numbers of institutions that did any kind of reporting of BSI rates. Changing physician behavior continues to be a challenge, and more research is needed in this important area.

Patients with end-stage renal disease who require hemodialysis are at extremely high risk of *S. aureus* bacteremia.[36,37] Engemann et al. undertook a descriptive study of the clinical outcome of 210 patients undergoing hemodialysis who had *S. aureus* bacteremia 12 weeks following the bacteremia.[9] Because the study did not contain an unexposed group (patients without *S. aureus* bacteremia), it was not possible to determine the mortality attributable to this infection. Of the 210 patients who comprised the study population, 165 (78.6%) were African American; the mean duration of dialysis was 2.9 years. A troubling finding was that the most frequent hemodialysis access was a tunneled, cuffed intravascular catheter (55.7%) rather than a fistula or graft, which are associated with much lower rates of BSI.[38] Not unexpectedly, the major source of BSI was hemodialysis access (88%) and a considerable proportion of BSI episodes were caused by methicillin-resistant *S. aureus* (33%), which, in a recent study by the same group of investigators, was shown to be associated with fivefold higher mortality compared with methicillin-sensitive *S. aureus* among patients undergoing hemodialysis.[39] Thirty-one percent of the patients suffered complications, the most frequent of which was infective endocarditis (17%).

The authors carefully measured relevant costs for 143 patients for whom cost data were available and estimated that the mean cost of treating an episode of *S. aureus* bacteremia was $24,034. An effective way to greatly reduce the incidence of *S. aureus* bacteremia among patients undergoing hemodialysis would be to expeditiously create a fistula or implant a graft as soon as it becomes apparent that long-term hemodialysis will be necessary. Unfortunately, a recent annual survey from the Centers for Disease Control and Prevention found that the percentage of patients undergoing long-term hemodialysis with a catheter increased from 12.7% in 1995 to 24.0% in 2000.[40]

Candida species have emerged as a major nosocomial pathogen and, according to data from the National Nosocomial Infections Surveillance System, are the fourth

most common cause of BSI in the United States.[41] Morgan et al. performed a large matched cohort study comparing patients who had candidemia with those who did not matched on age, hospital type, year of admission, discharge diagnoses, and duration of hospitalization before the onset of candidemia.[10]

Exposed patients were identified through laboratory surveillance in Baltimore and Baltimore County, Maryland, and Connecticut during 1998 to 2000; the non-exposed group comprised hospitalized patients without candidemia. The excess mortality due to candidemia was 19% in Connecticut and 24% in Baltimore and Baltimore County. However, when treatment was taken into account in the multivariable analysis, adequate treatment (defined by the authors as any systemic antifungal given for 7 days after the first blood culture positive for candidemia) was associated with a 50% to 60% reduction in mortality. The time frame for measuring mortality was not provided. This information is important to determine a temporal relationship between candidemia and mortality when assessing causality. The lack of data regarding microbiology and source of candidemia is a limitation of the study, as these factors may influence morbidity and mortality. Due to the unavailability of data, the investigators were not able to match on or adjust for severity of illness, an important confounding factor.

It is puzzling and unexplained that a considerable number of patients with candidemia did not receive treatment (39% of 178 patients from Connecticut and 30% of 257 patients from Baltimore and Baltimore County). This study predates the widespread availability of the new agents caspofungin and voriconazole and it will be interesting to discover, in future studies, whether these novel agents have an impact on survival from candidemia.

Morgan et al. provide useful data on the economic outcomes of candidemia. The investigators measured total hospital charges and calculated costs using cost-to-charge ratios and compared these data with those for a baseline patient (a patient who did not have candidemia, did not require critical care, and was 30 to 39 years old). Treatment of candidemia (but not candidemia per se) was associated with an increased hospital stay of 7 to 18 days and increased costs of approximately $7,000 to $25,000.

The morbidity and mortality associated with BSI emphasize the importance of continued efforts for prevention. Adherence to evidence-based recommendations is essential. In addition, novel technology, such as anti-infective lock solutions, for the prevention of intravascular device–related BSI offers great promise and should be explored further.

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