ORIGINAL ARTICLE

Impact of Switching from an Open to a Closed Infusion System on Rates of Central Line–Associated Bloodstream Infection: A Meta-Analysis of Time-Sequence Cohort Studies in 4 Countries

Dennis G. Maki, MD; Victor D. Rosenthal, MD, MSc, CIC; Reinaldo Salomao, MD; Fabio Franzetti, MD; Manuel Sigfrido Rangel-Frausto, MD

q1 BACKGROUND. We report a meta-analysis of 4 identical time-series cohort studies of the impact of switching from use of open infusion containers (glass bottle, burette, or semirigid plastic bottle) to closed infusion containers (fully collapsible plastic containers) on central line–associated bloodstream infection (CLABSI) rates and all-cause intensive care unit (ICU) mortality in 15 adult ICUs in Argentina, Brazil, Italy, and Mexico.

q2 METHODS. All ICUs used open infusion containers for 6–12 months, followed by switching to closed containers. Patient characteristics, adherence to infection control practices, CLABSI rates, and ICU mortality during the 2 periods were compared by χ^2 test for each country, and the results were combined using meta-analysis.

RESULTS. Similar numbers of patients participated in 2 periods (2,237 and 2,136). Patients in each period had comparable Average Severity of Illness Scores, risk factors for CLABSI, hand hygiene adherence, central line care, and mean duration of central line placement. CLABSI incidence dropped markedly in all 4 countries after switching from an open to a closed infusion container (pooled results, from 10.1 to 3.3 CLABSIs per 1,000 central line–days; relative risk [RR], 0.33 [95% confidence interval {CI}, 0.24–0.46]; $P < .001$). All-cause ICU mortality also decreased significantly, from 22.0 to 16.9 deaths per 100 patients (RR, 0.77 [95% CI, 0.68–0.87]; $P < .001$).

q3 CONCLUSIONS. Switching from an open to a closed infusion container resulted in a striking reduction in the overall CLABSI incidence and all-cause ICU mortality. Data suggest that open infusion containers are associated with a greatly increased risk of infusion-related bloodstream infection and increased ICU mortality that have been unrecognized. Furthermore, data suggest CLABSIs are associated with significant attributable mortality.

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Critically ill patients hospitalized in intensive care units (ICUs) commonly require central lines for administration of large volumes of parenteral fluids, blood products, intravenous medications such as pressors, and hemodynamic monitoring. The greatest iatrogenic threat to the safety of these patients is healthcare-associated infection, especially central line–associated bloodstream infection (CLABSI).[1,2]

There are 2 major sources of CLABSI: (1) colonization of the catheter, or *catheter-related infection,* and (2) contamination of the fluid administered through the device, or *infusate-related infection.*[3] Contaminated infusate has been shown to be the cause of most epidemics of nosocomial bloodstream infection and has not been thought to be a common cause of endemic CLABSI.[4] Recent pathogenetic studies using molecular subtyping have shown that most CLABSIs with noncuffed and nontunneled short-term vascular catheters derive from microorganisms in the patient's cutaneous microflora that gain access to the implanted device, colonize the external surface or lumen, most often during catheter insertion, and subsequently produce CLABSI.[5-8] All of these studies have been done in developed Western countries where closed infusion systems, consisting of nonvented, fully collapsible plastic fluid containers, are used exclusively.

There are 2 types of intravenous fluid containers in use worldwide: a glass bottle, burette, or semirigid plastic bottle that must be externally vented to allow ambient air to enter for the fluid to egress (an open infusion container), and a fully collapsible plastic container that does not require external venting for the bag to empty (a closed infusion container). Open systems with rigid containers were used worldwide for more than 75 years until a nationwide outbreak of gram-negative bacteremia was traced to the intrinsically con-

From the University of Wisconsin School of Medicine and Public Health, Madison (D.G.M.); Colegiales and Bernal Medical Centers, Buenos Aires, Argentina (V.D.R.); Santa Marcelina Hospital, Sao Paulo, Brazil (R.S.); Sacco Hospital, Milan, Italy (F.F.); and Specialties Instituto Mexicano del Seguro Social Hospital, Mexico City, Mexico (M.S.R.-F.).

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TABLE 1. Patient Characteristics, Device Use, and Intensive Care Unit (ICU) Length of Stay during the 2 Study Periods

Variable	No. (%) of patients: Open container period (n = 2,237)	No. (%) of patients: Closed container period (n = 2,136)	RR (95% CI)	P
Sex				
Male	1,262 (56.4)	1,216 (56.9)	1.01 (0.96–1.06)	
Female	975 (43.6)	920 (43.1)	0.99 (0.92–1.06)	
Underlying diseases				
Endocrine disease	385 (20.2)	459 (21.9)	1.08 (0.96–1.22)	.197
Cardiac failure	577 (30.3)	686 (32.7)	1.08 (0.98–1.18)	.102
Angina pectoris	447 (23.5)	438 (20.9)	0.89 (0.79–1.00)	.049
Cardiac surgery	558 (29.3)	489 (23.3)	0.80 (0.72–0.88)	<.001
COPD	128 (6.7)	193 (9.2)	1.37 (1.10–1.70)	.004
Cancer	70 (3.1)	56 (2.6)	0.84 (0.59–1.18)	.316
Renal impairment	111 (5.8)	116 (5.5)	0.95 (0.74–1.22)	.684
Hepatic failure	26 (1.4)	45 (2.1)	1.57 (0.97–2.54)	.062
Abdominal surgery	206 (9.2)	191 (8.9)	0.97 (0.80–1.17)	.759
Thoracic surgery	2 (0.1)	6 (0.3)	2.49 (0.50–12.33)	.246
Trauma	3 (0.2)	10 (0.5)	2.77 (0.76–10.04)	.106
Previous infection	70 (3.7)	182 (8.7)	2.36 (1.80–3.09)	<.001
Stroke	52 (2.7)	62 (3.0)	1.08 (0.75–1.55)	.681
Immunocompromised	43 (2.3)	56 (2.7)	1.18 (0.80–1.75)	.400
Device use				
Foley catheter	1,982 (88.6)	1,820 (85.2)	0.96 (0.94–0.98)	<.001
Mechanical ventilator	1,304 (58.3)	1,215 (56.9)	0.98 (0.93–1.03)	.346
Age, mean ± SD, years	61.8 ± 17.22	60.7 ± 17.08	…	.029
ASIS, mean ± SD	3.1 ± 1.26	3.2 ± 1.23	…	.007
ICU stay, mean ± SD, days	7.6 ± 9.41	7.3 ± 8.13	…	.203

NOTE. ASIS, Average Severity of Illness Score; CI, confidence interval; COPD, chronic obstructive pulmonary disease; RR, relative risk.

taminated screwcap closures for glass intravenous fluid bottles of one United States manufacturer in 1970–1971,[9] and several smaller outbreaks were associated with other manufacturers' glass bottles and open intravenous infusion systems several years later.[10] During the late 1970s and early 1980s, closed infusion systems with fully collapsible plastic containers came into universal use throughout North America and most of Western Europe. Additional advantages associated with these flexible bags include less breakage and subsequently less clean-up and waste, reduced weight, easier disposal, and greater durability. However, in many parts of the world, particularly Latin America, Asia, Africa, Eastern Europe, Germany, and Italy, open infusion systems with vented glass or semirigid plastic bottles are still used almost exclusively. Over the past 35 years, there have been reports of outbreaks of bloodstream infection traced to contaminated infusate associated with the use of open intravenous infusion systems (in the United Kingdom in the 1970s and in Mexico,[11] Brazil,[12,13] Greece,[13,14] and Egypt[15] later). The risk of endemic intravenous fluid contamination during system setup, admixture preparation, and administration is much higher with open intravenous infusion systems, compared with the risk in closed systems.[16]

Because of the potential increased risk of contamination of infusate during administration with open systems, we undertook a pilot time-series cohort study in the ICUs of 2 Argentine hospitals, evaluating the impact of switching from the use of semirigid plastic infusion containers to fully collapsible plastic containers on rates of CLABSI.[17] The incidence of CLABSI decreased 72% (from 6.5 to 2.4 CLABSIs per 1,000 central line–days; $P = .02$); most striking, 17 patients with CLABSI (2.8%) died during the period when the open infusion container was in use, compared with only 1 (0.2%) during use of the closed infusion container ($P = .003$).

These findings prompted 3 additional identical interrupted time-series cohort studies in 13 ICUs in Mexico,[18] Brazil,[19] and Italy.[20] We report a meta-analysis of the results of these 4 studies that followed a common protocol.

METHODS

Source of Patients

Fifteen ICUs in 7 hospitals, each of which had been an active member of the International Nosocomial Infection Control Consortium (INICC) for at least 1 year, participated in this study.[21-23] There were 4 ICUs in 2 hospitals in Argentina,[17] 3

TABLE 2. Infection Control Practices of the 15 Intensive Care Units (ICUs) during the 2 Study Periods

Process surveillance	Open container period	Closed container period	RR (95% CI)	*P*
Central line exposure, % (central line–days/ICU days)	88.9 (15,189/17,087)	86.4 (13,456/15,574)	0.97 (0.95–0.99)	.017
Mean no. of days of central line placement (central line–days/ patients with central line)	6.79 (15,189/2,237)	6.30 (13,456/2,136)	0.93 (0.91–0.95)	<.001
Hand hygiene adherence, % (no. of performed instances/no. of opportunities)	71.0 (8,472/11,931)	73.7 (9,164/12,437)	1.04 (1.01–1.07)	.014
Dressing, % (no. of performed instances/no. of opportunities)				
Sterile gauze or polyurethane	96.5 (13,282/13,768)	98.7 (16,968/17,196)	1.02 (1.00–1.05)	.052
Good condition	91.2 (12,560/13,768)	97.2 (16,717/17,196)	1.07 (1.04–1.09)	<.001

Note. During both periods, all 15 ICUs used maximum sterile barriers for central line insertion and routinely used 3-way stopcocks; none of the ICUs used chlorhexidine for cutaneous antisepsis or special technologies for central lines (antimicrobial-coated catheters or biopatch chlorhexidine dressing). CI, confidence interval; RR, relative risk.

ICUs in 1 hospital in Brazil,[19] 4 ICUs in 3 hospitals in Mexico,[18] and 4 ICUs in 1 hospital in Italy.[20] All of these ICUs have had long-standing active nosocomial infection control programs and operate at the highest level of complexity in their respective countries, providing critical care for medical, surgical, and trauma patients.

Ethics committee approval for the studies was provided in Brazil, Italy, and 2 of the 3 hospitals in Mexico. Because the study procedures were not considered to exceed the scope of standard medical care, the ethics committees waived approval in the third Mexican hospital and both hospitals in Argentina.

Background on INICC

INICC[21-23] is an international nonprofit, open, multicenter, collaborative healthcare-associated infection control program with a surveillance system based on that of the US National Healthcare Safety Network (NHSN, formerly the National Nosocomial Infection Surveillance system [NNIS]).[24] It is the first multinational research network established to control nosocomial infections in hospitals through the analysis of data collected on a voluntary basis by its member hospitals. INICC now comprises an active network of more than 300 ICUs in 40 countries around the world, and at the present time it is the only source of aggregate standardized international data on the epidemiology of nosocomial infection in the developing world.[21-23]

Open infusion systems or combinations of open and closed systems are used for administration of intravenous fluids and medications in all of the member INICC hospitals.[21] From its inception, the consortium has focused on surveillance and control of device-associated infection in the ICU, because it addresses the healthcare setting with the most vulnerable patients who have the heaviest exposure to invasive devices and highest rates of nosocomial infection.[21] INICC uses the surveillance methods and definitions for nosocomial infection developed by the Centers for Disease Control and Prevention (CDC) for the long-standing NNIS/NHSN program in US hospitals.[25,26] It vigorously promotes the consistent implementation of simple, inexpensive, evidence-based measures for prevention of nosocomial infection, education, and performance feedback of *outcome surveillance* (CLABSI rates) and *process surveillance* (rates of adherence to basic infection control measures) to reduce rates of device-associated infection.[27-30]

Outcome surveillance includes rates of CLABSI, ventilator-associated pneumonia, and catheter-associated urinary tract infection per 1,000 device-days. Each healthcare-associated infection reported is adjudicated centrally at the INICC office in Buenos Aires, Argentina, where it is scrutinized to be certain that criteria are fulfilled to justify its recording as a healthcare-associated infection.[22]

Process surveillance is designed to monitor adherence to easily measurable, important control measures, such as hand hygiene adherence by healthcare workers, on the basis of the frequency with which hand hygiene is performed when clearly indicated, as monitored by randomly selected, unannounced 1-hour observation periods 3 times per week. Vascular catheter care adherence is also monitored and recorded, including hand hygiene before and after catheter insertion or redressing an intravascular catheter, presence of a sterile gauze or polyurethane dressing on the insertion site, recording the date of catheter insertion and the last administration set change, and replacement of the gauze dressing every 48 hours and transparent semipermeable membrane dressings at least every 7 days, with the date and time of the dressing change recorded.

The following practices, which have not yet been incorporated into formal process surveillance, are also vigorously promoted in the INICC ICUs: limiting catheter placements in the femoral vein, use of maximal sterile barrier precautions during the insertion procedure, disinfection of the insertion site with 2%– 4% chlorhexidine, and prompt removal of vascular catheters when they are no longer needed.

Definitions

When CLABSI was suspected, the central venous catheter was removed aseptically and the distal 5 cm was removed and cultured, using the standardized semiquantitative method.[31] Concomitant blood cultures were drawn percutaneously in most cases. In each hospital, standard laboratory methods

TABLE 3. Outcome by Country and Overall, during the 2 Study Periods

Variable	Open container period	Closed container period	RR (95% CI)	*P*
Rate of CLABSI per 1,000 central line–days (no. of CLABSIs/no. of central line–days)				
Argentina	10.0 (37/3,686)	3.5 (7/2,024)	0.34 (0.15–0.77)	.006
Brazil	6.5 (28/4,297)	3.2 (13/4,041)	0.49 (0.26–0.95)	.03
Italy	8.2 (29/3,545)	3.5 (12/3,426)	0.43 (0.22–0.84)	.01
Mexico	16.1 (59/3,661)	3.2 (13/4,055)	0.20 (0.11–0.36)	<.001
Overall	10.1 (153/15,189)	3.3 (45/13,456)	0.33 (0.24–0.46)	<.001
ICU all-cause mortality, % (no. of deaths/ no. of patients)				
Argentina	41.6 (249/598)	37.0 (141/381)	0.89 (0.76–1.04)	.15
Brazil	18.8 (91/483)	16.0 (103/642)	0.85 (0.66–1.10)	.22
Italy	4.1 (25/608)	5.3 (30/565)	1.29 (0.77–2.17)	.33
Mexico	23.4 (128/548)	16.1 (88/548)	0.69 (0.54–0.88)	.002
Overall	22.0 (493/2237)	16.9 (362/2136)	0.77 (0.68–0.87)	<.001

NOTE. CI, confidence interval; CLABSI, central line-associated bloodstream infection; ICU, intensive care unit; RR, relative risk.

were used to identify microorganisms, and standardized susceptibility testing was performed.

CDC-NNIS program definitions were used to define device-associated infections (CLABSI, catheter-associated urinary tract infection, and ventilator-associated pneumonia) for all 4 studies. CLABSI was defined as either laboratory-confirmed bloodstream infection or clinical primary nosocomial sepsis. The definitions are as follows:

Laboratory-confirmed CLABSI. A patient with a central line who had a recognized pathogen isolated from one or more percutaneous blood cultures after 48 hours of catheterization; the pathogen cultured from the blood was not related to an infection at another site; and the patient had one or more of the following signs or symptoms: fever (temperature, $\geqslant$38°C), chills, or hypotension. With skin commensals (diphtheroids, *Bacillus* species, *Propionibacterium* species, and coagulase-negative staphylococci or micrococci), the organism was recovered from 2 or more separate blood cultures.[25,26]

Clinical primary nosocomial sepsis. A patient with a central line who had at least one of the following clinical signs, with no other recognized cause: fever (temperature, $\geqslant$38°C), hypotension (systolic blood pressure, $\leqslant$90 mm Hg), or oliguria ($\leqslant$20 mL/h), but either blood cultures were not performed or no organisms were recovered from blood cultures; there was no apparent infection at another site; and the physician instituted antimicrobial therapy for sepsis.[25]

Design of the Study

The studies in each country's ICUs were designed to measure the effect of switching from an open infusion container to a closed infusion container on rates of CLABSI and all-cause ICU mortality. The study design included a 4- to 23-month lead-in phase, during which ICU personnel were provided with training in hand hygiene and adherence to central line care to standardize practices, followed by the comparative phase. During the open infusion container period, which lasted 8–12 months, glass bottles, burettes, or semirigid plastic fluid containers were used exclusively; during the closed container period of the comparative phase, which lasted 6–12 months, fully collapsible plastic intravenous fluid containers were used exclusively.

Infusion Containers Studied

The open infusion containers studied within the individual study ICUs were commercially available glass bottles (ICUs within Brazil, Mexico, and Italy), burettes (ICUs within Mexico), and semirigid plastic containers (ICUs within all 4 countries); all of these containers required external venting. The closed infusion container used in each ICU during the final period of the study was a fully collapsible plastic container that did not require any external venting to empty and that had injection ports that were self sealing (Viaflex or Viaflo; manufactured and provided by Baxter).

Data Collection

All patients within a study ICU with a central line in place for at least 24 hours composed the study population. Demographic data, major medical diagnoses, Average Severity of Illness Score on ICU entry, all invasive medical devices, and nosocomial infections identified while hospitalized in the ICU were recorded on standard INICC surveillance forms during the study. Process surveillance data were collected as previously noted in the Background on INICC.

Decisions to evaluate patients for suspected infection and to perform blood cultures and other indicated diagnostic studies were made independently by the patients' attending physicians. Standard laboratory methods were used to identify microorganisms recovered from blood cultures and catheter segment cultures.[22]

Each patient case report was reviewed centrally at the INICC office in Buenos Aires, Argentina, where it was scrutinized to be certain that no CLABSI was inadvertently omitted

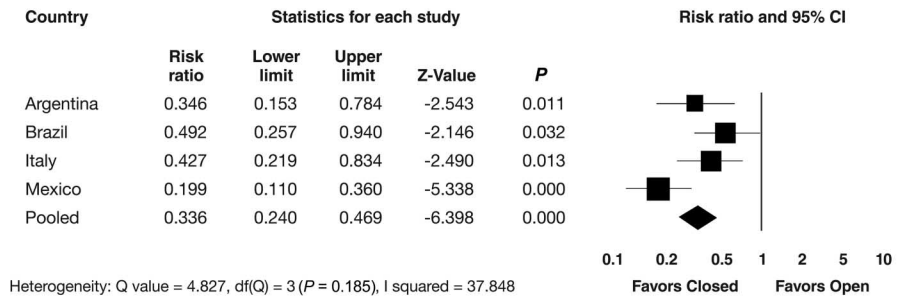

FIGURE 1. Meta-analysis of the no. of central line–associated bloodstream infections per 1,000 central line–days. CI, confidence interval.

(because of either an omitted culture or a negative culture result) and to ensure that CDC-NNIS program criteria were fulfilled to justify the recording of each CLABSI.

Outcome Measures

Primary outcome measures included the results of outcome surveillance, rates of CLABSI expressed both per 100 patients and per 1,000 central line–days, and all-cause ICU mortality. Secondary outcome measures included the microbiological profile of CLABSI, adherence to hand hygiene, and monitored central line care, in relation to the results of process surveillance.

Statistical Methods

Pooled analysis. The aggregate characteristics of patients hospitalized, the microbiologic profile of CLABSI, and the results of process surveillance during the open period and closed period were compared using the χ^2 test or the Fisher exact test for dichotomous variables and the unmatched Student *t* test for continuous variables. Relative risk (RR) ratios with 95% confidence intervals (CIs) were used to compare rates of CLABSI during the open period with those during the closed period in each country. *P* values of less than .05 by 2-tailed tests were considered to be statistically significant.

Meta-analysis. Meta-analysis was performed to assess CLABSI rate and percent mortality using the Mantel-Haenszel fixed-effects model, and heterogeneity in the results of the studies was assessed using the χ^2 test for heterogeneity and the I^2 measure of inconsistency.[32,33] Forest plots were generated using Comprehensive Meta-analysis (version 2; Biostat).

RESULTS

From August 1999 through February 2006, 4,373 adult patients admitted to the study ICUs were enrolled and participated in 1 of the 4 country's studies, 2,237 (15,189 central line–days) during the open infusion container period of the study and 2,136 (13,456 central line–days) during the closed infusion container period. The numbers of patients in each period within each country were very similar, ranging from 483 to 608 during the open infusion container period and from 381 to 642 during the closed infusion container period. Patients in the 2 study periods were very similar demographically and with regard to major medical diagnoses (including diabetes), Average Severity of Illness Score, distribution of medical and surgical patients, mechanical ventilation, exposure to urinary catheters, and mean duration of central line placement (Tables 1 and 2).

The incidence of CLABSI during the open infusion container period within the individual participating countries ranged from 6.5 to 16.1 CLABSIs per 1,000 central line–days, with an overall rate of 10.1 CLABSIs per 1,000 central line–days (Table 3). During the closed infusion container period, it ranged from 3.2 to 3.5 CLABSIs per 1,000 central line–days, with an overall rate of 3.3 CLABSIs per 1,000 central line–days. Most notably, the incidence decreased significantly within each country. The decrease ranged from 51% to 81%,

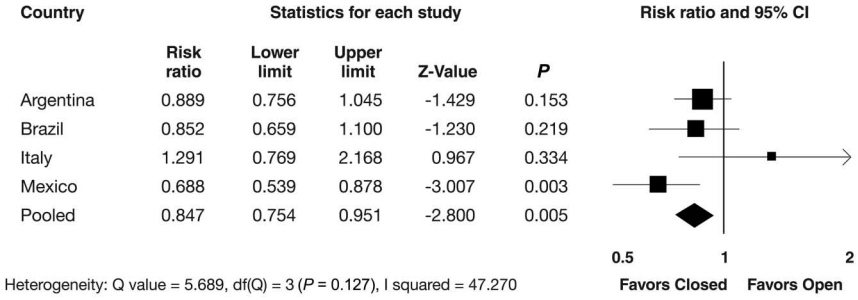

FIGURE 2. Meta-analysis of the percentage of patient mortality. CI, confidence interval.

TABLE 4. Microbial Profile of Central Line–Associated Bloodstream Infections (CLABSIs) during the 2 Study Periods

Variable	Open container period		Closed container period		RR (95% CI)	*P*
	No. of CLABSIs	No. of CLABSIs/1,000 central line–days	No. of CLABSIs	No. of CLABSIs/1,000 central line–days		
Causative microorganism						
Gram-positive	56	3.7	22	1.6	0.44 (0.27–0.72)	<.001
Enterococcus species	6	…	2	…	…	
Staphylococcus aureus	20	…	15	…	…	
Coagulase-negative staphylococci	22	…	3	…	…	
Other	8	…	2	…	…	
Gram-negative	35	2.3	7	0.5	0.22 (0.10–0.50)	<.001
Acinetobacter species	7	…	3	…	…	
Klebsiella species	5	…	2	…	…	
Escherichia coli	4	…	0	…	…	
Pseudomonas species	3	…	0	…	…	
Alcaligenes species	2	…	0	…	…	
Enterobacter species	9	…	0	…	…	
Haemophilus species	0	…	1	…	…	
Proteus species	3	…	0	…	…	
Serratia marcescens	1	…	1	…	…	
Nonidentified	1	…	0	…	…	
Fungi	5	0.3	2	0.1	0.45 (0.09–2.31)	.32
Candida species	5	…	2	…	…	
Clinical sepsis	57	3.8	14	1.0	0.28 (0.15–0.49)	<.001
Total	153	10.1	45	3.3	0.31 (0.24–0.46)	<.001

NOTE. CI, confidence interval; RR, relative risk.

with an overall reduction of 67% (RR, 0.33 [95% CI, 0.24–0.46]; $P < .001$). The forest plot presented in Figure 1 shows that both the pooled ($P < .001$) and all 4 individual by-country analyses favored the closed infusion container. All of the analyses achieved statistical significance (Figure 1). There was no significant heterogeneity between countries ($P = .185$)

There was a decrease in all-cause ICU mortality that ranged from 3% to 7% during the closed infusion container period in 3 of the 4 countries (Table 3); following the switch from the open to the closed container, overall mortality decreased 5% (RR, 0.77 [95% CI, 0.68–0.87]; $P < .001$). The forest plot in Figure 2 shows that both the pooled analysis ($P = .005$) and the individual by-country analyses for all but Italy favored the closed infusion container. However, only the results from Mexico demonstrated statistical significance ($P = .003$). When Mexico is omitted from the meta-analysis, the result continues to favor the closed infusion container, but the *P* value for the pooled analysis is no longer significant ($P = .120$). Conversely, the inclusion of 4 additional studies of the same size and effect as for Italy would be required to change the pooled analysis from significant ($P = .005$) to nonsignificant ($P = .078$). The test for heterogeneity showed a trend toward there being a difference between countries in mortality ($P = .127$). This heterogeneity was mainly due to the difference in mortality in Italy, compared with the mortality in the 3 Latin American countries.

As seen in Table 4, approximately two-thirds of the CLABSIs were microbiologically documented and one-third represented cryptogenic central line–associated clinical sepsis, a category of CLABSI recognized by the CDC-NHSN.[24] Highly significant decreases in CLABSI were seen in all major microbiologic categories, including bacteremia due to gram-positive organisms, bacteremia due to gram-negative organisms, and cases of clinical sepsis without microbiologic documentation, but the magnitude of the decrease was most striking for bacteremia due to gram-negative organisms (RR, 0.22 [95% CI, 0.10–0.50]; $P < .001$). Gram-negative bacilli were recovered from 35 microbiologically documented CLABSIs during the open infusion container period but only 7 CLABSIs during the closed infusion container period ($P < .001$).

DISCUSSION

The US government has become keenly aware of the substantial risks of central lines in ICUs, and in 2007 the US Congress passed legislation denying federal reimbursement for the incremental hospital costs of CLABSIs.[34] Prospective studies in the Western industrialized countries have shown that hospitals that take a multidisciplinary systematic approach to the management of central lines within ICUs have achieved striking reductions in the incidence of CLABSI.[35-40]

Such an approach focuses on education of all personnel who insert and care for central lines, limits insertions in the femoral vein, mandates maximal sterile barriers during catheter insertion, mandates disinfection of catheter insertion sites with tincture of chlorhexidine rather than iodine-based antiseptics, mandates proactive removal of unneeded catheters, and provides feedback surveillance of CLABSI rates.

However, as we have previously shown[22,41] and reaffirm in this report (Table 3), ICUs in developing countries have rates of CLABSI up to 5 times higher than rates reported from North American ICUs. The limited-resource countries do not have laws mandating hospital infection control programs, and hospital accreditation is not required. Funds and resources for infection control are very limited, nurse-to-patient staffing ratios are far lower on average than in ICUs of the developed countries, and there are far fewer experienced nurses, all of which have been shown to greatly increase risks of device-associated nosocomial infection.[42,43] Moreover, 2% tincture of chlorhexidine has not been affordable by the hospitals of most developing countries. Finally, open infusion systems still are used almost universally.[20,44]

INICC was established in 1998 to begin to meet the needs of the hospitals and patients of the developing world,[42] relying upon education of ICU personnel in basic infection control and performance feedback of outcome and process surveillance data to reduce prohibitively high rates of device-associated nosocomial infection.[28]

The use of open infusion systems that use glass bottles or semirigid plastic containers for intravenous fluid appears to pose unappreciated but very significant increased risks of cryptogenic infusion-associated bloodstream infection. Patients at risk during the 2 periods of the similar time-sequence studies performed in the ICUs of the 4 countries were comparable with respect to risk factors for CLABSI as well as Average Severity of Illness Score, the best predictor of ICU mortality (Tables 1 and 2). However, a marked decrease in the incidence of CLABSI was seen in each of the 4 country's studies, and overall there was a 67% rate reduction (Table 3). Even more impressively, all-cause ICU mortality also decreased commensurately, paralleling the decrease in rates of CLABSI (Table 3).

Recent case-control studies[45-47] have challenged the validity of earlier studies showing that CLABSI are associated with significant attributable mortality,[45,48,49] particularly because so many are caused by coagulase-negative staphylococci that rarely produce septic shock or multiorgan failure. But it must be pointed out that it can be very difficult in an ICU to adequately match control patients who do not have CLABSI with case patients who do have CLABSI for all of the factors that might influence hospital mortality.[50] Moreover, in all of the past studies examining attributable mortality of CLABSI, the cases and controls were identified by hospital clinical surveillance data. Surveillance data in general overestimate the risk of CLABSI with central lines while underestimating the true risk with other types of intravascular devices, because not every device in use in the hospital during the surveillance period is routinely scrutinized as occurs in a prospective research study. We believe that the findings of our study provide new and powerful evidence that shows that CLABSIs significantly increase hospital mortality, making efforts to prevent CLABSI even more essential.

There remains one overarching, as yet unanswered, question that is posed by the findings of these studies: exactly why does the use of glass or semirigid plastic fluid containers, compared with the use of flexible, fully collapsible containers, have such an impact on the incidence of CLABSI and ICU mortality? We believe that the differences in the microbiologic profile of CLABSI seen with the 2 systems may provide insight. The transition from an open to a closed infusion container was associated with a disproportionately greater decrease in CLABSIs caused by gram-negative bacilli (RR, 0.22; $P < .001$; Table 4), consistent with our original hypothesis[44] that closed systems reduce contamination of in-use infusate by gram-negative bacilli that have the capacity to multiply rapidly in glucose-containing intravenous admixtures.[51]

Outbreaks of infusion-associated cryptogenic bacteremia over the past 40 years have virtually all been associated with the use of open infusion systems.[20,44,52] Moreover, the limited studies performed over this period have shown that in-use extrinsic contamination of infusate during intravenous system setup, admixture preparation, and fluid administration has been much higher with open systems, compared with such contamination with closed systems.[44,53,54] q7

This study has limitations, the most important of which is that these were not prospective randomized studies, and furthermore it was not possible to mask the clinicians caring for the patients to the treatment groups. However, most of the characteristics of patients during both periods of the study—in terms of vulnerability to CLABSI and other device-associated nosocomial infection—were similar, as were risk factors for hospital mortality, including Average Severity of Illness Score. The striking decrease in CLABSI seen almost immediately after transition from an open to a closed infusion container in the studied ICUs of each country strongly suggests that the differences in the infusion containers during the 2 study periods was the cause.

Catheter-associated urinary tract infection and ventilator-associated pneumonia were also analyzed to determine whether there were any changes in the ICU that might impact other healthcare-associated infections. During the study, we found a significant reduction of CLABSI rate but no significant overall reduction in the rates of ventilator-associated pneumonia (27.7 and 27.5 cases of ventilator-associated pneumonia per 1,000 mechanical ventilator–days during the open and closed container periods, respectively; $P = .959$). Although there was a significant reduction in the overall rate of catheter-associated urinary tract infection during the closed container period (11.5 and 8.3 catheter-associated urinary tract infections per 1,000 Foley catheter–days during the open and closed container periods, respectively; $P = .011$), it was

largely attributable to the results from Argentina (18.3 and 12.0 catheter-associated urinary tract infections per 1,000 Foley catheter–days during the open and closed container periods, respectively; $P = .042$). Thus, the change to a closed infusion container in all 4 countries was consistently associated only with the reduced CLABSI rate in the studies.

No new infection control interventions, training programs, products, or technologies were introduced during the comparative study periods in each country, and all of the investigators, key ICU personnel, classifications, and diagnostic techniques remained constant throughout each study.

The data from individual studies and the meta-analysis do not identify the epidemiologic mechanisms for the differences seen. Whether they might derive from entry of airborne microorganisms or, possibly, entry of contaminants on the external vent of the open infusion container at the time of setup or during the course of fluid administration is unknown. In addition, epidemiologic data showing that the microorganisms contaminating a vent port were the same as those that caused infection or were found in culture of the intravenous infusate were not collected. Further studies are needed to better understand the striking differences that have been seen.

In summary, many countries still use rigid, externally vented open infusion containers. The findings of these 4 individual country studies and this meta-analysis suggest strongly that switching to a closed infusion container—nonvented, fully collapsible plastic containers for infusate—could greatly reduce rates of CLABSI and hospital mortality. Furthermore, these data affirm strongly that CLABSIs are associated with significant attributable mortality.

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Address reprint requests to Victor Rosenthal, MD, MSc, CIC, Corrientes Ave 4580, Floor 11, Apartment A, Buenos Aires 1195, Argentina (victor_rosenthal@inicc.org).

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