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Multinational prospective cohort study over 24 years of the risk factors for ventilator-associated pneumonia in 187 ICUs in 12 Latin American countries: Findings of INICC

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1. Introduction

A global research network for healthcare-associated infections (HAI) was established in 2002 when the International Nosocomial Infection Control Consortium (INICC) was created [1]. Its major objective is to promote evidence based interventions of infection prevention in order to reduce the rate of HAIs and the mortality, bacterial resistance, excessive length of stay (LOS), and cost they cause [2]. International reports comprising data on ventilator-associated pneumonia (VAP) and clinical outcomes were published by INICC in 2006 [3], 2008 [4], 2010 [5], 2012 [6], 2014 [7], 2016 [8], 2019 [9], and 2021 [10]. According to INICC published data [3-10], the VAP rates in Latin America and other middle income countries (LMIC) are much higher than those in high income countries.

The crude mortality rate among ICU patients without HAI was also discovered by INICC to be 17.12% (95% CI = 16.93–17.32), for those with VAP it was found to be 42.32% (95% CI = 40.61–44.09), and for those with VAP plus central line associated bloodstream infection (CLABSI) plus catheter associated urinary tract infections (CAUTI), it was found to be 63.44% (95% CI = 55.99–71.60). [10].

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Regarding risk factors (RF) analysis, Bochicchio et al. conducted a prospective observational cohort study of 766 trauma patients admitted to the intensive care unit (ICU), who received mechanical ventilation (MV) for >or = 48 h, and who did not have pneumonia on admission. Logistic regression analyses controlled for all variables related significantly to VAP. A significantly greater proportion of male patients developed VAP. Also Patients with VAP had a longer duration of MV. On the other hand transfusion of blood products was an independent risk factor for VAP, and the risk increased with more units transfused. [11]. Rocha et al. conducted a case study vs. patients control under MV and hospitalized into clinical-surgical adults ICU from March/2005 to March/2006. Patients under MV for over 48 h were included in the study including 84 with diagnosis of VAP, and 191 without VAP (control group). By multivariate analysis the RFs predisposing for VAP were MV time and MV > seven days, tracheostomy and use of > or = three antibiotics [12]. Joseph et al. performed a prospective study over a period of 15 months to determine the incidence and the RFs for development of VAP in critically ill adult patients admitted in different ICUs of Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), a tertiary care hospital in Pondicherry, India. Univariate analysis indicated that the following were significantly associated with VAP: impaired consciousness, tracheostomy, re-intubation, emergency intubation, and nasogastric tube. Emergency intubation and intravenous sedatives were found to be the specific RFs for early onset VAP, while tracheostomy and re-intubation were the independent predictors of late-onset VAP by multivariate logistic regression analysis [13].

The above-mentioned studies and other several studies have analyzed the impact on VAP of male patients [11], trauma patients [14], post-surgical patients [14], burns patients [14], history of smoking [14], low serum albumin concentration [14], high score on the American Society of Anesthesiologists Physical Status Classification System [14], Acute respiratory distress syndrome [14], COPD [14], lung injury [14], upper respiratory tract colonization [14], sinusitis [14], longer duration of surgery [14], biofilm on the surface and within lumen of the endotracheal tube [14], duration of MV [11,12,14], frequent change in ventilator circuit [14], lack of use of heat and moist exchange humidifiers [14], tracheostomy [12-14], emergency intubation [13], frequent reintubation [13,14], open suctioning systems [14], supine position [14], enteral feeding [14], nasogastric tube [13], paralytic agents [14], impaired consciousness [13], intravenous sedatives [13], transfusion of blood products [11], use of > or = three antibiotics [12], and patients transported out of ICU [14].

But as of the publication date, no study has simultaneously looked at many different countries to identify risk factors for VAP in critical care units. Furthermore, no study has examined the relationship between any of the following variables over an 24-year time span: income level per country according with World Bank, facility ownership, type of hospitalization, and ICU type. The goal of the current research is to analyze the effects of some of these variables and other variables as possible VAP RFs.

2. Methods

2.1. Study population and design

Between July 1st, 1998, and February 10th, 2022, over 24 years, a prospective observational cohort research was undertaken on patients hospitalized to 187 ICUs of 95 hospitals in 45 locations throughout 12 Latin American nations (Venezuela, El Salvador, Brazil, Ecuador, Argentina, Colombia, Costa Rica, Mexico, Panama, Peru, Cuba, Dominican Republic).

2.2. Prospective cohort in ICUs and surveillance of healthcare associated infections

Data for each patient were collected at the time of ICU admission. From the moment of admission till release, infection prevention professionals (IPP) visited by each patient's bedside every day. All adult and pediatric patients hospitalized in an ICU, with or without HAIs, were prospectively included in this research, and their data were collected using standardized paper forms from 1998 to 2012 and the INICC Surveillance Online System (ISOS) from 2013 to 2022.

IPPs bring a tablet to the bedside of each hospitalized patient in the ICU, sign in to ISOS, and upload the patient's data [2]. In addition to information about the patient's age, type of hospitalization, use of invasive devices (central line [CL], MV, urinary catheter [UC]), and presence of infection, the information is provided since the time of admission and includes information about the setting, such as the country, city, name of the hospital, and the type of ICU. Every day until the patient is discharged, IPPs upload to ISOS details regarding each patient's invasive devices (CL, MV, UC) and positive cultures (blood, urine, and respiratory samples). [2].

An infectious diseases specialist approaches the patient to check for the existence of a HAI if IPPs notice any signs or symptoms of one (CLABSI, VAP, or CAUTI). IPPs are required to evaluate at a patient's signs and symptoms, cultures, X-rays, and other specified criteria to see if they meet definitions of HAI, according to the CDC/National Healthcare Safety Network (CDC/NHSN). [15].

The current and updated CDC definition of HAIs has been used by all IPPs of all participant hospitals over the 24 years of this study. That is, our IPPs started using the new updated definitions whenever the CDC changed their definitions. IPPs should check all the CDC/NHSN criteria to identify the existence of a HAI and the kind of HAI by uploading the results of a culture to the ISOS, which immediately displays a notification and refers the IPP to an online module of the ISOS (CLABSI, VAP, CAUTI) [2].

The ISOS performs daily device utilization checks. The ISOS alerts the IPPs when a bias in patient-days or device use is found between admission and discharge. It is likely that IPP omitted to upload to ISOS the use of devices or the patient's discharge from the hospital if the patient is being managed in the ICU without any devices in place. The ISOS will notify the IPP to upload any missing devices or to upload the patient's discharge if it detects a day when no devices of any sort were used. In other words, ISOS requests that IPPs investigate the reason a patient in an ICU lacks any devices. This method greatly reduces biases related to device usage, patient days, and discharge conditions. [2].

Patients whose data were missing were not included in the analysis. The participating hospitals' Institutional Review Boards granted their approval for this study. The identity of patients and hospitals are kept confidentially.

2.3. INICC surveillance online system

The characteristics of specific patients or the number of device-days associated with specific patients are not mentioned in the standard CDC/NSHN methodology, which specify that HAI denominators are collected from all patients as pooled data. [15].

The CDC NHSN criteria and methodologies are used in the ISOS, an online platform being used INICC HAI surveillance. [15]. Additionally, ISOS includes the gathering of patient-specific data with several factors for each patient, including both patients with and without HAI. By being able to compare data from all patients admitted to the ICU by various characteristics, the VAP RFs can be calculated. [2]. From the data uploaded to ISOS, HAIs are identified, HAI rates are estimated, and the MV/ device utilization ratio is calculated using the CDC/NHSN criteria and methodologies. [15].

2.4. Validation of diagnosis of healthcare associated infections

The ISOS's HAI validation tool helps to increase the sensitivity, specificity, and accuracy of surveillance data. Each HAI reported by an IPP is validated, and carefully examined to make sure the criteria have been met to support its reporting as a HAI. The screen clearly displays a red sign in order to notify any revisions or additions that are required. To enable the identification of unreported but genuine HAI, the validation process also entails the examination of data submitted for patients who are presumably uninfected. To achieve this, the ISOS automatic validation system displays an online message to the IPP asking to check CDC/NHSN criteria for that putative HAI, should the ISOS suspect a HAI, when the IPP uploads a culture to the ISOS but does not confirm a HAI based on the uploaded culture, the date that the culture was taken, and the result of the culture. Every month, the ISOS provides the IPP an XLS file containing a list of estimates about HAIs that haven't been verified. [2].

2.5. Study definitions

2.5.1. Ventilator

Any device used to support, assist, or control respiration through the application of positive pressure to the airway when delivered via an artificial airway, specifically an oral/nasal endotracheal or tracheostomy tube.

2.5.2. Definitions of VAP

It is used during surveillance were those published by CDC in 1991 [16] and all their subsequent updates through 2022 [17].

2.5.3. Ventilator-associated pneumonia

A pneumonia where the patient is on MV for >2 consecutive calendar days on the date of event, with day of ventilator placement being Day 1, **AND** the ventilator was in place on the date of event or the day before [17].

2.5.4. Clinically defined pneumonia

Two or more serial chest imaging test results with at least **one** of the following: New and persistent **or** Progressive and persistent; Infiltrate; Consolidation; Cavitation; Pneumatoceles, in infants ≤1 year old. For ANY PATIENT, at least **one** of the following: Fever; Leukopenia; or leukocytosis; For adults ≥70 years old, altered mental status with no other recognized cause. And at least **two** of the following: New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements; New onset or worsening cough, or dyspnea, or tachypnea; Rales or bronchial breath sounds; Worsening gas exchange; increased oxygen requirements; or increased ventilator demand [17].

2.5.5. Pneumonia with common bacterial or filamentous fungal pathogens and specific laboratory findings

Two or more serial chest imaging test results with at least **one** of the following: New and persistent **or** **p**rogressive and persistent Infiltrate; Consolidation; Cavitation; Pneumatoceles, in infants ≤1 year old. At least **one** of the following: Fever; Leukopenia or leukocytosis; For adults ≥70 years old, altered mental status with no other recognized cause. And at least **one** of the following: New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements; New onset or worsening cough, or dyspnea, or tachypnea; Rales or bronchial breath sounds; Worsening gas exchange; increased oxygen requirements; or increased ventilator demand. At least **one** of the following: Organism identified from blood; Organism identified from pleural fluid; Positive quantitative culture or corresponding semi-quantitative culture result from minimally-contaminated LRT specimen; ≥5% BAL-obtained cells contain intracellular bacteria on direct microscopic exam; Positive quantitative culture or corresponding semi-quantitative culture result of lung tissue; Histopathologic exam shows evidences of pneumonia [17].

2.5.6. World Bank country classifications by income level

The WB assigns the world's economies to four income groups—low, lower-middle, upper-middle, and high-income countries. The classifications are based on gross national income (GNI) per capita in the current USD. Low income are those countries with GNI less than USD 1045. Lower-middle income those with GNI from 1046 to 4095. Upper-middle income for those with GNI from 4096 to 12,695. High income for those with GNI >12,695 [18].

Mechanical ventilator device-utilization ratio: Mechanical ventilator (MV) device-utilization (MV/ DU) ratio was calculated as a ratio of MV-days to patient-days for each location type. As such, the MV/DU ratio of a location measures the use of invasive devices and constitutes an extrinsic RF for VAP. MV/DU ratio may also serve as a marker for the severity of illness of patients (i.e. severely ill patients are more likely to require an invasive device) which is an intrinsic RF for VAP [19].

2.5.7. Facility/institution ownership type

Publicly owned facilities owned or controlled by a governmental unit or another public corporation (where control is defined as the ability to determine the general corporate policy); ***not-for-profit privately owned*** facilities that are legal or social entities created for the purpose of producing goods and services, whose status does not permit them to be a source of income, profit or other financial gains for the unit(s) that establish, control or finance them; and, ***for-profit privately owned facilities*** that are legal entities set up for the purpose of producing goods and services and are capable of generating a profit or other financial gains for their owners [20].

2.6. Statistical analysis

Patients with and without VAP were compared using multiple logistic regression. Statistically significant variables were independently associated with an increased risk for VAP. The test statistic used was the Wald test, and the statistical significance level was set at 0.05. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for statistically significant variables were also given. These were calculated from the results of multiple logistic regression.

Since the sample sizes of patients receiving CPAP and tracheostomies without an MV were not balanced with those receiving other forms of respiratory support, these patients were removed from this study.

We estimated variables independently associated with the outcome (VAP), adjusted to the following prospectively collected data: (1) Gender (female, male), (2) age, (3) MV-days before acquisition of VAP, (4) MV/DU ratio as a marker of severity of illness of patient, (5) type of respiratory support (endotracheal tube connected to a mechanical ventilator, tracheostomy connected to a mechanical ventilator), (6) hospitalization type (medical, surgical), (7) LOS, (8) ICU type (medical-surgical, medical, pediatric, surgical, coronary, neuro-surgical, cardiothoracic, neurologic, trauma, pediatric oncology, adult oncology), (9) facility ownership (publicly owned facilities, not-for-profit privately owned facilities, for-profit privately owned facilities, university hospitals) [20], and (10) income per country according to WB (low, lower-middle, upper-middle, high) [18].

The evaluated outcome was the acquisition of VAP according to CDC/NHSN definitions [15]. All statistical analyses were performed using R software, version 4.1.3.

3. Results

A cohort, prospective, multicenter surveillance study of VAPs was carried out in 187 ICUs of 95 hospitals in 45 cities across 12 participating Latin American nations (Argentina, Brazil, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Mexico, Panama, Peru, and Venezuela). This is a cohort study, and the length of participation of hospitals is variable and ranged from 1.37 and 201.93 months (Mean, 40.66; SD, 41.68).

From July 1st, 1998 to February 10th, 2022, a period of 24 years, data on 67,437 critical patients was gathered. They were followed from admission to discharge from the ICU during 456,575 patient-days, and they acquired 1800 VAPs.

Table 1 shows data on setting and patient characteristics. Table 2 shows the VAP rate stratified per ICU type, income level according to the World Bank, and facility ownership.

Using multiple logistic regression, we found that the following variables are statistically significantly and independently linked to VAP (Table 3): Age, male gender, LOS, MV/DU ratio, endotracheal-tube compared with tracheostomy, surgical hospitalization, and public hospitals. Adult-oncology, medical-surgical, and surgical were the ICUs with the highest VAP risk.

4. Discussion

The age was associated with acquisition of VAP in our study. Similarly, Beardsley et al. carried out a study at a quaternary care children's hospital PICU. In 300 episodes of MV, there were 30 individual episodes of VAP. A Risk factor for development of any VAP included older age [21].

A correlation between VAP and male gender was found in the current analysis. Coincidentally, Bochicchio et al. at his study also identified that a significantly greater proportion of male patients developed VAP [11]. Also Garibaldi et al. identified that the acquisition of pneumonia was associated with male sex [22].

We found that LOS was linked to an increase in VAP risk. Coincidentally, Sofianou et al. carried out a prospective investigation to identify the VAP RF in patients requiring MV for >48 h. Relationship between VAP and LOS in ICU was revealed by logistic regression analysis. [23],

In addition, our study found a link between VAP and the MV/DU ratio. Similarly, Trouillet et al. conducted a study to identify risk factors for VAP. According to logistic regression analysis, duration of mechanical ventilation (MV) > or = 7 d (odds ratio [OR] = 6.0), was linked to acquisition of a VAP [24]. Nakaviroj et al. performed a study to determine the risk factors of VAP in the general surgical intensive care unit, Siriraj Hospital (SICU). During the period from June 1st, 2010 to June 30th, 2011, 228 adult patients admitted to the general SICU were recruited. Multiple logistic regression analyses showed that the median duration of MV was associated with acquisition of VAP [25].

We found that patients who used endotracheal tubes had a higher risk of VAP. In a 500-bed private community nonteaching hospital in the US, Ibrahim et al. conducted a prospective cohort research to identify VAP RF in a medical ICU and a surgical ICU. Contrarily, logistic regression analysis showed that the development of VAP was independently correlated with tracheostomy. [26].

The highest risk of VAP was also found to be in the adult-oncology, medical-surgical, and surgical ICUs. These ICUs are linked to the highest risk of VAP because they have the highest MV-DU ratio, which serve as an indicator of patients' illness severity. [27].

Furthermore, a correlation between VAP acquisition rates in public hospitals was discovered. The VAP rate per 1000 MV-days at public hospitals was 4.7; 95% CI 3.9–5.7; while at private hospitals was 3.5; 95% CI 2.6–4.5, according to a prior study done at PICUs. Public hospitals exhibited a higher risk for VAP as compared to private hospitals. [28].

Table 1
Setting and patient characteristics.

Period	07-01-1998 to 02-10-2022
Years, n	24
ICUs, n	188
Hospitals, n	92
Cities, n	43
Countries, n	10
Total patients, n	67,437
Total patients-days, n	455,575
Average LOS, mean, SD	mean = 6.76, SD = 6.94
VAP, n	1800
Survival status, n (%)	
Alive	57,673 (85.52%)
Death	9764 (14.48%)
Number of countries, stratified per income level according to World Bank	
Lower middle income country	1 (10.00%)
Upper middle income country	9 (90.00%)
Number of patients admitted per facility ownership, n (%)	
Publicly owned facilities	18,778 (27.85%)
For-profit privately owned facilities	36,884 (54.69%)
University hospitals	10,344 (15.34%)
Not-for-profit privately owned facilities	1431 (2.12%)
Number of patients per Hospitalization type	
Medical hospitalization, n (%)	44,230 (665.59%)
Surgical hospitalization, n (%)	23,207 (34.41%)
Number of patients admitted per type of ICU, n (%)	
Medical-Surgical ICU	41,817 (62.01%)
Coronary ICU	12,849 (19.05%)
Pediatric ICU	4244 (6.29%)
Surgical ICU	2859 (4.24%)
Medical ICU	2685 (3.98%)
Cardio-thoracic ICU	1338 (1.98%)
Neuro-Surgical ICU	645 (0.96%)
Neurologic ICU	99 (0.15%)
Adult-Oncology ICU	173 (0.26%)
Pediatric-Oncology ICU	13 (0.19%)
Respiratory ICU	532 (0.79%)
Trauma ICU	183 (0.27%)
Gender, n (%)	
Male	36,651 (54.35%)
Female	30,786 (45.65%)
Age, mean, SD	Mean = 55.3, SD = 24.41
Device-days and device utilization ratio	
MV/DU ratio, mean, SD	mean = 0.27, SD = 0.88
Total MV-days, n, mean, SD	155,362, mean = 2.30, SD = 6.27
Number of days using following types of respiratory support, n (%)	
Endotracheal tube connected to a MV	138,372 (89.06%)
Tracheostomy connected to a MV	8922 (5.74%)
Tracheostomy not connected to a MV	675 (0.24%)
CPAP	565 (0.36%)

ICU = intensive care unit; MV = mechanical ventilator; DU = device utilization; LOS = length of stay; VAP = Ventilator associated pneumonia; SD = standard deviation; CPAP = Continuous positive airway pressure.

Some of the VAP risk factors found in our study, such as age, gender, ICU type, facility ownership are not expected to change. According to the results, the RFs that have the most potential to make an impact are those that limit LOS and lower the MV/DU ratio. A set of guidelines based on evidence, such as those released by APIC/IDSA/SHEA to prevent VAPs, also could help to control patients utilizing MV. [29].

The extremely high VAP rate that is now present in Latin America has been demonstrated to be controllable. All of that is achieved by implementing the aforementioned APIC/SHEA/IDSA recommendations,

Table 2
Ventilator associated pneumonia rates stratified per ICU type, per type of respiratory support, per World Bank country classifications by income level, and per Facility ownership type.

	Patients, n	Patient days, n	VAP, n	MV-days, n	VAP rate	95% CI
ICU type*						
Adult-oncology	173	634	11	159	69.18	67.90–70.49
Trauma	183	884	2	134	14.93	14.28–15.60
Medical-surgical	41,817	287,575	1410	114,318	12.33	12.31–12.35
Coronary	12,849	75,827	113	11,130	10.15	10.09–10.21
Surgical	2859	14,758	52	5665	9.18	9.10–9.26
Pediatric	4244	34,831	135	16,329	8.27	8.22–8.31
Respiratory	532	6491	27	4618	5.85	5.78–5.92
Cardio-thoracic	1338	8969	20	3855	5.19	5.12–5.26
Medical	2685	19,504	27	8134	3.32	3.28–3.36
Neuro-surgical	645	5301	3	2194	1.37	1.32–1.43
Pooled	67,437	455,575	1800	166,608	10.80	10.79–10.82
Respiratory support type						
Endotracheal tube connected to a MV	20,153	187,141	1448	138,372	10.46	10.45–10.48
Tracheostomy connected to a MV	905	10,663	54	8922	6.05	6.00–6.10
CPAP	255	2235	13	565	23.01	22.62–23.41
Lower-middle income						
Publicly owned facilities	570	4352	31	2917	10.63	10.51–10.75
Upper-middle income						
Pooled	66,867	451,223	1769	163,691	10.81	10.79–10.82
Publicly owned facilities	18,208	135,443	933	67,055	13.91	13.89–13.94
For-profit privately owned facilities	36,884	232,831	670	63,721	10.51	10.49–10.54
University hospitals	10,344	72,455	102	28,178	3.62	3.60–3.64
Not-for-profit privately owned facilities	1431	10,494	64	4737	13.51	13.41–13.62

ICU = intensive care unit; CI = confidence interval; MV = mechanical ventilator; VAP = Ventilator associated pneumonia;
CPAP = Continuous positive airway pressure.
* ICUs are listed in order of the highest to lowest Ventilator associated pneumonia rate.

monitoring compliance with them, and providing performance feedback to health care workers. [30-37].

Our research has some limitations. First off, this study is not representative of all hospitals in Latin America because it is a component of a surveillance system in which institutions voluntarily participate for free. Second, it's likely that over time, changes in behavior or procedures may have had an impact on risk. Third, the IPPs of the participating hospitals did not gather data on the severity scores of the diseases and underlying illnesses. Instead, we adjusted the analysis to take into account this independent variable and utilized the MV/DU ratio as a measure of the severity of the patients' illnesses.

Table 3
Multiple logistic regression analysis of risk factors for Ventilator associated pneumonia.

	aOR	95% CI	P value
Age	1.01	1.00–1.01	<0.0001
Gender, male	1.39	1.26–1.56	<0.0001
Length of stay	1.11	1.11–1.12	<0.0001
MV-days	0.95	0.94–0.96	<0.0001
MV/DU ratio	1.17	1.13–1.21	<0.0001
Tracheostomy connected to a MV	5.39	3.76–7.72	<0.0001
Endotracheal tube connected to a MV	9.96	8.57–11.57	<0.0001
Surgical Hospitalization	1.44	1.29–1.61	<0.0001
Publicly owned facilities (Public)	1.45	1.07–1.96	0.02
For-profit privately owned facilities (Private)	0.75	0.56–1.03	0.07
University hospitals	0.31	0.22–0.45	<0.0001
Upper middle income country	0.73	0.46–1.14	0.16
Oncology Adult	12.17	5.05–29.36	<0.0001
Medical-Surgical ICU	3.47	2.14–5.64	<0.0001
Surgical ICU	2.48	1.41–4.38	<0.0001
Pediatric ICU	1.78	1.03–3.08	0.04
Coronary ICU	1.72	1.02–2.91	0.04
Medical ICU	0.59	0.29–1.22	0.15
Neuro-Surgical ICU	0.14	0.02–0.73	0.02
Respiratory ICU	1.83	0.97–3.45	0.06
Trauma ICU	1.99	0.44–8.95	0.37

ICU = intensive care unit; MV = mechanical ventilator; DU = device utilization; LOS = length of stay; VAP = Ventilator associated pneumonia; aOR = adjusted odds ratio; CI = confidence interval.

Author contributions

Rosenthal, V.D. was responsible for study conception and design, software development, technical support, drafting tutorials for surveillance process, training of data collectors, provision of study patients, data validation, data assembly, data interpretation, epidemiological analysis, drafting of the manuscript.

Zhilin Jin and Ruijie Yin contributed equally to building machine learning models and conducting statistical analysis, critical revision for important intellectual content, and final approval of the manuscript.

Remaining authors were involved in the provision of study patients.

All authors were involved in critical revision of the manuscript for important intellectual content, and final approval of the manuscript.

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Declaration of Competing Interest

All authors report no conflicts of interest related to this article. The Institutional Review Board of each hospital agreed to the study protocol, and patient confidentiality was protected by codifying the recorded information, making it only identifiable to the infection control team.

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