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## Major article

# Clinical impact and cost-effectiveness of split-septum and single-use prefilled flushing device vs 3-way stopcock on central line-associated bloodstream infection rates in India: a randomized clinical trial conducted by the International Nosocomial Infection Control Consortium (INICC)



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## Key Words:

Split septum  
Three-way stopcock  
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Randomized clinical trial  
Catheter-related infection  
Health care-acquired infection  
Hospital infection  
Bacteremia  
Developing countries  
Intensive care unit

**Background:** Three-way stopcocks (3WSCs) are open systems used on intravenous tubing. Split septums (SSs) are closed systems with preperced septums. Single-use prefilled flushing devices (SUFs) carry a lower risk of contamination than standard intravenous flushing. 3WSC and standard flushing are widely used in developing countries. This is the first randomized clinical trial (RCT) to compare rates of central line-associated bloodstream infection (CLABSI) between patients using an SS + SUF and those using a 3WSC.

**Methods:** An RCT with 1096 patients in 5 adult intensive care units was conducted between April 2012 and August 2014 to evaluate their impact on CLABSI rates. Centers for Disease Control and Prevention/National Healthcare Safety Network definitions were applied and International Nosocomial Infection Control Consortium methodology were followed.

**Results:** The study cohort included 547 patients and 3619 central line (CL)-days for the SS + SUF group, and 549 patients and 4061 CL-days for the 3WSC group. CLABSI rates were 2.21 per 1000 CL-days for SS + SUF and 6.40 per 1000 CL-days for 3WSC (relative risk, 0.35; 95% confidence interval [CI], 0.16-0.76;  $P = .006$ ). The SS + SUF group had significantly better cumulative infection-free catheter survival compared with the 3WSC group (hazard ration, 0.33; 95% CI, 0.15-0.73;  $P = .006$ ). Using an SS + SUF represents savings of \$402.88 and an increase in quality-adjusted life years of 0.0008 per patient. For each extra dollar invested in an SS + SUF, \$124 was saved.

**Conclusion:** The use of SS + SUF is cost-effective and associated with a significantly lower CLABSI rate compared with the use of 3WSC.

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Central line (CL)–associated bloodstream infections (CLABSIs) are responsible for increased length of stay, and attributable mortality in high-income<sup>1</sup> and limited-resource countries,<sup>2</sup> including India,<sup>3</sup> as well as for increased health care costs, as reported in studies from high-income countries<sup>1</sup> and Latin America.<sup>2,4</sup> The incidence of CLABSI is often underestimated in limited-resource countries, in which basic infection control programs might not be systematically implemented.<sup>5</sup> CLABSI rates in intensive care units (ICUs) are 3–5 times higher in limited-resources countries than in high-income countries, as reported by the International Nosocomial Infection Control Consortium (INICC) in pooled studies,<sup>5</sup> and particularly in India.<sup>3</sup> The socioeconomic level of a country has an impact on rates of health care–associated infection (HAI) in ICU settings in developing countries.<sup>6,7</sup> However, to date only 2 studies addressing this issue have been published, which showed higher CLABSI rates in pediatric ICUs in lower-middle-income countries compared with upper-middle-income countries,<sup>6</sup> and significantly higher CLABSI rates in neonatal ICU patients from low-income countries than in lower-middle or upper-middle-income countries.<sup>7</sup>

In the developing countries, including India,<sup>8</sup> it has been demonstrated that CLABSI rates can be reduced by more than 50%<sup>8–14</sup> by adopting a multidimensional approach with the simultaneous implementation of 6 elements: (1) a bundle of interventions, (2) education, (3) outcome surveillance, (4) process surveillance, (5) feedback on CLABSI rates and consequences, and (6) performance feedback.

The technology related to the needleless system has evolved over time. A stopcock is a valve or turning plug that controls the flow of fluid from a container through a tube. A 3-way stopcock (3WSC) can be used on intravenous (IV) tubing to turn off one solution and turn on another. It is open to the air without a membrane when cover is not in place, and for that reason is considered an open IV system. The needleless split-septum (SS) device is a simple needleless connector with a prepierced septum that can be of a blunt cannula or luer-lock design, and it is considered a closed IV connector.

Needleless luer-activated systems or needleless mechanical valve (MV) devices with or without positive-pressure displacement are available; however, CLABSI outbreaks associated with their use have been reported in acute care hospitals.<sup>15</sup> Several recent studies have shown that MV IV devices can be associated with a higher incidence of CLABSI compared with SS connectors.<sup>16–18</sup> According to the recommendations published in the guidelines of the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN)<sup>19</sup> and the Joint Commission International,<sup>20</sup> SS devices should be used instead of MV devices. Although the Society for Health Care Epidemiology of America and the Infectious Diseases Society of America have stated that the optimal design for infection prevention is an unresolved issue,<sup>17</sup> in the guidelines published in 2008,<sup>21</sup> recommendations included avoiding the routine use of positive-pressure needleless connectors with MVs before a thorough assessment of risks, as well as the routine use of currently marketed devices associated with an increased risk of CLABSI.<sup>21</sup>

Flushing is an important element of intermittent IV therapy with a risk of contamination, and a single-use prefilled flushing (SUF) device carries a lower risk of contamination.<sup>22</sup>

To our knowledge, to date there are no published randomized clinical trials (RCTs) or quasi-experimental studies comparing infection rates in SS and 3WSC needleless connectors. Several previous quasi-experimental studies have evaluated the impact after switching from SS to MV needleless connectors, which resulted in increased rates of CLABSI.<sup>16,18,23,24</sup> Only 1 recent study, by Pohl et al,<sup>25</sup> compared labor and material costs per use and

contamination rates in SS and 3WSC. The results for average process costs were statistically significantly lower for the closed access system (SS) than for the luer lock caps (3WSC) (€2.55 vs €3.92). The contamination rate was 8% for the 3WSC (4 out of 50 samples positive), compared with 0% for SS (0 out of 50 samples).<sup>25</sup>

This is the first RCT to examine the effect of using SS + SUF vs 3WSC on the incidence rate of CLABSI and to assess the cost-effectiveness of the 2 types of devices, which is sufficient ethical and theoretical justification for conducting this particular trial and, through its publication, increasing and spreading awareness on this public health burden in India—the second largest country of the world, with a population of approximately 1,300,000,000 people,<sup>26</sup> as well as throughout the developing world where 3WSCs are in use.<sup>2,27</sup>

## METHODS

### *Background on the INICC*

The INICC is an international, nonprofit, open, multicenter HAI surveillance network with a methodology based on CDC NHSN guidelines.<sup>28,29</sup> The INICC is the first research network established to measure and control HAIs in hospitals worldwide through the analysis of standardized data collected on a voluntary basis by its member hospitals. Gaining new members since its international inception in 2002, the INICC now comprises nearly 2000 hospitals in 500 cities of 66 countries in Latin America, Asia, Africa, the Middle East, and Europe, and has become the sole source of aggregate standardized international data on the epidemiology of HAI internationally.<sup>5</sup>

### *Setting*

The study was carried out in 5 medical surgical adult ICUs, with a total of 82 beds of 2 tertiary-level hospitals, members of the INICC in the Indian cities of Mumbai and Coimbatore, with a 1:1 nurse:bed ratio. Each hospital had an infection control team with 1 infection control practitioner and 1 physician. The infection control team member in charge of surveillance at each hospital had more than 2 years of experience in monitoring HAI rates and infection control practices. Both ICUs had been using 3WSC devices before initiation of the study. The Institutional Review Board at each hospital approved the RCT protocol. Patient confidentiality was protected by codifying the recorded information, making it identifiable only to the infection control team.

### *Subjects and design*

The study design was a 2-center RCT comparing the clinical impact and cost-effectiveness of using SS + SUF vs 3WSC on the incidence rate of CLABSI. All patients were recruited in 2 ICUs between April 2012 and August 2014. Patients were eligible for the trial if they needed a CL for starting or continuing treatment in the ICU.

CLs were placed under strict aseptic conditions, and exit sites were covered with transparent, oxygen-permeable dressings. Exit site care involved inspection of the catheter exit site, cleaning with chlorhexidine, and covering with a new transparent dressing.

The patients were block-randomized to each group using specialized statistical software (R version 3.0.2, blockrand package; R Project for Statistical Computing, Vienna, Austria).

### Statistical analysis

All statistical analyses were performed using SPSS version 10.0 (SPSS, Chicago, IL). Independent *t* tests were used for the comparison of continuous variables between groups and skewed variables were analyzed with the Mann-Whitney *U* test. A Multivariate Cox proportional hazards regression model was performed to estimate the association between the type of device and the cumulative infection-free catheter survival. Hazard ratio (HR) and 95% confidence interval (CI) were reported for each variable. Possible covariates considered in the multivariate model included age, sex, average severity illness score (ASIS) and the presence of underlying diseases. Covariate variables were selected using a stepwise forward procedure, with a variable entry limit fixed at a significance level of 0.05. Proportionality assumptions were tested by visual examination of log minus log plots and calculation of Schoenfeld residuals.<sup>30</sup>

### Cost-effectiveness analysis

A cost-effectiveness analysis was performed considering a health care payer perspective. For each alternative, the CL-days were multiplied for \$520, which is the daily cost of hospitalization in India according to the study by Mathai et al.<sup>31</sup> The cost of the 3WSC device is \$0.35, whereas the cost of implementing the SS + SUF is \$3.59 (SS, \$3.22; SUF, \$0.37). The effectiveness measure was the quality adjusted life years (QALYs). According to a study by Sznajder et al.,<sup>32</sup> the QALY reduction for a patient in ICU is 0.37 per day. An extra decrement of 0.2 QALYs was assumed for patients at age 65 years, and an annual decrement of 0.005 for each year over 65 was considered as well.<sup>33</sup> Both costs and QALYs were estimated for each patient of this trial using the parameters mentioned above, and the mean was calculated for the 3WS and SS + SUF groups.

### INICC surveillance methods

The INICC surveillance program included surveillance of device-associated HAI rates (rates of CLABSI per 1000 CL-days), use of invasive devices (CLs), their adverse effects, including length of stay, mortality rates, microorganism profile, and bacterial resistance, and patient characteristics, such as, age, sex, ASIS, and underlying diseases.<sup>34</sup> Investigators were required to complete outcome surveillance forms at their ICUs.

CLABSI definitions and surveillance methods were performed applying the definitions for HAI developed by the CDC for the NHSN program.<sup>29</sup> ASIS, as historically used by the CDC NNIS,<sup>35</sup> was used instead of Acute Physiology and Chronic Health Evaluation (APACHE) II score owing to budget limitations of participating ICUs from this limited-resource country.

### Definitions

#### Stopcock

A valve or turning plug that controls the flow of fluid from a container through a tube. A 3-way stopcock can be used on IV tubing to turn off 1 solution and turn on another.

#### 3WSC device

This sterile medical luer lock stopcock is used to indicate the direction of flow in rotating male luer connectors. Its rotating male luer makes the 3WSC convenient to connect with other accessories. It is open to the air without a membrane when the cover is not in place and thus is considered an open IV system.

#### SS device

The SS device is a simple needleless connector with a prepierced septum that can be of a blunt cannula or luer-lock design. Male luer end (from syringe tip or IV set) simply pushes open the sides of the SS, allowing fluid to enter the lumen directly. SS connectors have no internal moving parts.

#### SUF device

Flushing is an important element of intermittent IV therapy, and carries a risk of contamination. With multidose vials, 10 steps are required to aseptically flush a central venous catheter, compared with 4 st with an SUF device. Use of an SUF device has been strongly recommended.<sup>22</sup> Single-use IV flush vials reduce the risk of CLABSI.<sup>22</sup>

## RESULTS

### Clinical analysis

During the entire trial, a total of 1096 patients were hospitalized in 2 medical/surgical adult ICUs, with 20 beds in each, during 9937 bed-days, amounting to 7680 CL-days. The first ICU to participate was enrolled in April 2012, and the most updated data included our analysis dates from August 2014.

The clinical characteristics of the 2 groups are presented in [Table 1](#). There were no statistically significant between-group differences in terms of age, sex, ASIS, or underlying diseases, such as thoracic surgery, respiratory failure, coronary failure, heart failure, cancer, and previous infection, among others ([Table 1](#)).

Five hundred forty-seven patients were randomized to the SS + SUF group (case patients), and 549 patients were randomized to the 3WSC group (control patients). In the SS + SUF group, there were 8 CLABSIs, for an overall rate of 2.21 CLABSIs per 1000 CL-days. In the 3WSC group, there were 26 CLABSIs, for an overall rate of 6.4 CLABSIs per 1000 CL-days. These results show an overall lower CLABSI rate in the SS + SUF group (2.21 vs 6.4 CLABSIs per 1000 CL-days; relative risk [RR], 0.35; 95% CI, 0.16-0.76; *P* = .006) ([Table 2](#)).

During the trial period, 160 patients died, including 76 in the SS + SUF group and 84 in the 3WSC group (RR, 0.91; 95% CI, 0.64-1.2; *P* = .542). Although the mortality rate was lower in the SS + SUF group compared with the 3WSC group (14% vs 15%), the difference was not statistically significant, because this trial was not designed to include the minimum sample size required to reach the power needed to detect statistically significant differences ([Table 2](#)).

The results of the Cox analysis showed that use of the SS + SUF significantly improved cumulative infection-free catheter survival compared with the 3WSC (HR, 0.33; 95% CI, 0.15-0.73; *P* = .006). None of the covariates was found to be significant in the final model.

### Microbiological analysis

The microorganism profile is shown in [Figure 1](#). The predominant microorganisms were *Enterococcus* spp (37.5%) in the SS + SUF group and *Klebsiella* spp (36.4%) in the 3WSC group. The bacterial resistance analysis showed that *Enterococcus* spp strains were 100% resistant to gentamicin in both groups. Resistance was high in *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* strains as well.

**Table 1**  
Patient characteristics in the SS and 3WSC groups

Characteristic	SS SUF group	3WSC group	RR (95% CI)	P value
Patients, n	547	549		
Bed days, n	4404	4933		
Male sex, n (%)	358 (65)	375 (68)	1.04 (0.90-1.21)	.56
Surgical admission, n (%)	280 (51)	299 (54)	1.06 (0.90-1.25)	.46
Age, y, mean $\pm$ SD	60.2 $\pm$ 17.7	60.3 $\pm$ 16.7	1.00	.98
ASIS score, mean $\pm$ SD	3.14 $\pm$ 0.7	3.22 $\pm$ 0.8	1.03	.13
Underlying diseases, n (%)				
Endocrine-metabolic	197 (36)	198 (36)	1.00 (0.82-1.22)	.99
Heart failure	250 (46)	262 (48)	1.04 (0.88-1.24)	.62
Coronary failure	121 (22)	125 (23)	1.03 (0.80-1.32)	.82
Respiratory failure	49 (9)	49 (9)	1.00 (0.67-1.48)	.99
Renal failure	52 (10)	61 (11)	1.17 (0.81-1.69)	.41
Liver failure	8 (1)	6 (1)	0.75 (0.26-2.15)	.59
Cardiac surgery	50 (9)	52 (9)	1.04 (0.70-1.53)	.86
Abdominal surgery	29 (5)	38 (7)	1.31 (0.81-2.12)	.28
Thoracic surgery	10 (2)	5 (1)	0.50 (0.17-1.46)	.19
Stroke/coma	68 (12)	62 (11)	0.91 (0.64-1.28)	.58
Cancer	35 (6)	22 (4)	0.63 (0.37-1.07)	.08
Previous infection	69 (13)	68 (12)	0.98 (0.70-1.37)	.92

**Table 2**  
CLABSI rate and mortality in the SS and 3WSC groups

Variable	SS SUF group	3WSC group	RR (95% CI)	P value
Patients, n	547	549		
CL-days, n	3619	4061		
CLABSIs, n	8	26		
CLABSIs per 1000 CL-days, n	2.21	6.40	0.35 (0.16-0.76)	.006
CLABSI rate per 100 patients, %	1.5	4.7	0.31 (0.14-0.68)	.002
Deaths, n	76	84		
Deaths, %	14	15	0.91 (0.64-1.24)	.54

CLAB, central line bloodstream infection; RR, relative risk; CI, confidence interval.

### Cost-effectiveness analysis

In the 3WSC group, the total cost of patients with CLABSI was US \$3846.84 considering the daily hospitalization cost and the device cost, with a utility score of 0.9903 QALYs per patient. In the SS + SUF group, the total cost of patients with CLABSI was US\$3443.96, with a utility score of 0.9911 QALYs per patient. This shows that the use of the SS + SUF dominates the use of 3WSC, meaning that this strategy is cost-effective and QALY-increasing. Use of the SS + SUF device would provide a savings of US\$402.88 and an increase of 0.0008 QALY per patient from the health care payer perspective. This means that for each extra dollar invested in SS, \$124 could be saved.

### DISCUSSION

In this RCT, significant differences in CLABSI incidence rate and cost-effectiveness were observed in the SS + SUF group compared with the 3WSC group. Coincidentally, use of the SS + SUF device significantly improved cumulative infection-free catheter survival compared with use of the 3WSC device.

It is worth noting that the protocol for CL management and care was similar in the 2 ICUs over the entire trial period, and that patient characteristics, including age, sex, ASIS, and underlying diseases, were similar in the 2 groups. In addition, we also found a lower mortality rate in the SS + SUF group compared with the 3WSC group, although the difference did not reach statistical significance. As mentioned above, this was related to the design of the trial, which did not include a minimum sample size required to reach the power needed to find statistically significant differences.

This is the first RCT that has been conducted to compare infection rates associated with the use of SS + SUF and 3WSC devices. Previous quasi-experimental studies published in the scientific literature have compared SS and MV devices. In 1 such study, Salgado et al found that the CLABSI rate was significantly higher during the needleless MV device period than during the needleless SS device period (5.95 CLABSIs per 1000 CL-days vs 1.79 CLABSIs per 1000 CL-days; RR, 3.32; 95% CI, 2.88-3.83;  $P < .001$ ).<sup>16</sup> Similarly, Rupp et al found that a higher rate of CLABSI during a period of MV use, compared with the period before MV use (14% vs 6.5%;  $P = .17$ , in cases with a polymicrobial etiology, and 28.1% vs 17.7%;  $P = .18$  in cases caused by gram-negative organisms).<sup>24</sup>

Compared with standard rates in high-income countries, the rate of CLABSI in the 3WSC group (6.4 CLABSIs per 1000 CL-days) was approximately 5-fold higher than the CLABSI rate of 1.1 per 1000 CL-days in the United States as determined by the CDC NSHN,<sup>36</sup> and more than 4-fold higher than the rate of 1.4 in Europe reported by the Krankenhaus Infektions Surveillance System.<sup>37</sup>

Compared with pooled CLABSI rates from other developing countries, the CLABSI rate found in our 3WSC group (6.4 CLABSIs per 1000 CL-days) was similar to the rate reported in the fifth international INICC report published in 2014 (4.8 CLABSIs per 1000 CL-days; 95% CI, 4.7-4.9).<sup>5</sup> Within the scope of other studies addressing the burden of CLABSIs in India, the CLABSI rate in our 3WSC group was similar to the rate of 7.92 CLABSIs per 1000 CL-days found in a 2007 study.<sup>3</sup>

In previous studies performed by INICC member hospitals, it was shown that the implementation of a 6-component multidimensional approach for CLABSI resulted in significant reductions in CLABSI rates in Argentina (45.9 vs 11.1 CLABSIs per 1000 CL-days),<sup>13</sup> in Mexico (46.3 vs 19.5 CLABSIs per 1000 CL-days),<sup>12</sup> in Turkey (22.7 vs 12.0 CLABSIs per 1000 CL-days),<sup>9</sup> in India (6.4 vs 3.9 CLABSIs per 1000 CL-days),<sup>8</sup> in adult ICUs of 15 countries (16.0 vs 7.4 CLABSIs per 1000 CL-days),<sup>14</sup> in pediatric ICUs of 5 countries (10.7 vs 5.2 CLABSIs per 1000 CL-days),<sup>10</sup> and in neonatal ICUs of 4 countries (21.4 vs 9.7 CLABSIs per 1000 CL-days).<sup>11</sup> However, in none of the previous studies conducted by INICC the CLABSI rate was lower than 5.2 CLABSIs per 1000 CL-days, as was achieved in the SS + SUF group.<sup>8-14</sup> This finding is consistent with the fact that according to the INICC, between 88% and 94% of hospitals in the developing world use 3WSC devices instead of SS + SUF devices.<sup>14</sup>

In the present study, our comparison showed that using SS + SUF devices would save \$402.88 per patient. This means that for each extra dollar invested in SS + SUF, \$124 could be saved.

A review of the literature identified only 1 recent study, by Pohl et al, that compared costs per use between SS and 3WSC devices.<sup>25</sup> The results for average process costs were statistically significantly lower with the use of SS devices ( $\text{€}2.55$  vs  $\text{€}3.92$ ).<sup>25</sup>

Regarding the microorganisms profile, the predominant microorganisms identified *Enterococcus* spp (25%) in the SS + SUF group and *Klebsiella* spp (20%) in the 3WSC group. In a study by Salgado et al, a significantly higher percentage of CLABSIs caused by gram-negative organisms was found during the needleless MV device period compared with the SS device period (39.5% vs 8%;  $P = .007$ ).<sup>16</sup>

### CONCLUSION

During the trial period, the use of SS + SUF devices was associated with a significantly lower CLABSI rate and was more cost-effective compared with the use of 3WSC devices. These findings suggest that the 3WSC devices are unsafe and more expensive for use in patients, whereas the SS devices are safer and more cost-effective.



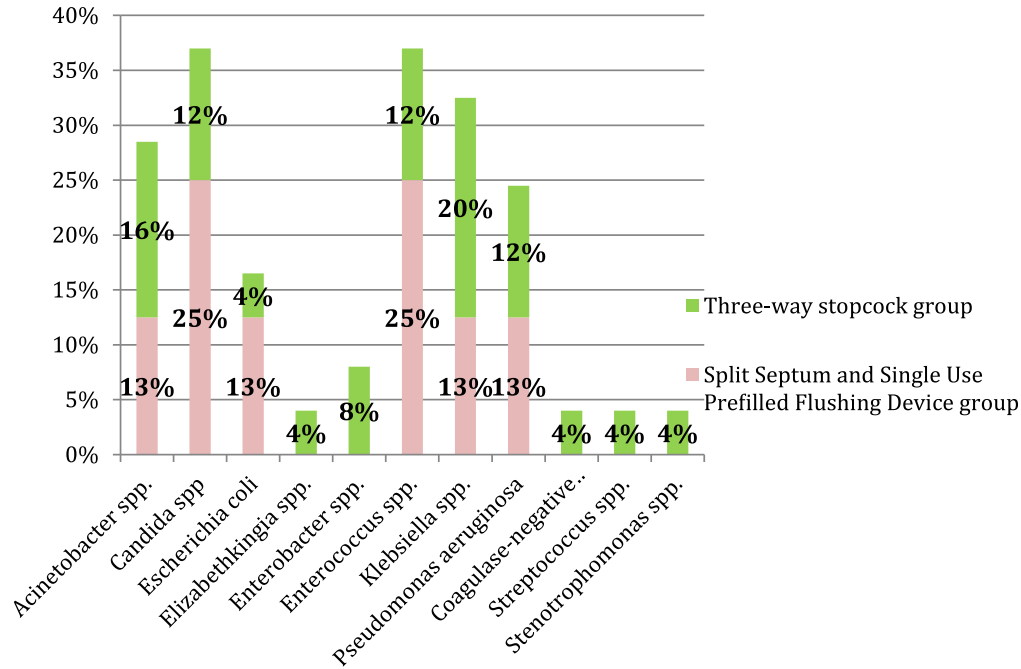


Fig 1. Microorganism profile in the SS and 3WSC groups.

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## References

- Stone PW, Braccia D, Larson E. Systematic review of economic analyses of health care-associated infections. *Am J Infect Control* 2005;33:501-9.
- 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;31:475-80.
- Mehta A, Rosenthal VD, Mehta Y, Chakravarthy M, Todi SK, Sen N, 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;67:168-74.
- Higuera F, Rangel-Frausto MS, Rosenthal VD, Soto JM, Castanon J, Franco G, 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;28:31-5.
- Rosenthal VD, Maki DG, Mehta Y, Leblebicioglu H, Memish ZA, Al-Mousa HH, et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 43 countries for 2007-2012: device-associated module. *Am J Infect Control* 2014;42:942-56.
- Rosenthal VD, Jarvis WR, Jamulitrat S, Silva CP, Ramachandran B, Duenas L, et al. Socioeconomic impact on device-associated infections in pediatric intensive care units of 16 limited-resource countries: International Nosocomial Infection Control Consortium findings. *Pediatr Crit Care Med* 2012;13:399-406.
- Rosenthal VD, Lynch P, Jarvis WR, Khader IA, Richtmann R, Jaballah NB, et al. Socioeconomic impact on device-associated infections in limited-resource neonatal intensive care units: findings of the INICC. *Infection* 2011;39:439-50.
- Jaggi N, Rodrigues C, Rosenthal VD, Todi SK, Shah S, Saini N, et al. Impact of an International Nosocomial Infection Control Consortium multidimensional approach on central line-associated bloodstream infection rates in adult intensive care units in eight cities in India. *Int J Infect Dis* 2013;17:e1218-24.
- Leblebicioglu H, Ozturk R, Rosenthal VD, Akan OA, Sirmatel F, Ozdemir D, et al. Impact of a multidimensional infection control approach on central line-associated bloodstream infections rates in adult intensive care units of 8 cities of Turkey: findings of the International Nosocomial Infection Control Consortium (INICC). *Ann Clin Microbiol Antimicrob* 2013;12:10.
- Rosenthal VD, Ramachandran B, Villamil-Gomez W, Armas-Ruiz A, Navoa-Ng JA, Matta-Cortes L, et al. Impact of a multidimensional infection control strategy on central line-associated bloodstream infection rates in pediatric intensive care units of five developing countries: findings of the International Nosocomial Infection Control Consortium (INICC). *Infection* 2012;40:415-23.
- Rosenthal VD, Duenas L, Sobreyra-Oropeza M, Ammar K, Navoa-Ng JA, de Casares AC, et al. Findings of the International Nosocomial Infection Control Consortium (INICC), part III: effectiveness of a multidimensional infection control approach to reduce central line-associated bloodstream infections in the neonatal intensive care units of 4 developing countries. *Infect Control Hosp Epidemiol* 2013;34:229-37.
- Higuera F, Rosenthal VD, Duarte P, Ruiz J, Franco G, Safdar N. The effect of process control on the incidence of central venous catheter-associated bloodstream infections and mortality in intensive care units in Mexico. *Crit Care Med* 2005;33:2022-7.
- Rosenthal VD, Guzman S, Pezzotto SM, Crnich CJ. Effect of an infection control program using education and performance feedback on rates of intravascular device-associated bloodstream infections in intensive care units in Argentina. *Am J Infect Control* 2003;31:405-9.
- Rosenthal VD, Maki DG, Rodrigues C, Alvarez-Moreno C, Leblebicioglu H, Sobreyra-Oropeza M, et al. Impact of International Nosocomial Infection Control Consortium (INICC) strategy on central line-associated bloodstream infection rates in the intensive care units of 15 developing countries. *Infect Control Hosp Epidemiol* 2010;31:1264-72.
- Maragakis LL, Bradley KL, Song X, Beers C, Miller MR, Cosgrove SE, et al. Increased catheter-related bloodstream infection rates after the introduction of a new mechanical valve intravenous access port. *Infect Control Hosp Epidemiol* 2006;27:67-70.
- Salgado CD, Chinnes L, Paczesny TH, Cantey JR. Increased rate of catheter-related bloodstream infection associated with use of a needleless mechanical valve device at a long-term acute care hospital. *Infect Control Hosp Epidemiol* 2007;28:684-8.

17. Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;35(Suppl 2): S89-107.
18. Field K, McFarlane C, Cheng AC, Hughes AJ, Jacobs E, Styles K, et al. Incidence of catheter-related bloodstream infection among patients with a needleless, mechanical valve-based intravenous connector in an Australian hematology-oncology unit. *Infect Control Hosp Epidemiol* 2007;28:610-3.
19. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011;52:e162-93.
20. Joint Commission. International accreditation standards for hospitals, including standards for academic medical center hospitals. 5th ed. Oak Brook [IL]: Joint Commission Resources; 2013.
21. Marschall J, Mermel LA, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol* 2008;29(Suppl 1):S22-30.
22. Joint Commission. Preventing central line-associated infections: a global challenge, a global perspective. 2012. Available from: [http://www.jointcommission.org/preventing\\_clabsi/](http://www.jointcommission.org/preventing_clabsi/). Accessed November 4, 2014.
23. Jarvis WR, Murphy C, Hall KK, Fogle PJ, Karchmer TB, Harrington G, et al. Health care-associated bloodstream infections associated with negative- or positive-pressure or displacement mechanical valve needleless connectors. *Clin Infect Dis* 2009;49:1821-7.
24. Rupp ME, Sholtz LA, Jourdan DR, Marion ND, Tyner LK, Fey PD, et al. Outbreak of bloodstream infection temporally associated with the use of an intravascular needleless valve. *Clin Infect Dis* 2007;44:1408-14.
25. Pohl F, Hartmann W, Holzmann T, Gensicke S, Kolbl O, Hautmann MG. Risk of infection due to medical interventions via central venous catheters or implantable venous access port systems at the middle port of a three-way cock: luer lock cap vs luer access split septum system (Q-Syte). *BMC Infect Dis* 2014;14:41.
26. Taneja N, Gill SS, Biswal M, Kumar A, Gupta AK, Parwej S, et al. Working awareness of healthcare workers regarding sterilisation, disinfection, and transmission of bloodborne infections and device-related infections at a tertiary care referral centre in north India. *J Hosp Infect* 2010;75:244-5.
27. Raad II. The pathogenesis and prevention of central venous catheter-related infections. *Middle East J Anaesthesiol* 1994;12:381-403.
28. National Healthcare Safety Network, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Atlanta [GA]: Centers for Disease Control and Prevention; 2013.
29. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32.
30. Hosmer DW, Lemeshow S, May S. Applied survival analysis: regression modeling of time-to-event data. 2nd ed. New York [NY]: Wiley; 2008.
31. Mathai AS, Phillips A, Kaur P, Isaac R. Incidence and attributable costs of ventilator-associated pneumonia (VAP) in a tertiary-level intensive care unit (ICU) in northern India. *J Infect Public Health* 2014;8:127-35.
32. Sznajder M, Aegerter P, Launois R, Merliere Y, Guidet B, CubRea. A cost-effectiveness analysis of stays in intensive care units. *Intensive Care Med* 2001;27:146-53.
33. Dick AW, Perencevich EN, Pogorzelska-Maziarz M, Zwanziger J, Larson EL, Stone PW. A decade of investment in infection prevention: a cost-effectiveness analysis. *Am J Infect Control* 2015;43:4-9.
34. Rosenthal VD, Maki DG, Graves N. The International Nosocomial Infection Control Consortium (INICC): goals and objectives, description of surveillance methods, and operational activities. *Am J Infect Control* 2008;36:e1-12.
35. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections 1988. *Z Arztl Fortbild (Jena)* 1991;85:818-27.
36. Dudeck MA, Weiner LM, Allen-Bridson K, Malpiedi PJ, Peterson KD, Pollock DA, et al. National Healthcare Safety Network (NHSN) report, data summary for 2012: device-associated module. *Am J Infect Control* 2013;41:1148-66.
37. Geffers C, Gastmeier P. Nosocomial infections and multidrug-resistant organisms in Germany: epidemiological data from KISS (the Hospital Infection Surveillance System). *Dtsch Arztebl Int* 2011;108:87-93.