Editorial

Impact of Nosocomial Infections on Outcome: Myths and Evidence

Jordi Rello, MD, PhD

The flight of Icarus from Crete to escape the tyranny of Minos, and his fall to the sea when he flew too close to the sun, is one of the best known of the Greek myths. At the end of the 20th century, it is an undisputed fact that patients with nosocomial infections (NI) have high crude mortality and that most patients who die in the intensive-care unit (ICU) die of infection. Multiple clinical trials pursuing survival beyond 28 days after the life-threatening infectious event repeatedly have ended in failure. The drawbacks of crude mortality are its failure to adjust for severity and its failure to identify related deaths, but the infectious event is likely to be a major contributor to death. Nevertheless, the exact contribution of the initiating event (or its severity) and the amount of excess mortality that can be attributed to the development of NI are issues that are understood only partially.

Recent data from prospective studies[1] of surveillance of NI in the ICU setting show that 35.1% of all ICU-acquired bacteremias occurred in patients with intravascular catheters, and it is believed that most primary episodes are secondary to these devices.[2] Catheter-related (CR) bloodstream infections (BSIs) can be associated with a very wide spectrum of severity, ranging from fever that disappears after catheter withdrawal to endocarditis or septic thrombophlebitis, requiring surgical therapy and prolonging length of stay (LOS). Pittet et al,[3] in a surgical ICU, reported that the estimated mortality rate for nosocomial BSIs was 35% (95% confidence interval [CI_{95}], 25%-45%). Although intravenous catheters were responsible for less than 25% of BSIs,[4] these findings have been generalized, and the myth that all NI, including CR BSI, present high mortality is still widely believed.

The article by Soufir et al[5] in this issue of the Journal is a provocative and well-designed case-control study that evaluates whether these infections are responsible for excess mortality in critically ill patients. Major complications were observed in more than one half of exposed patients, and their attending physicians reported that 21% of these patients died as a consequence of the CR BSI episode. Notably, though, after appropriate matching, no association between the development of CR BSI and increased ICU mortality could be detected. It could be argued that their findings may be biased by the exclusion of most episodes caused by coagulase-negative staphylococci (CNS), but this limitation in fact would contribute to overemphasizing the mortality in the current study population and thus add strength to their conclusion.

In our experience, in an ongoing study involving up to 2,000 patients with over 48 hours of stay in a medical-surgical ICU, 63.2% of episodes of CR BSI were caused by CNS. Fifty-seven new episodes of CR BSI were documented, representing an incidence of 2.85 episodes per 100 ICU admissions (data not shown). Forty-nine cases were matched to uninfected controls based upon a number of factors, including the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score at admission, underlying disease, age, and prior days of exposure to risk. Six of 31 patients (19.3%) with CNS bacteremia died in the hospital, whereas crude hospital mortality was 27.8% (5/18) in the group of pathogens other than CNS. As in Soufir et al's study, no significant differences in mortality were found between exposed and unexposed patients.

The first implication of this (ie, that CR BSI may not have an attributable mortality) is important in that it calls into question the myth that as many as 50,000 people die of BSI yearly in the United States.[6] The current evidence con-

From the Intensive Care Department, Hospital de Sabadell, Barcelona, Spain.
Address reprint requests to Jordi Rello, MD, PhD, Intensive Care Department, Hospital de Sabadell, Parc Tauli s/n Sabadell, 08206 Barcelona, Spain; JRELLO@CSPT.ES.
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tradicts earlier suggestions that BSI is associated with high attributable mortality and that some of these deaths conceivably could be avoided by implementing specific preventative measures on patients with intravascular lines. In my opinion, the attributable mortality found in prior studies of NI may have been overvalued by deficiencies in study design, including inadequate adjustment for confounding factors. In contrast, the lower figures reported in recent studies rest on more appropriate assessment of severity and matching.

In 1986, Forgacs et al[7] evaluated bacteremia in the ICU over a 15-year period and found that mortality was 60.4% in patients with BSI, compared with only 13.1% in those without BSI. In 1991, Smith et al[8] were the first to attempt to control for severity of illness by matching patients based upon predicted mortality estimated by the APACHE II scoring system. The bacteremic group had a crude mortality of 82.4%, whereas the control group had an observed mortality of 52.9%, yielding an attributable mortality of 29.5%. This figure was similar to the attributable mortality (35%) estimated by Pittet et al[3] in 1994. My main criticism of this study regards matching: exposure to risk was not always equivalent, because some matched controls had shorter LOS than their respective cases when developing BSI. Clearly, a potential case who developed BSI after 20 days of stay cannot be matched with a potential control who was discharged from the ICU before this period of time, because the effect will be to overestimate mortality and LOS for cases.

An outstanding aspect of the study by Soufir et al[5] is that it is the first to match patients with CR BSI according to the severity of illness at the onset of bacteremia rather than on admission, as other authors have done.[3,7,8] This makes sense, because the mean (±standard deviation) duration from ICU admission to onset of CR BSI was 16.8±9.6 days, and the severity of illness could have changed substantially prior to infection. Similarly, it is well known in the analysis of survival in patients with sepsis that the predicted mortality based on scores determined at ICU admission undervalue the observed mortality.[9] Indeed, the Mortality Probability Models II prediction based on determining severity 72 hours after admission adjusted better for observed mortality. These observations recently have been confirmed by our group, demonstrating that the degree of severity of illness at diagnosis of pneumonia in intubated patients (ventilator-associated pneumonia) is the most important predictor of survival in this population.[10,11]

The current evidence showing that development of CR BSI may represent a marker of severity rather than an independent risk factor for mortality also confirms prior findings suggested by multivariate analysis. In a large prospective study[12] involving 1,745 patients with nosocomial BSI at a single tertiary-care hospital, isolation of *Candida* species was the only independent microbiological predictor of mortality. Indeed, among primary BSIs, CR infections were associated with a significantly lower risk (odds ratio, 0.58; CI_{95}, 0.39-0.86) of death in the study population. In addition, BSI due to CNS (the most common etiology associated with CR BSI) tended to predict a favorable outcome and therefore relatively low mortality. Similarly, in a recent multicenter study on BSI acquired in the ICU involving 30 hospitals in Spain, Vallés et al[13] reported that, in comparison with other sources, particularly intra-abdominal infection or pneumonia, intravascular catheters were the source associated with the lowest impact on survival. Consequently, the possibility of reducing the risk of death by preventing CR BSI in the ICU seems unrealistic.

However, these infections would have great public health importance in an era of cost containment if they were associated with an increased LOS and the expenditure of more resources. CR BSI acquired in the ICU significantly affected the in-hospital outcome in survivors in our study population, even after controlling for severity of illness. The excess LOS was 19.6±49.2 (CI_{95}, −1.1-40.4) days in survivors, representing an additional cost of $3,470 per CR BSI survivor in the ICU. Interestingly, this effect was particularly strong among surviving patients from episodes caused by CNS, with an excess length of hospital stay of 31 days (P=.02). Pittet et al, in their study of BSI,[4] reported that the infection also was associated with doubled LOS in the ICU, an excess LOS of 24 days in survivors, a significant economic burden. In the light of these figures, I believe that the annual cost arising from the infectious complications of CR BSI in the ICU justifies new efforts to reduce the incidence of these complications.[14,15]

The debate about the impact of NI on outcome will continue, but current evidence is providing a new perspective on the myth that its effect is decisive. The study by Soufir et al, as well as other studies in critically ill patients, gives clear-cut evidence of the key role of severity of illness on evaluating outcome in patients with NI. While we know that assessment of severity done on admission can predict the overall survival of a cohort of patients, we have learned now that this analysis no longer should be used to measure the probability of surviving an episode of NI developed some days later. We also should refine the methods of matching to improve our understanding of the contribution of NI on outcome: unexposed patients should be matched on the day their individual pair developed the infection by the degree of severity of illness documented immediately before the onset of the infectious complication. Traditional approaches that simplify the process of matching no longer should be considered appropriate.

REFERENCES

1. Rello J, Ricart M, Mirelis B, Quintana E, Gurgui M, Net A, et al. Nosocomial bacteremia in a medical-surgical intensive care unit: epidemiologic characteristics and factors influencing mortality in 111 episodes. *Intensive Care Med* 1994;20:94-98.
2. Rello J, Quintana E, Mirelis B, Gurgui M, Net A, Prats G. Polymicrobial bacteremia in critically ill patients. *Intensive Care Med* 1993;19:22-25.
3. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271:1598-1601.
4. Pittet D, Wenzel RP. Nosocomial bloodstream infection in the critically ill. *JAMA* 1994;272:1820.
5. Soufir L, Timsit J-F, Mahe C, Carlet J, Regnier B, Chevret S. Attributable morbidity and mortality of catheter-related septicemia in critically ill patients: a matched, risk-adjusted cohort study. *Infect Control Hosp Epidemiol* 1999;20:396-401.

6. Wenzel RP, Edmond MB. The evolving technology of venous access. *N Engl J Med* 1999;340:48-50.
7. Forgacs IC, Eykyn SJ, Bradley RD. Serious infection in the intensive therapy unit: a 15-year study of bacteremia. *QJM* 1986;60:773-779.
8. Smith RS, Meixler S, Simberkoff M. Excess mortality in critically ill patients with nosocomial bloodstream infection. *Chest* 1991;100: 164-167.
9. Le Gall JR, Lemeshow S, Leleu G, Klar J, Huillard J, Rué M, et al. Customized probability models for early severe sepsis in adult intensive care patients. *JAMA* 1995;273:644-650.
10. Rello J, Rué M, Jubert P, Muses G, Soñora R, Vallés J, et al. Survival in patients with nosocomial pneumonia: impact of the severity of illness and the etiologic agent. *Crit Care Med* 1997;25:1862-1867.
11. Rello J, Vallés J. Mortality as an outcome in hospital-acquired pneumonia. *Infect Control Hosp Epidemiol* 1998;19:795-797.
12. Pittet D, Li N, Woolson RF, Wenzel RP. Microbiological factors influencing the outcome of nosocomial bloodstream infections: a 6-year validated, population-based model. *Clin Infect Dis* 1997;24:1068-1078.
13. Vallés J, León C, Alvarez-Lerma F. Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. *Clin Infect Dis* 1997;24:387-395.
14. Segura M, Alvarez-Lerma F, Tellado JM, Jimenez-Ferreres J, Oms L, Rello J, et al. A clinical trial on the prevention of catheter-related sepsis using a new hub model. *Ann Surg* 1996;223:363-369.
15. Darouiche RO, Raad II, Heard SO, Thornby JI, Wenker OC, Gabrielli A, et al. A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med* 1999;340:1-8.