EDITORIAL

Lost in Translation

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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] and with greatly increased treatment costs[1,2,4] and attributable mortality.[1-3,5] Prevention of intravascular device–related (IVDR) BSI is fundamental to the patient safety movement, especially for patients requiring long-term vascular access for chemotherapy, parenteral nutrition, or hemodialysis. This issue of the journal contains 5 articles on the subject of healthcare-associated BSI: Warren et al.[6] discuss the formidable challenges in translation of evidence-based medicine to evidence-based practice for prevention of IVDR BSI; Braun et al.[7] compare the effect of using differing methods to ascertain rates of healthcare-associated BSI; Maragakis et al.[8] describe a very troubling increased incidence of BSI in association with a widely used commercial needleless connector; Menyhay and Maki[9] report the results of a simulation study of the effectiveness of conventional alcohol preparation of needleless luer-activated valve connectors with 70% alcohol and the efficacy of a novel antiseptic-barrier cap; and Huang et al.[10] assess the utility of 2 blood cultures for diagnosis of BSI caused by coagulase-negative staphylococci (CNS) in neonates.

In recent years, a number of randomized controlled trials of preventive strategies for IVDR BSI have been conducted, and measures such as use of maximal barrier precautions for intravascular device insertion[11] and use of chlorhexidine for cutaneous antisepsis[12] have been shown unequivocally to greatly reduce the risk of IVDR BSI. It has also become apparent, however, that rigorous proof of efficacy, although necessary, is unfortunately not sufficient for these and other proven control measures to become an integral part of clinical practice.[13,14] Much attention has focused on the factors that hinder implementation of evidence-based guidelines and that must be surmounted before these guidelines can be consistently incorporated into clinical practice to improve patient care.[15-17] A number of evidence-based guidelines for the prevention of IVDR BSI have been published; the most recent was published by the Centers for Disease Control and Prevention (CDC) Healthcare Infection Control Practices Advisory Committee (HICPAC) in 2002.[18]

In this issue, Warren et al.[6] report the findings of a survey undertaken to determine whether key evidence-based recommendations in the 1996 CDC guideline for prevention of BSIs[18a] that addressed short-term intravascular devices, including central venous catheters (CVCs) and peripherally-inserted CVCs, have been adopted by US hospitals. The authors surveyed 10 hospitals associated with the CDC Prevention Epicenters Program, all academic tertiary-care centers. Although the response rate was only 57% for the 25 intensive care units surveyed, and although it is unlikely that these academic centers are representative of US acute-care hospitals in general, the findings are disturbing. As of April 2002, only 28% of the units that responded had a policy regarding the use of maximal sterile barrier precautions at the time of CVC insertion, and only half had a formal training program for aseptic and safe insertion of CVCs. Despite the fact that multiple studies have shown routine replacement of CVCs has no benefit for prevention of infection, in 16% of the intensive care units, catheters were still being routinely replaced, with the goal of preventing CVC-associated BSIs. The study does not provide data regarding the rates of IVDR BSI in the units surveyed, nor do we know to what extent the policies reflect actual clinical practice. Nonetheless, the variability among units noted by Warren et al.[6] indicates that greater standardization and more uniform application of evidence-based guidelines is needed.

It must be emphasized that this survey was conducted 3 and a half years ago, and we think it is highly likely that the findings are no longer applicable to current hospital practices. We believe that the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) care bundle (ie, group of best practices)[19] and the Institute of Healthcare Improvement "Save 100,000 Lives" campaign[20] have had a powerful effect on implementation of infection control measures for prevention of IVDR BSI in hospitals. Nearly all of our sister hospitals in southern Wisconsin have ongoing programs that focus on the JCAHO care bundle for prevention of IVDR BSI; the University of Wisconsin Hospital was surveyed by JCAHO in October 2005, and the surveyors specifically sought hard evidence that our institutional programs for protecting patients against IVDR BSI addressed most of the issues contained in the survey.

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Exploring the reasons for the variability in catheter insertion and in care policy and practice was not an objective of the study by Warren et al.,[6] but there is an urgent need to better understand the barriers that impede effective translation of evidence-based guidelines into practice. Rubinson et al.[21] performed a cross-sectional survey of 1000 physicians, with the goal of identifying and characterizing self-reported barriers to implementation of important evidence-based recommendations for prevention of IVDR BSI, on the basis of the 1996 CDC guideline.[18a] They found that high outcome expectancy was associated with greater adherence to recommendations but that awareness of the guideline per se did not influence adherence. The challenge of translating scientific evidence into clinical practice indicates that promulgation of a guideline must be supplemented by an intensive effort to assure a high level of adherence. Barriers to adherence may differ from institution to institution, but a multifaceted, systems-based approach, with a strong institutional commitment, has been shown to be highly effective for prevention of IVDR BSI.[22]

To determine the magnitude of the problem of IVDR BSI and to gauge the success of interventions for prevention, accurate measurement of BSI rates is essential, especially in light of legislation in many states that now mandates public reporting of rates of healthcare-associated infection.[23] Rates of healthcare-associated BSI may be calculated in a number of ways: using either clinical or administrative data, using either hospital-wide or unit-specific data, with or without data on the source of BSI (primary or secondary), and with or without application of risk adjustment. In this issue, Braun et al.[7] report the findings of a multiple-center observational study that undertook to measure BSI rates and used a variety of definitions and data collection approaches to ascertain whether differences in measurement affected the BSI rates found and the rankings of the hospitals. The authors show that differing denominator data, definitions of BSI, and methods of risk adjustment greatly affect the BSI rates derived. Therefore, benchmarking between institutions may be very misleading—even meaningless—if the methods of rate calculation are not uniform. These results highlight the urgent need to standardize definitions, methods of data collection, and methods of rate calculations for IVDR BSI and all reportable healthcare-associated infections across all reporting institutions.

Needleless connectors were developed, in response to demands for enhanced safety for healthcare workers, to prevent needlestick injuries and are integral components of infusion systems in use across North America. The 3 major design categories of needleless connectors are the split septum design, the luer-activated valve, and the luer valve with positive displacement. Numerous commercial products are available within each category. Although needleless connectors, when properly used, clearly reduce the risk of needlestick injuries associated with accessing the intravascular device or injection ports,[24-27] a handful of reports published over the past decade have raised niggling concerns about a potential increased risk of iatrogenic BSI associated with their use.[28-32] Most of these studies have been retrospective and uncontrolled, and suboptimal usage of the device, rather than the device itself, may have been responsible for the increased incidence of BSI in some settings. The few randomized trials comparing needleless connection devices with standard connectors have found relative reductions in BSI rates with the use of the needleless device under study, ranging from 84% to 86%,[33,34] and the most recent CDC HICPAC guideline on prevention of IVDR BSI concludes that, "when used properly, needleless devices do not adversely affect the incidence of BSI."[18(p11)]

In this issue of the journal, Maragakis et al.[8] describe a sharp increase in BSI rates following introduction of a new needleless connector with a positive-pressure mechanical valve designed to prevent reflux of blood into the catheter. BSI rates increased from a baseline rate (pooled across all ICUs) of 1.5 cases per 1000 catheter-days to 2.4 cases per 1000 catheter-days ($P = .03$). A shift in the microbial profile of IVDR BSI was also seen, with a much higher proportion of cases caused by gram-negative bacilli (an increase from 17.7% to 28.1%) or multiple organisms (an increase from 6.5% to 14%). Rates of IVDR BSI fell back to baseline levels after the institution discontinued use of the new needleless connector and resumed use of the needleless connector used previously, which did not have a positive-pressure mechanical valve.

As Maragakis et al.[8] point out, their study was retrospective and uncontrolled, thus making it difficult to be certain that the new needleless connector was *the* causal factor in the strikingly increased incidence of BSI they observed. Details regarding the type of training and education provided to healthcare staff before introduction of the new connector are not provided; as prior studies have suggested, suboptimal use may be one reason for an intravascular device to be associated with an increased risk of BSI. Although the authors state that their investigations did not uncover major violations of infection control policies at the time of the BSI outbreak, it is unclear whether a formal procedural review was undertaken.

In the study of Maragakis et al.,[8] the administration set and the end caps were changed every 96 hours. Until recently, the manufacturer of the positive-pressure needleless connector did not provide recommendations regarding the frequency of connector change. The manufacturer now recommends that the connector be changed every 72 hours or 100 activations, whichever comes first. In an earlier study of IVDR BSI in the home-care setting, Do An et al.[28] found that altering the frequency of end cap change from once weekly to once every 2 days greatly reduced the risk of BSI, suggesting that the mechanism for BSI associated with use of the device involves contamination from the point of access. It is essential to remain vigilant regarding any undesirable consequences associated with use of needleless connectors, which are now nearly universally used in US hospitals. Future studies exploring this association should endeavor to confirm that a

needleless device is being used properly, to better ascertain whether an increased risk of BSI is causally related to the design of the device itself or to the way the device is used.

Although needleless connectors and injection ports are recognized sites of access for microbial contamination, no national standard exists defining the best and recommended form of antiseptic preparation for prevention of microbial entry when the needleless connector or injection port is accessed. There are, to our knowledge, no clinical trials that have prospectively examined the efficacy of various approaches to disinfection for prevention of CVC-related BSI. The most recent CDC HICPAC guideline has recommended that vascular catheter hubs, needleless connectors, and injection ports be disinfected before being accessed, and this recommendation is classified as category 1B[18]; but the guideline does not recommend any specific disinfection agent or protocol. In most US healthcare centers, the practice is to disinfect catheter hubs, needleless connectors, and injection ports by swabbing of the membranous septum with 70% isopropyl alcohol; however, the study of Menyhay and Maki[9] and limited prior studies[35-37] show that this may not reliably eliminate septal surface contamination. It is noteworthy that novel technological approaches to preventing contamination of CVC administration-set connections by use of a povidone-iodine "shield"[35] or a novel antiseptic-containing connector[36,37] have been shown to reduce rates of CVC-associated BSI in studies done in Europe in settings where there was a very high baseline rate of CVC-associated BSI.

Also in this issue of the journal, Menyhay and Maki[9] report the results of a simulation study of the effectiveness of conventional preparation of needleless luer-activated valve connectors with 70% alcohol and the efficacy of a novel antiseptic-barrier cap that, when threaded onto a luer-adaptable connector, rapidly sterilized a surface contaminated with $\sim 10^5$ colony forming units of *Enterococcus faecalis*.[9] Of 60 contaminated connectors inserted after application of the novel antiseptic cap for 10 minutes, only 1 (1.6%) showed any microbial growth, compared with 15 control devices that showed heavy bacterial growth ($P < .001$). This was an in vitro study, and this novel antiseptic device needs to be tested in clinical trials to determine its efficacy. Novel technology is probably the most effective way to prevent contamination at the point of access and should be studied further.

Coagulase-negative staphylococci are a major cause of healthcare-associated infection,[38-41] especially in immunocompromised patients and neonates and, according to data from the National Nosocomial Infections Surveillance system, are the foremost cause of healthcare-associated BSI in the United States.[42] They are also major components of the normal skin and mucosal microflora, and in clinical practice it is a major challenge to distinguish true bacteremia caused by coagulase-negative staphylococci from contamination that occurs at the time when blood is obtained for culture. The lack of an adequate reference standard for definition of true bacteremia—which is defined variably as a patient's receipt of antibiotics for more than 4 days, or an explicit note in the medical record that the physician diagnosed a true bacteremia, or the CDC's surveillance criteria for primary BSI—makes it difficult to compare methods that distinguish between contamination and bacteremia. Detection of genes putatively associated with virulence has yielded conflicting results,[43-46] and the role of this method in clinical decision making appears to be limited. Strain typing and antibiogram analysis of isolates also do not provide rapid or very useful adjunctive information to aid in clinical decision making. A recent study in children showed that the use of the time to positivity of blood culture for growth of coagulase-negative staphylococci in a continuously monitored blood culture system (Bactec; Becton Dickinson) was useful in distinguishing between contamination and bacteremia; a time to positivity of $\leqslant 15$ hours had a positive predictive value of 84% for diagnosis of true bacteremia.[47]

One important, widely accepted criterion for true bacteremia is the isolation of coagulase-negative staphylococci from *multiple* blood cultures. Use of this criterion presumes that the isolates represent a single clone of the pathogen—which may or may not be valid, since all persons are normally colonized by multiple clones of coagulase-negative staphylococci. If blood samples for culture are collected from different body sites, the contamination of each blood sample during the collection process is an independent, chance event. Therefore, multiple cultures positive for coagulase-negative staphylococci are less likely to represent contamination than true bacteremia. Comparing strain clonality with the clinical criteria for BSI, Seo et al.[48] found that patients with 3 or more positive blood culture results were more likely to have same-strain bacteremia than were patients with only 2 positive culture results (11 of 15 [73%] vs 8 of 27 [30%]; $P = .006$). Unfortunately, there was poor agreement between strain relatedness and clinical definitions of bacteremia.[48] Using mathematical modeling, Tokars[49] found that the positive predictive value for bacteremia was 55% for 1 positive culture result for a single sample cultured, but increased to 98% for 2 positive culture results if both blood samples were obtained percutaneously.

In line with current evidence, Huang et al.[10] report in this issue of the journal that, in neonates with clinical sepsis, 12 of 13 cultures of percutaneously obtained, paired blood samples yielded the same strain, a finding that suggests infection rather than contamination. The authors do not provide data on the courses of the patients in the intensive care unit or the courses of a comparator group of patients from whom only a single blood sample for culture was drawn. Moreover, they provide no reference standard for true bacteremia, such as a quantitative clinical scoring system.[50]

Finally, reducing the rate of contamination of blood cultures may best control the huge adverse clinical and economic impact of contamination of blood cultures with coagulase-negative staphylococci. Multiple prospective trials have found that chlorhexidine or tincture of iodine are much more ef-

fective than povidone iodine for cutaneous antisepsis before drawing the blood sample, providing 50% lower rates of contamination, on average.[51-55] Having a team of trained phlebotomists to collect all blood for culture,[56] providing feedback to phlebotomists regarding contamination rates,[57] and tracking of the blood-culture contamination rate[58] as a quality indicator are all practices that have been shown to lower contamination rates.

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