Commentary

Estimating Excess Length of Stay Due to Central Line–Associated Bloodstream Infection: Separating the Wheat from the Chaff

Christopher J. Crnich, MD, MS

(See the article by Barnett et al, on pages 1106–1114.)

The central line is an instrumental tool of modern health care with great potential to heal and a corresponding potential for harm. Central line–associated bloodstream infection (CLABSI), once thought to be unavoidable in many patients, is now recognized as largely preventable. In recent years, a number of studies have documented impressive reductions in rates of CLABSI through standardization of insertion practices.1,2 Reductions in rates of CLABSI have also been achieved through the judicious application of novel technologies.3,5 Nevertheless, implementation of interventions to prevent CLABSI requires a considerable investment in resources and manpower that hospitals could deploy alternatively on other quality improvement projects. Therefore, it is not enough to know whether an intervention to prevent CLABSI works; it is equally important to know whether the intervention is cost-effective.

A starting point for any cost-effectiveness study is an accurate understanding of the outcomes attributable to the complication. As the primary driver of costs, length of stay (LOS) is the most important outcome that must be addressed in cost-effectiveness studies of interventions for prevention of CLABSI.6 Unfortunately, published estimates of LOS attributable to CLABSI vary widely—from 5 to 20 days7,8—and have, on at least one occasion,9 contributed to the uncertainty surrounding the cost-effectiveness of interventions to prevent CLABSI.

Although contextual differences due to patient population, microbial profile of causative pathogens, and therapeutic management of infection may explain some of the variation in LOS in published studies, bias deriving from methods used to estimate LOS play a far greater role. A number of factors associated with accurate attribution of LOS and the bias that can arise with different methodological approaches are highlighted in Figure 1. In Figure 1, a hypothetical patient is admitted to an intensive care unit (ICU), develops CLABSI on day 4, and has a total hospital stay of 10 days, with the black area representing the LOS that is attributable to CLABSI. Although not explicitly shown in Figure 1, it is assumed that there are a variety of patient and contextual characteristics that also influence the total LOS (eg, severity of illness and age) and that imperfect adjustment will lead to misattribution of hospital days that would have occurred anyway (even if the CLABSI event had never occurred). The accuracy of the estimate of attributable LOS is therefore contingent on the extent to which these characteristics can be measured and adjusted for as well as the total number of days that are eligible for analyses.

In example A, an investigator elects to treat CLABSI as a time-independent event and therefore all days of hospitalization are included in the analysis. Because methods used to adjust for confounding are imperfect and because the time-dependency of CLABSI is ignored, this type of analysis will lead to the largest overestimation of attributable LOS.10 In example B, the investigator recognizes that CLABSI is a time-dependent event and considers only those days after CLABSI as eligible for the analysis but does not adjust for confounding variables, leading to exaggerated estimates of attributable LOS. In example C, the investigator attempts to deal with confounding in the design phase of the study by matching to make control subjects more like case patients on a variety of known confounding variables. However, this process is imperfect at best and counterproductive at worst (eg, if the process used for matching leads to the introduction of selection bias11). Example D demonstrates the problem of competing events. In this example, the CLABSI event actually leads to death on day 5. If competing events are prevalent in the study sample, then estimates of attributable LOS may actually be biased toward the null.

Finally, in example E, the investigator uses advanced statistical methods to explicitly model LOS attributable to CLABSI. The qualifier “advanced” is important in this example, because use of the standard regression methods with which we are most familiar will likely not result in estimates

From the University of Wisconsin School of Medicine and Public Health and the William S. Middleton Veterans Affairs Hospital, Madison, Wisconsin.

Received July 21, 2010; accepted July 23, 2010; electronically published October 4, 2010.

Infect Control Hosp Epidemiol 2010; 31(11):1115-1117

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figure 1. impact of different methodological approaches for estimating the attributable length of stay (A-LOS) in a hypothetical patient who develops central line–associated bloodstream infection (CLABSI). Black bars, the actual length of stay attributable to CLABSI. E-LOS, length of stay eligible for inclusion in analyses.

of attributable LOS that are any less biased than the matched analysis described in example C. Although standard regression methods can account for the time-dependency of CLABSI and the presence of time-independent confounders (eg, Cox regression), use of standard statistical regression methods will lead to biased estimates of attributable LOS for several reasons. First, standard regression models cannot account for competing events (example D).12 Second, adjusting for confounders that are time-dependent (eg, severity of illness) can paradoxically bias attributable LOS estimates toward the null in standard regression models.13 Finally, standard regression models do not account for the bidirectional relationship between CLABSI and LOS (ie, increasing LOS will increase the risk of CLABSI, and CLABSI will increase the risk of a prolonged LOS). If this endogenous variable bias is not dealt with explicitly in the model, estimates of attributable LOS can be exaggerated in unpredictable directions.11

Not surprisingly, identifying and appropriately specifying a statistical model that accounts for all of these potential sources of bias is methodologically rigorous and explains why the use of such a model in the study of healthcare-associated infections has remained largely unexplored.

In this issue of the journal, Barnett et al14 analyzed the impact of CLABSI on LOS by means of prospectively collected data from 11 ICUs in Central and South America. The authors elected to use a multistate approach to model the association between CLABSI and LOS. This methodological approach allowed the authors to explicitly model the onset of CLABSI, thereby avoiding the time-dependent bias that arises from misattribution of hospital days accumulated before the onset of this event (example A in Figure 1). Moreover, by including competing events in their model, the authors were able to address the potential for underestimation of LOS due to premature deaths in patients who developed CLABSI (example D in Figure 1). Finally, by extending their model to include age and severity of illness covariates, the authors were able to adjust their analysis for confounders that may bias the association between CLABSI and LOS (example C in Figure 1). Consistent with other published studies, the authors found that CLABSI increased LOS in 10 of the 11 study ICUs. However, in contrast to previously published studies, the LOS attributable to CLABSI varied only from 0.8 to 4.7 days across participating sites. This estimate is considerably smaller than those identified in the majority of previously published studies that examined this association (ranging from approximately 5 to 20 days) but are consistent with those of a study by Beyersmann et al15 that employed multistate methods. When Beyersmann et al15 studied the LOS attributable to a variety of different healthcare-associated infections, primary bloodstream infection extended the ICU LOS by only approximately 3 days.

Like all published studies, the analysis by Barnett et al14 in this issue is not without its limitations. The authors adjusted their analyses only for age and severity of illness. More importantly, severity of illness was modeled as a time-independent covariate rather than a time-dependent covariate. Studies have shown that the evolution of severity of illness before the onset of CLABSI can have a significant impact on estimates of attributable LOS.16 However, inclusion of severity of illness as a time-dependent covariate in models faces a number of logistical and methodological challenges. First, severity of illness is collected cross-sectionally at admission in most hospitals, and collecting this information longitudinally may be unfeasible in many centers. Second, severity of illness may function both as a confounder and as an intermediary in the association between CLABSI and LOS, and without the use of specific statistical adjustment methods, inclusion of severity of illness as a time-dependent covariate may actually bias attributable LOS estimates toward the null.13

These limitations notwithstanding, the work of Barnett et al14 represents an important step toward a more accurate understanding of the impact of CLABSI on health outcomes, and future investigations should strive to build upon the approach taken in their study.
ACKNOWLEDGMENTS

Potential conflicts of interest. C.J.C. reports no conflicts of interest relevant to this article.

Address reprint requests to Christopher J. Crnich, MD, MS, University of Wisconsin School of Medicine and Public Health, 1685 Highland Avenue, Madison, WI 53705-2281 (cjc@medicine.wisc.edu).

REFERENCES