ORIGINAL ARTICLE

Excess Length of Stay Due to Central Line–Associated Bloodstream Infection in Intensive Care Units in Argentina, Brazil, and Mexico

Adrian G. Barnett, PhD; Nicholas Graves, PhD; Victor D. Rosenthal, MD; Reinaldo Salomao, MD; Manuel Sigfrido Rangel-Frausto, MD

OBJECTIVE. To estimate the excess length of stay in an intensive care unit (ICU) due to a central line–associated bloodstream infection (CLABSI), using a multistate model that accounts for the timing of infection.

DESIGN. A cohort of 3,560 patients followed up for 36,806 days in ICUs.

SETTING. Eleven ICUs in 3 Latin American countries: Argentina, Brazil, and Mexico.

PATIENTS. All patients admitted to the ICU during a defined time period with a central line in place for more than 24 hours.

RESULTS. The average excess length of stay due to a CLABSI increased in 10 of 11 ICUs and varied from −1.23 days to 4.69 days. A reduction in length of stay in Mexico was probably caused by an increased risk of death due to CLABSI, leading to shorter times to death. Adjusting for patient age and Acute Severity of Illness Score tended to increase the estimated excess length of stays due to CLABSI.

CONCLUSIONS. CLABSIs are associated with an excess length of ICU stay. The average excess length of stay varies between ICUs, most likely because of the case-mix of admissions and differences in the ways that hospitals deal with infections.

Infect Control Hosp Epidemiol 2010; 31(11):000-000

Vascular access poses significant potential risks of iatrogenic complications in general but of central line–associated bloodstream infection (CLABSI) in particular. Almost 60% of all types of nosocomial bacteremia originate from some form of vascular access.[1] In 2002, we established an International Nosocomial Infection Control Consortium in Latin America and in other countries of the developing world and found that rates of CLABSI in the intensive care units (ICUs) of the hospitals of these countries are 3–5 times higher than rates in North American ICUs.[2-13]

Patients with CLABSI tend to stay longer in the ICU than patients who avoid infection. Numerous estimates of the excess length of stay in the hospital due to CLABSI have been reported in the literature and range from 2.7[14] to 48.5 days.[15] Forty-eight different estimates have been published,[16] and these were derived from the following range of methods: unadjusted comparison between those with infection and those without infection; matched cohort studies, in which patients with an infection are matched to infection-free patients on variables thought to influence length of stay[17,18]; the concurrent method, in which expert opinion is used to assess excess stay; and comparison of infected patients with uninfected patients by statistical analyses, such as multivariable regression in which infection is a binary independent variable and length of stay is the continuous dependent variable.[19]

There is a discussion in the literature about biases that arise from the various methods used to find the independent effect of infection on length of stay.[14,20-22] An important challenge—that is currently underresearched—is to account for the timing of infection.[20,23] The challenge arises because infection prolongs stay but longer stays increase the chance of infection. This creates a complex dependence between length of stay and infection and means that standard statistical methods cannot be used. Methods that account for the time-dependent nature of infection are recognized as critically important for accurately measuring the excess lengths of stay in the hospital due to infection.[23]

The aim of this paper is to apply a statistical method that

From the Institute of Health and Biomedical Innovation and School of Public Health, Queensland University of Technology, Kelvin Grove, Australia (A.G.B., N.G.); the International Nosocomial Infection Control Consortium, Buenos Aires, Argentina (V.D.R.); Santa Marcelina Hospital, Sao Paulo, Brazil (R.S.); and Specialties IMSS Hospital, Mexico City, Mexico (M.S.R.-F.).

 0899-823X/2010/3111-00XX$15.00. DOI: 10.1086/656593
Received February 26, 2010; accepted May 19, 2010; electronically published September XX, 2010.

accounts for the timing of infection and thus will accurately estimate the excess length of stay due to a CLABSI. We used data from 11 ICUs in Argentina, Brazil, and Mexico.

METHODS

Data Collection

The data were collected by the International Nosocomial Infection Control Consortium,[24] which is a nonprofit, multicenter, collaborative healthcare-acquired infection control program that employs a surveillance system[2-13] based on the US National Healthcare Safety Network.[25] In this study, we look at the CLABSI results in 4 ICUs from 2 hospitals in Argentina,[2,3] 3 ICUs from 1 hospital in Brazil,[9] and 4 ICUs from 3 hospitals in Mexico.[6]

The laboratory techniques used, training programs for data collectors, definitions of infection, and surveillance activities are described in detail by Rosenthal et al.[24] All patients hospitalized in the ICU for more than 24 hours were prospectively followed up; detailed information was collected on each day. The following variables were used in this analysis: hospital name and location; dates of admission, discharge, and death; date, type, and site of healthcare-acquired infection; presence of central line; Average Severity of Illness Score (ASIS); and age. In this study, we used data only from patients with a central line, because these patients are the exposed population and this is the group in whom we want to measure the risks of infection. No other exclusion criteria were applied.

Statistical Methods

We used a multistate approach to model the excess length of stay due to CLABSI. This method has previously been applied to modeling length of stay.[20] The article by Putter et al[26] serves as a tutorial on multistate and competing risks models. A strength of multistate models is their ability to incorporate time-dependent exposures. In this study, CLABSI is the key time-dependent exposure, because it can happen at any time during a patient's stay. The bias of using other methods (such as matching studies) for estimating the effects of time-dependent exposures has been demonstrated.[23] The bias of not accounting for time-dependent exposure depends on the effect of the exposure on length of stay. If the exposure has no effect, the biased analysis will wrongly predict an excess length of stay; if the exposure does extend length of stay, then the biased analysis will overestimate this excess; and if the exposure shortens length of stay, the biased analysis will underestimate this reduction.[23]

Figure 1 shows the multistate model of a patient's day-to-day flow in the ICU. On each day a patient either could die, could be infected, could be discharged, or could stay another day (in which case the process is repeated). Each of these events has a probability, labelled P(Stay, Discharge, or Death). One event must occur for each patient on each day, so P(Stay) + P(Discharge) + P(Death) = 1. In the language of state-space models, these probabilities are the *transition rates,* and

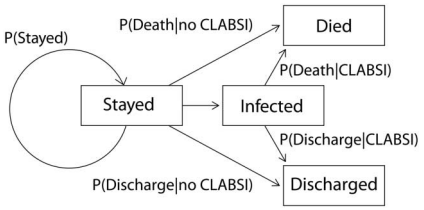

FIGURE 1. Multistate model of a patient's day-to-day transitions in an intensive care unit. CLABSI, central line–associated bloodstream infection; P, probability. The vertical line "|" means conditional on.

Death and Discharge are *absorbing states.*[26] To model the effect of a CLABSI, we allowed the transition rates to depend on infection status. Therefore, we have P(Stay|CLABSI) and P(Stay|no CLABSI), and similarly for the probability of discharge and death. The vertical line "|" means conditional on.

The proportion of patients remaining in the ICU by day t is the survivor function $S(t)$, familiar to standard survival analysis.[27] In this context, the "survivor" function models the proportion of patients remaining in the ICU and should not be confused with a patient's ultimate survival.

We estimated the survivor function at day t by multiplying the probabilities of staying from day 1 up to day t. The probability of staying is dependent on whether the patient has a CLABSI, so we have the following 2 survivor functions:

$$S(t|\text{no CLABSI}) = P(\text{stay} = 1|\text{no CLABSI}) \ldots P(\text{stay} = t-1|\text{no CLABSI}), P(\text{stay} = t|\text{no CLABSI}),$$

$$S(t|\text{CLABSI on day } d) = P(\text{stay} = 1|\text{no CLABSI}) \ldots P(\text{stay} = d-1|\text{no CLABSI}), P(\text{stay} = d|\text{CLABSI}) \ldots P(\text{stay} = t-1|\text{CLABSI}), P(\text{stay} = t|\text{CLABSI}),$$

where d is the day the patient was infected, and the above survivor function switches from "no CLABSI" to "CLABSI" on this day. To calculate the excess length of stay due to infection on day d, we subtract the survivor functions from the day of infection onward

$$E(\text{excess LoS}|\text{CLABSI on day } d) = \sum_{t=d}^{m} S(t|\text{CLABSI on day } d) - S(t|\text{no CLABSI}),$$

where $E(\ )$ means the expected value. In practice, we do not need to evaluate this sum over every day, but only up to some limit m, because for large values of t the survivor functions become very small. In this analysis we use a limit of $m = 60$ days. To get the average excess length of stay, we multiplied the expected excess length of stay by the probability of CLABSI as follows:

$$E(\text{excess LoS}) = \sum_{d=1}^{m} E(\text{excess LoS}|\text{CLABSI on day } d) \times P(\text{CLABSI on day } d). \quad (1)$$

This equation gives the average excess length of stay for a patient acquiring a CLABSI at any time during his or her stay. The probability of CLABSI on day d is estimated using the observed distribution of CLABSI times. These stages of estimating the excess length of stay are the same as those used by Beyersmann et al,[23] although the approaches are different because we estimated survival using a multinomial model, whereas they used Cox proportional hazards.

Software is available to calculate the average excess length of stay, using the method described in Beyersmann et al[23] in the "etm" library of the R package.[28] An advantage of the method shown here over that described in Beyersmann et al[23] is that this method is able to adjust for covariates in the estimation of the excess length of stay.[29] Therefore, we show results for estimated excess lengths of stay due to CLABSI for a range of patient characteristics. We show the mean excess lengths of stay and 95% credible interval. A 95% credible interval is similar to the familiar 95% confidence interval but has the simpler interpretation of having a 95% probability of containing the true value.[27]

Beside CLABSI, there are other hospital-acquired infections, such as urinary tract infection or ventilator-associated pneumonia, which also may prolong a patient's ICU stay. To remove the influence of these other infections, we censored patients with any other hospital-acquired infection as of the date of acquisition of the other infection. For example, a patient may have been discharged after 5 days and may have contracted a urinary tract infection on day 2. Rather than exclude this patient, we analyzed him or her as infection free up to day 2. For another example, consider a patient discharged after 5 days who acquired a CLABSI on day 2 and urinary tract infection on day 4. Again, rather than excluding this patient, we analyzed him or her as infection free up to day 2 and then as infected for days 2 to 4. Using censoring means that the maximum amount of data on length of stay is used, while still comparing only patients with CLABSI to patients who are infection free. Those studies that exclude patients with other infections estimate the extra length of stay due to infection, compared with patients who had no other infection during their stay. Using censoring, we can estimate the extra length of stay due to infection, compared with patients who were infection free. If there was a secondary infection that was related to the primary infection, then the length of stay was not censored.

Our models were fitted in a Bayesian framework with JAG software,[30] using vague priors for all unknown parameters. We used 5,000 Markov chain Monte Carlo samples after a burn-in of 5,000. The convergence of the chains was checked using the "coda" library in R.[31]

For comparison with our multistate model, we fitted a model that ignores the time-dependence of infection. These estimates were made by fitting a generalized linear model, with a dependent variable of days from admission to discharge and an independent variable of CLABSI (yes or no).[27] We assumed a γ distribution and used a log-link function.

For the descriptive statistics of the study sample, we use the mean and standard deviation for continuous variables that were approximately normally distributed, and we used the median and interquartile range otherwise.

RESULTS

Patients and CLABSIs

A total of 3,560 patients with central lines were evaluated: 1,029 from Argentina, 960 from Brazil, and 1,571 from Mexico (Table 1). Four patients were excluded because it was not recorded whether they died or were discharged. The characteristics of the remaining patients with central lines are shown in Table 1 for the 11 ICUs. There is variability between the ICUs in terms of mean age, ASIS, death rate, and number of CLABSIs per 1,000 central line–days. The rate of CLABSI ranged from 4.5 to 21.8 cases per 1,000 central line–days.

Excess Length of Stay

The estimated proportions of patients remaining in the ICU over days since admission are shown in Figure 2 for 2 of the 9 ICUs. The curves show the proportion of patients remaining in the ICU by means of the combined data from patients who were discharged or died. Separate curves are shown for infection-free patients and patients with a CLABSI on day 10. We used day 10 to illustrate the divergence in survival curves after infection. Before infection, the survival curves for infection-free patients and infected patients are identical.

In Argentina, in hospital 1, medical-surgical ICU, the curve for infection-free patients is below the infected curve, indicating a faster time to discharge or death in these patients. Similar curves were found in most of the other ICUs. However, in Mexico, hospital 1, medical-surgical ICU, the survival curve for infected admissions was below the curve for infection-free admissions, indicating a faster time to discharge or death for infected patients.

The estimated excess lengths of stay due to a CLABSI are shown for the 11 ICUs in Table 2. The table shows the estimates from a γ model that ignores the time to infection and from a multistate model that accounts for time to in-

TABLE 1. Descriptive Data by Intensive Care Unit (ICU) for 3,560 Patients with a Central Line, March 1999–April 2005

Country, hospital, ICU	Dates	No. of patients	No. of days in ICU	Age, mean ± SD, years	ASIS, mean ± SD	No. of deaths (% of patients)	No. of CLABSIs/1,000 central line–days	LOS, median (IQR), days
Argentina								
Hospital 1, coronary ICU	Mar 99–Mar 02	318	3,726	66 ± 11.6	3.0 ± 0.90	66 (21)	9.9	9 (7–14)
Hospital 1, medical-surgical ICU	Mar 99–Apr 02	329	4,031	73 ± 12.8	3.1 ± 1.11	197 (60)	14.4	10 (5–16)
Hospital 2, coronary ICU	Jan 01–Apr 02	164	1,263	73 ± 12.6	3.3 ± 0.92	49 (30)	10.9	6 (4–9)
Hospital 2, medical-surgical ICU	Jan 01–May 02	218	2,609	74 ± 13.0	3.3 ± 0.81	109 (50)	6.7	8 (5–14)
Brazil[a]								
Medical-surgical ICU 1	Oct 03–Apr 05	273	2,243	59 ± 16.3	3.7 ± 1.04	37 (14)	4.5	6 (3–10)
Medical-surgical ICU 2	Oct 03–Apr 05	371	5,425	53 ± 19.0	3.9 ± 0.72	101 (27)	6.6	9 (5–20)
Medical-surgical ICU 3	Oct 03–Apr 05	316	4,858	51 ± 19.2	3.9 ± 0.72	83 (26)	6.6	9 (5–21)
Mexico								
Hospital 1, medical-surgical ICU	Jun 02–Nov 03	341	2,926	46 ± 17.3	3.8 ± 0.76	138 (40)	21.8	7 (4–11)
Hospital 1, neurosurgical ICU	Jun 02–Nov 03	309	2,884	46 ± 18.1	4.1 ± 0.96	69 (22)	13.9	6 (4–11)
Hospital 2, medical-surgical ICU	Sep 02–Dec 03	673	4,989	56 ± 17.7	3.5 ± 1.04	122 (18)	12.4	5 (3–9)
Hospital 3, medical-surgical ICU	Dec 02–Dec 03	248	1,852	62 ± 16.9	3.6 ± 0.87	24 (10)	8.8	6 (4–9)

NOTE. The total no. of days in the ICU for all patients with a central line was 36,806. ASIS, acute severity illness score; CLABSI, central line–associated bloodstream infection; IQR, interquartile range; LOS, length of stay.

[a] All 3 ICUs were in the same hospital.

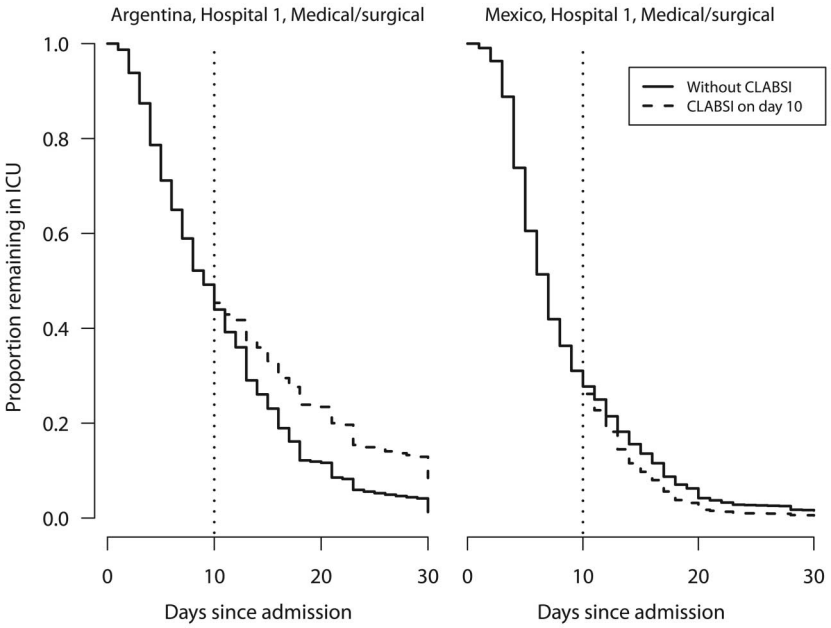

FIGURE 2. Estimated proportion remaining in the intensive care unit (ICU) by days since admission (0 to 30 days) for patients without a central line–associated bloodstream infection (CLABSI) *(solid lines)* and for patients infected on day 10 *(dashed lines)*. Results for 2 of the 9 ICUs.

fection. In 10 of the 11 ICUs, the γ model gave an estimated extra length of stay that was greater than that given by the multistate model. The greatest difference was in Brazil, medical-surgical ICU 3, where the estimated extra length of stay was 5.20 days longer using the γ model. For the rest of this article, we discuss the results of only the multistate model.

The longest excess length of stay was in Argentina, hospital 1, coronary ICU, in which a CLABSI increased the average length of stay by 4.69 days. The shortest length of excess stay was 0.78 days in Brazil, medical-surgical ICU 1.

In 10 of the 11 ICUs, a CLABSI increased the average excess length of stay, and in 6 ICUs, this increase was statistically significant. In Mexico, hospital 1, medical-surgical ICU, contracting a CLABSI decreased the length of stay by an average of 1.23 days (although the credible interval of -2.53 to 0.46 days shows that this decrease is not statistically significant). The shorter average stays of infected patients in this ICU are also shown in Figure 2, where the curve for infected patients is below that for noninfected patients.

In Table 3 we show the excess lengths of stay after adjusting for patient age and ASIS. By controlling for these other factors, which can have a strong influence on length of stay, we hope to show the independent effect of CLABSI on length of stay. We show the total excess length of stay, from equation 1, for 3 levels of ASIS covering patients at the extremes of illness severity. In general, after adjusting for age and ASIS, the excess lengths of stay due to CLABSI are longer. Also, the estimated lengths of stay change greatly depending on the ASIS. In Argentina, hospital 1, coronary ICU, the healthiest patients had the greatest excess length of stay (8.60 days), whereas the sickest patients had the shortest (3.37 days). In Brazil, medical/surgical ICU 3, the opposite pattern occurred, with the sickest patients having the longest excess stay due to infection (13.57 days) and the healthiest patients having the shortest (2.63 days). In Mexico, hospital 1, medical/surgical ICU, the sickest patients had a statistically significant shorter length of stay (2.26 days). It is important to note that the 95% credible intervals for many of these estimates in Table 3 are quite wide, indicating uncertainty in the actual excess length of stay.

Microbial Profile of the CLABSIs

The microbial profile of the CLABSIs by country is shown in Table 4. For all 3 countries, the majority of laboratory-confirmed CLABSI isolates were gram positive (ranging from 56% to 63%), identified as either *Staphylococcus aureus* or coagulase-negative staphylococci. From 34% to 42% of isolates were attributed to a variety of gram-negative species. All fungi were identified as *Candida* species.

DISCUSSION

We used a multistate model that accounted for the time to infection and therefore avoided the time-dependent bias. When using a γ model that ignored the time to infection, the estimated extra lengths of stay due to infection were greater in 10 of the 11 ICUs (Table 2). This is not surprising, because the time-dependent bias leads to an overestimation

TABLE 2. Estimated Excess Length of Stay Due to a Central Line–Associated Bloodstream Infection Using a γ Model and Multistate Model

	Mean no. of days (95% credible interval)	
Country, hospital, ICU	Gamma model	Multistate model
Argentina		
Hospital 1, coronary ICU	6.44 (2.17–13.51)	4.69 (−2.12 to 16.28)
Hospital 1, medical-surgical ICU	5.18 (1.39–10.88)	3.51 (−0.68 to 8.92)
Hospital 2, coronary ICU	4.32 (1.26–9.98)	2.31 (0.61–3.78)
Hospital 2, medical-surgical ICU	7.22 (2.40–16.11)	3.24 (−2.76 to 14.28)
Brazil[a]		
Medical-surgical ICU 1	2.32 (−2.45 to 14.96)	0.78 (−2.47 to 7.56)
Medical-surgical ICU 2	7.97 (4.06–13.64)	4.28 (1.64–7.20)
Medical-surgical ICU 3	8.37 (4.40–14.14)	3.17 (0.65–6.04)
Mexico		
Hospital 1, medical-surgical ICU	2.22 (0.23–4.88)	−1.23 (−2.53 to 0.46)
Hospital 1, neurosurgical ICU	4.92 (2.06–9.44)	4.06 (0.33–9.30)
Hospital 2, medical-surgical ICU	4.42 (2.20–7.79)	3.61 (0.19–9.67)
Hospital 3, medical-surgical ICU	3.24 (−1.56 to 18.87)	3.97 (0.23–8.96)

NOTE. ICU, intensive care unit.
[a] All 3 ICUs were in the same hospital.

of the effects on infection.[32] This highlights the importance of accounting for the time of infection and indicates that many previous estimates of the excess length of stay due to infection are overestimates.

The results from the multistate models showed a pronounced variation in excess length of stay between the different ICUs (Table 2). In Argentina, hospital 1, coronary ICU, a CLABSI extended the average length of stay by 4.69 days, whereas in Mexico, hospital 1, medical-surgical ICU, a CLABSI reduced length of stay by an average of 1.23 days. This shorter length of stay for infected patients is, at first, counterintuitive. Some of the reduced length of stay is due to a shorter time to death, probably because the CLABSIs lead to an increased patient morbidity and hence increased risk of death. This argument is supported by the strongest reduction in length of stay in this ICU being in the sickest admissions (−2.26 days) (Table 3). Therefore, patients who were already quite sick were the most debilitated by a CLABSI and experienced the biggest increased risk of death. Mexico, hospital 1, medical-surgical ICU, had the sickest population of the 11 ICUs studied. It also had the highest rate of CLABSI (21.8 cases per 1,000 central line–days) (Table 1).

After adjusting for age and ASIS, the average excess lengths of stay due to a CLABSI tended to increase (Table 3). One exception was Mexico, hospital 3, where the adjusted lengths of stay were somewhat shorter than the unadjusted estimates (Table 2), although the credible intervals for the adjusted lengths of stay were wide (particularly for ASIS 3 and ASIS 5). The reduction in length of stay after adjustment may have occurred because infections in this hospital tended to happen in the oldest or sickest patients (2 groups that are both associated with increased lengths of stay).

We attempted to adjust for the potentially important confounders of age and ASIS, but it is possible that we have missed some other important confounders. However, a study of nosocomial pneumonia showed that adjusting even for 13 confounders did not redeem the bias of not accounting for the time of infection.[33] Failing to model an important confounder is unlikely to be as important as failing to model the time of infection.

These findings are valuable to decision makers who wish to predict the change to total costs and health outcomes from reducing risks of infection. Because most of the costs of running a hospital cannot be avoided in the short run,[34,35] they are considered fixed; there will be little cash savings from preventing cases of healthcare-acquired infection. Instead, bed-days will be released, and these have a positive economic value as long as demand for acute hospital services exceeds the supply. Understanding the number of bed-days released by effective infection control is therefore important when making decisions about adopting additional infection control. Choosing a monetary valuation for these bed-days and understanding the health benefits from preventing infection are also important if the complete economic argument for prevention is to be made.[36]

If healthcare services are managed centrally by government and if the supply of health care is owned by the state, then an appropriate valuation of bed-days may emerge from eliciting a willingness-to-pay from high-level decision makers who control the allocation of public sector resources. If healthcare services are decentralized in a pseudomarket, then the willingness-to-pay for the marginal bed-day could be observed from the behavior of patients or of their health insurers. Neither approach is ideal, because there is imperfect information about the real costs and benefits of health care.[37] A willingness-to-pay economics approach, however, is preferred over the use of accounting data to estimate costs. Hospital accountants and economists have quite different objec-

TABLE 3. Estimated Excess Length of Stay Due to a Central Line–Associated Bloodstream Infection after Adjusting for Patient Age and Acute Severity of Illness (ASIS) Score

	Mean no. of days (95% credible interval)		
Country, hospital, ICU	ASIS 1	ASIS 3	ASIS 5
Argentina			
Hospital 1, coronary ICU	8.60 (−3.93 to 21.72)	6.45 (−1.50 to 18.21)	3.37 (−0.75 to 12.32)
Hospital 1, medical-surgical ICU	6.25 (1.02–11.80)	3.54 (−0.86 to 9.09)	1.20 (−2.16 to 6.45)
Hospital 2, coronary ICU	3.25 (0.91–5.27)	2.58 (0.82–4.09)	0.52 (0.05–1.57)
Hospital 2, medical-surgical ICU	0.00 (−0.27 to 0.47)	0.43 (−5.33 to 13.36)	12.10 (2.52–21.25)
Brazil[a]			
Medical-surgical ICU 1	1.17 (−0.43 to 6.04)	2.62 (−1.31 to 11.05)	4.33 (−3.28 to 15.38)
Medical-surgical ICU 2	0.28 (−0.12 to 1.26)	1.42 (−0.56 to 4.58)	3.65 (−0.68 to 8.43)
Medical-surgical ICU 3	2.63 (0.39–7.40)	8.18 (2.85–15.26)	13.57 (6.05–20.86)
Mexico			
Hospital 1, medical-surgical ICU	−0.01 (−0.45 to 0.64)	−0.52 (−1.63 to 0.98)	−2.26 (−4.17 to –0.02)
Hospital 1, neurosurgical ICU	0.07 (−0.02 to 0.26)	0.85 (−0.16 to 3.21)	8.32 (2.23–14.50)
Hospital 2, medical-surgical ICU	0.30 (−0.01 to 1.02)	2.45 (−0.02 to 7.47)	5.26 (−0.41 to 14.73)
Hospital 3, medical-surgical ICU	0.06 (−0.13 to 1.16)	0.47 (−1.42 to 10.49)	0.35 (−7.47 to 17.78)

NOTE. ASIS 1, surgical patients who require routine postoperative observation only; ASIS 3, patients who need continuous nursing care and monitoring; ASIS 5, physiologically unstable patients who are in a coma or shock and who require cardiopulmonary resuscitation or intensive medical and nursing care with frequent reassessment. Estimates are from equation 1. ICU, intensive care unit.

[a] All 3 ICUs were in the same hospital.

tives and treat fixed costs quite differently, and the purpose of collecting these data is to address economics-type questions.

Using a good statistical method to estimate additional bed-days is crucial, because biased estimates are likely to lead to poor decision making. The estimated excess lengths of stay in this article are somewhat shorter than those in similar articles. Our estimates are based on a model that accounts for the time-dependence of infection. If we assume that a CLABSI does increase the average length of stay, then previous estimates that ignored the time-dependence would have overestimated the excess.[23] Our results are some of the most reliable in this area and indicate that previous analyses may have somewhat overstated the effect of hospital-acquired infection on length of stay.

We found that the excess length of stay due to a CLABSI varied between ICUs and also depended on the sickness of the patient. This suggests that it may be difficult to generalize these results to other ICUs, and that the value of preventing a CLABSI in a certain ICU ideally would be based on data from that specific ICU. Prospective surveillance studies are ideal for estimating the extra length of stay due to infection, but new studies should be sure to be adequately powered to detect a possibly small increase in length of stay.[38]

The heterogeneity in the results shown here is mirrored by the heterogeneity in previous estimates in the literature. One important difference is that our results are based on the same statistical method, so the differences in results must be due to the differences in the case mix of patients, the available resources of the ICU, the infection control practices, or the bacterial strains. In most of the ICUs in this study, a CLABSI extended the overall length of ICU stay (by 0.78 to 4.69 days) (Table 2), leading to increased costs arising from the missed opportunity to deploy bed-days to some other productive use. In one ICU, a CLABSI reduced the length of stay, because infection increased the risk of death and therefore shortened stays for some patients. The small gain in cost for freeing up these bed-days would be greatly offset by the loss of life. Good decisions about preventing infection should account for changes to costs and health benefits.[36]

ACKNOWLEDGMENTS

Computational resources and services used in this work were provided by the High Performance Computer and Research Support Unit, Queensland University of Technology, Brisbane, Australia. Data collection was conducted by infection control nurses of the participating hospitals. The data entering process was conducted by the data management team at International Nosocomial Infection Control Consortium Headquarters in Buenos Aires, Argentina. Dr Jose Martinez Soto was the primary physician at Gabriel Mancera IMSS Hospital, Mexico City, Mexico. Dr Francisco Higuera was the primary physician at the General Hospital, Mexico City, Mexico.

Financial support. Baxter (grants to A.G.B. and N.G. for analysis and writing; to R.S., M.S.R.-F., Dr Francisco Higuera, and Dr Jose Martinez Soto to serve as principal investigators; and to V.D.R. to serve as infection control coordinator; and supplies of Viaflo and Viaflex for use during the closed-container period of each study).

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

Address reprint requests to Adrian G. Barnett, PhD, Institute of Health and Biomedical Innovation and School of Public Health, 60 Musk Avenue, Queensland University of Technology, Kelvin Grove, Australia (a.barnett@qut.edu.au).

TABLE 4. Microbial Profile of Culture-Documented Central Line–Associated Bloodstream Infections in Argentina, Brazil, and Mexico

Microorganism	Argentina (n = 32)	Brazil (n = 41)	Mexico (n = 36)
Gram-positive bacteria, no. (%)	20 (63)	25 (61)	20 (56)
Staphylococcus aureus	12	13	7
Coagulase-negative staphylococci	6	10	12
Enterococcus species	2	2	1
Gram-negative bacteria, no. (%)	11 (34)	14 (34)	15 (42)
Escherichia coli	3	…	…
Acinetobacter species	1	6	2
Alcaligenes species	…	1	1
Enterobacter species	2	3	5
Klebsiella species	3	4	2
Proteus species	2	…	1
Pseudomonas species	…	…	2
Serratia species	…	…	2
Yeasts, no. (%)	1 (3)	2 (5)	1 (3)
Candida species	1	2	1

NOTE. Data are no. of microorganisms, unless otherwise specified.

REFERENCES

1. Crnich CJ, Maki DG. The role of intravascular devices in sepsis. *Curr Infect Dis Rep* 2001;3(6):496–506.
2. Rosenthal VD, Guzman S, Orellano PW. Nosocomial infections in medical-surgical intensive care units in Argentina: attributable mortality and length of stay. *Am J Infect Control* 2003;31(5):291–295.
3. Rosenthal VD, Guzman S, Crnich C. Device-associated nosocomial infection rates in intensive care units of Argentina. *Infect Control Hosp Epidemiol* 2004;25(3):251–255.
4. Rosenthal VD, Maki DG, Salomao R, et al. Device-associated nosocomial infections in 55 intensive care units of 8 developing countries. *Ann Intern Med* 2006;145(8):582–591.
5. Moreno CA, Rosenthal VD, Olarte N, et al. Device-associated infection rate and mortality in intensive care units of 9 Colombian hospitals: findings of the International Nosocomial Infection Control Consortium. *Infect Control Hosp Epidemiol* 2006;27(4):349–356.
6. Ramirez Barba EJ, Rosenthal VD, Higuera F, et al. Device-associated nosocomial infection rates in intensive care units in four Mexican public hospitals. *Am J Infect Control* 2006;34(4):244–247.
7. Mehta A, Rosenthal VD, Mehta Y, et al. Device-associated nosocomial infection rates in intensive care units of seven Indian cities: findings of the International Nosocomial Infection Control Consortium (INICC). *J Hosp Infect* 2007;67(2):168–174.
8. Leblebicioglu H, Rosenthal VD, Arikan OA, et al. Device-associated hospital-acquired infection rates in Turkish intensive care units: findings of the International Nosocomial Infection Control Consortium (INICC). *J Hosp Infect* 2007;65(3):251–257.
9. Salomao R, Rosenthal VD, Grimberg G, et al. Device-associated infection rates in intensive care units of Brazilian hospitals: findings of the International Nosocomial Infection Control Consortium. *Rev Panam Salud Publica* 2008;24(3):195–202.
10. Cuellar LE, Fernandez-Maldonado E, Rosenthal VD, et al. Device-associated infection rates and mortality in intensive care units of Peruvian hospitals: findings of the International Nosocomial Infection Control Consortium. *Rev Panam Salud Publica* 2008;24(1):16–24.
11. Rosenthal VD, Maki DG, Mehta A, et al. International Nosocomial Infection Control Consortium report, data summary for 2002–2007, issued January 2008. *Am J Infect Control* 2008;36(9):627–637.
12. Rosenthal VD. Central line–associated bloodstream infections in limited-resource countries: a review of the literature. *Clin Infect Dis* 2009;49(12):1899–1907.
13. Madani N, Rosenthal VD, Dendane T, Abidi K, Zeggwagh AA, Abouqal R. Healthcare-associated infections rates, length of stay, and bacterial resistance in an intensive care unit of Morocco: findings of the International Nosocomial Infection Control Consortium (INICC). *Int Arch Med* 2009;2(1):29.
14. Beyersmann J, Gastmeier P, Grundmann H, et al. Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. *Infect Control Hosp Epidemiol* 2006;27(5):493–499.
15. Stone PW, Gupta A, Loughrey M, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase–producing *Klebsiella pneumoniae* outbreak in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2003;24(8):601–606.
16. Graves N, Hakton K, Robertus L. Chapter 17: costs of healthcare associated infection. In: Ferguson J, Cruikshank M, eds. National Surveillance of Health Care Associated Infection in Australia. Australian Commission on Safety and Quality in Health Care (ACSQHC), 2008.
17. Rosenthal VD, Guzman S, Migone O, Crnich CJ. The attributable cost, length of hospital stay, and mortality of central line–associated bloodstream infection in intensive care departments in Argentina: a prospective, matched analysis. *Am J Infect Control* 2003;31(8):475–480.
18. Higuera F, Rangel-Frausto MS, Rosenthal VD, et al. Attributable cost and length of stay for patients with central venous catheter–associated bloodstream infection in Mexico City intensive care units: a prospective, matched analysis. *Infect Control Hosp Epidemiol* 2007;28(1):31–35.
19. Basu A, Manning W, Mullahy J. Comparing alternative models: log vs Cox proportional hazard? *Health Econ* 2004;13:749–765.
20. Schulgen G, Kropec A, Kappstein I, Daschner F, Schumacher M. Estimation of extra hospital stay attributable to nosocomial infections: heterogeneity and timing of events. *J Clin Epidemiol* 2000;53:409–417.
21. Graves N, Weinhold D, Birrell F, et al. The effect of healthcare-acquired infection on length of hospital stay and cost. *Infect Control Hosp Epidemiol* 2007;28:280–292.
22. Graves N, Weinhold D, Roberts JAR. Correcting for bias when estimating the cost of hospital-acquired infection: an analysis of lower respiratory tract infections in nonsurgical patients. *Health Econ* 2005;14(7):755–761.
23. Beyersmann J, Wolkewitz M, Schumacher M. The impact of time-dependent bias in proportional hazards modelling. *Stat Med* 2008;27(30):6439–6454.

24. Rosenthal V, Graves N, Maki D. An International Nosocomial Infection Control Consortium (INICC) goals and objectives, description of surveillance methods and operational activities. *Am J Infect Control* 2008;36(9):e1–e12.
25. Edwards JR, Peterson KD, Andrus ML. National Healthcare Safety Network (NHSN) report, data summary for 2006, issued June 2007. *Am J Infect Control* 2007;35:290–301.
26. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multistate models. *Stat Med* 2007;26(11):2389–2430.
27. Dobson AJ, Barnett AG. *An Introduction to Generalized Linear Models. Texts in Statistical Science.* 3rd ed. Boca Raton, FL: Chapman & Hall/CRC, 2008.
28. Allignol A. etm: Empirical Transition Matrix. Version 0.4-7. http://cran.r−project.org/web/packages/etm/etm.pdf. Published 2009. Accessed September 14, 2010.
29. Barnett A, Batra R, Graves N, Edgeworth J, Robotham J, Cooper B. Using a longitudinal model to estimate the effect of methicillin-resistant *Staphylococcus aureus* infection on length of stay in an intensive care unit. *Am J Epidemiol* 2009;170(9):1186–1194.
30. Plummer M. JAGS, version 1.0.3 manual. http://ftp2.es.freebsd.org/FreeBSD/distfiles/jags/jags_user_manual.pdf. Published September 9, 2008. Accessed September 14, 2010.
31. Plummer M, Best N, Cowles K, Vines K. coda: Output analysis and diagnostics for MCMC. In: 2009:R, version 0.13-4.
32. Beyersmann J, Gastmeier P, Wolkewitz M, Schumacher M. An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation. *J Clin Epidemiol* 2008;61:1216–1221.
33. Beyersmann J, Kneib T, Schumacher M, Gastmeier P. Nosocomial infection, length of stay, and time-dependent bias. *Infect Control Hosp Epidemiol* 2009;30:273–276.
34. Kahn JM, Rubenfeld GD, Rohrbach J, Fuchs BD. Cost savings attributable to reductions in intensive care unit length of stay for mechanically ventilated patients. *Med Care* 2008;46:1226–1233.
35. Roberts RR, Frutos PW, Ciavarella GC, et al. Distribution of fixed vs variable costs of hospital care. *JAMA* 1999;281(7):644–649.
36. Graves N, Halton K, Lairson D. Economics and preventing hospital-acquired infection— broadening the perspective. *Infect Control Hosp Epidemiol* 2007;28(2):178–184.
37. Scott RD, Soloman SL, McGowan JE. Applying economic principles to health care. *Emerg Infect Dis* 2001;7(2):282–285.
38. Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an end point. *Biometrics* 1982;38:163–170.