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Development of a Weighted-Incidence Syndromic Combination Antibiogram (WISCA) to guide empiric antibiotic treatment for ventilator-associated pneumonia in a Mexican tertiary care university hospital

Jaime Briseno-Ramírez[1,3,5], Adolfo Gómez-Quiroz[2], Brenda Berenice Avila-Cardenas[2], Judith Carolina De Arcos-Jiménez[3,5], Leonardo Perales-Guerrero[1], Jaime F. Andrade-Villanueva[4] and Pedro Martínez-Ayala[4,5*]

Abstract

Background Ventilator-associated pneumonia (VAP) is a significant nosocomial infection in critically ill patients, leading to high morbidity, mortality, and increased healthcare costs. The diversity of local microbiology and resistance patterns complicates the empirical treatment selection. The Weighted-Incidence Syndromic Combination Antibiogram (WISCA) offers an innovative tool to optimize empirical antibiotic therapy by integrating local microbiological data and resistance profiles.

Objective To develop a WISCA tailored for VAP in a Mexican tertiary care university hospital, aiming to enhance empirical antibiotic coverage by addressing the unique pathogen distribution and resistance patterns within the institution.

Methods This retrospective study included 197 VAP episodes from 129 patients admitted to a critical care unit between June 2021 and June 2024. Clinical and microbiological data, including pathogen susceptibility profiles, were analyzed using a Bayesian hierarchical model to evaluate the coverage of multiple antibiotic regimens. We also assessed the current impact of inappropriate empiric or directed treatment on in-hospital mortality using Cox regression models to support the development of a WISCA model.

Results The median age of the patients was 44 years (IQR 35–56), with *Acinetobacter baumannii* ($n=71$), Enterobacterales ($n=53$) and *Pseudomonas aeruginosa* ($n=36$) identified as the most frequently isolated pathogens. The developed WISCA models showed variable coverage based on antibiotic regimens and the duration of invasive mechanical ventilation (IMV). Inappropriate directed therapy during the VAP episode was associated with increased mortality, as were the diagnosis of Acute Respiratory Distress Syndrome (ARDS) and a high Sequential Organ Failure Assessment (SOFA) score ($p<0.01$).

*Correspondence:
Pedro Martínez-Ayala
pedro.martinez@cucs.udg.mx

Full list of author information is available at the end of the article

Conclusions The tailored WISCA with Bayesian hierarchical modeling provided more adaptive, subgroup-specific estimates and managed uncertainty better compared to fixed models. The implementation of this WISCA model demonstrated potential to optimize antibiotic strategies and improve clinical outcomes in critically ill patients in our hospital.

Topic Optimizing Empirical Antibiotic Therapy for Ventilator-Associated Pneumonia Using a Weighted-Incidence Syndromic Combination Antibiogram in a Mexican Tertiary Care Hospital.

Keywords Ventilator-associated pneumonia, Weighted incidence syndromic combination antibiogram, Bayesian hierarchical model, Antibiotic resistance, Empirical therapy, *Acinetobacter baumannii*

Introduction

Ventilator-associated pneumonia (VAP) is a prevalent nosocomial infection among critically ill patients, linked to high morbidity, mortality, and increased healthcare costs, affecting 10–25% of patients on invasive mechanical ventilation (IMV) for over 48 hours [1–4]. VAP patients experience significantly prolonged Intensive Care Units (ICU) stays, averaging an additional 13.6 days [5], and face approximately double the mortality risk compared to non-VAP patients (pooled OR, 2.03; 95% CI, 1.16–3.56) [6]. Economically, VAP episodes add an estimated $10,019 to $39,828 per patient due to extended ICU/hospital stays and additional interventions [5–8].

Risk factors for VAP include prolonged mechanical ventilation, extended hospitalization, advanced age, male sex, smoking, and pre-existing conditions such as coronary heart disease, diabetes, chronic obstructive pulmonary disease (COPD), traumatic brain injury, and immunosuppression [9–12]. Invasive procedures like tracheostomy, reintubation, and central catheter use also increase VAP risk [10, 12]. IMV patients are particularly vulnerable to VAP caused by multidrug-resistant organisms (MDROs), with pathogens often including resistant Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Enterobacterales, and methicillin-resistant *Staphylococcus aureus* (MRSA) [13–15]. Major risk factors for MDRO-associated VAP include prior broad-spectrum antibiotic use, prolonged hospitalization, colonization with resistant pathogens, and severe comorbidities [13, 15].

Effective empirical treatment of VAP is essential due to the infection's rapid progression and the rise of multidrug-resistant organisms [16]. Variability in local epidemiology and resistance patterns further complicates empirical antibiotic selection, underscoring the need for tools customized to local data [17, 18]. Currently, antimicrobial resistance (AMR) poses a global crisis, linked to increased morbidity, mortality, extended hospital stays, and higher healthcare costs [19–21]. Given AMR's prevalence, prompt recognition and etiologic diagnosis are critical to optimize antibiotic use, curb AMR emergence, and reduce *Clostridioides difficile* infections [21–23]. Notably, hospital ecology is a key factor for multidrug-resistant bacteria acquisition, especially in low-income countries [24–27].

The Weighted-Incidence Syndromic Combination Antibiogram (WISCA), developed by Hebert et al., [28], is an innovative tool designed to improve empirical prescribing by addressing the limitations of traditional antibiograms. Unlike conventional antibiograms, which assess single organism-drug combinations without accounting for the infection syndrome or multiple organisms, WISCA evaluates antibiotic regimens for specific syndromes (e.g., VAP, urinary tract infections), providing clinicians with the likelihood that a regimen will cover all relevant pathogens based on local pathogen frequency and susceptibility [28–29].

The Bayesian approach further enhances WISCA's utility compared to Hebert's original decision-tree model by better handling uncertainty and incorporating prior knowledge, which increases reliability, especially with limited data. This model delivers probability distributions for coverage, adjusts for intrinsic resistance, and allows for patient-specific factors, such as age and comorbidities, resulting in more accurate, tailored antibiotic recommendations [30–33].

This study aimed to develop and design a WISCA tailored for VAP treatment at a tertiary care university hospital in Mexico and to estimate the potential of improvement in adequate empiric or directed antibiotic coverage considering the unique pathogen landscape and resistance patterns within our institution. This approach not only seeks to optimize antibiotic use but also to provide a framework for other hospitals to develop their own WISCA models based on local data, fostering more effective and targeted empirical therapy for VAP.

Materials and methods

Ethics

This study involving humans was approved by the "Comité de Ética en Investigación en Ciencias de la Salud del Centro Universitario de Tlajomulco, Universidad de Guadalajara" (ethical approval number CUTLAJO/DS/CEICS/018/24) and conducted in accordance with the Helsinki declaration, national legislation, and institutional requirements. As the study was performed

retrospectively and only deidentified data were used, informed consent was waived.

Population and eligibility criteria

This is a retrospective study conducted in patients admitted to the critical care unit of the Internal Medicine Department, which primarily serves individuals aged 15–65 without underlying surgical conditions. We reviewed the medical records of patients classified under the International Classification of Diseases, 10th Edition (ICD-10) code J95.851: ventilator-associated pneumonia (VAP). Additionally, we examined cultures of respiratory samples, including endotracheal aspirates and samples obtained through tracheostomy tubes. The records were collected from patients admitted between June 2021 and June 2024.

In accordance with ATS/IDSA guidelines [34, 35], we verified through clinical records that patients met the criteria for a clinical syndrome of VAP, characterized by a gradual or sudden onset of symptoms occurring more than 48 hours after intubation. These symptoms included new or progressive and persistent radiographic infiltrates, accompanied by at least two of the following: fever exceeding 38 °C (100.4 °F), leukopenia (white blood cell count $< 4 \times 10^9$/L) or leukocytosis (white blood cell count $> 12 \times 10^9$/L), purulent tracheal secretions, and oxygenation decline. Supportive diagnostic testing was verified, including chest x-rays or CT scans, complete blood counts with differential, and lower respiratory tract sampling and culture. Respiratory samples, primarily obtained through semi-quantitative, noninvasive methods as recommended by ATS/IDSA Guidelines and standard in our institution [35], were essential to include only patients with positive culture results for developing the WISCA model. In some cases, bronchoalveolar lavage (BAL) was also performed. Patients younger than 15 years or those with more than 10% missing data in clinical records were excluded from the study.

Demographic data, along with the Charlson Comorbidity Index (CCI), Sequential Organ Failure Assessment (SOFA) score, and additional clinical parameters, were systematically collected from patient medical records. These data included variables such as the PaO2/FiO2 ratio, presence of Acute Respiratory Distress Syndrome (ARDS) following the criteria established by Matthay et al. [36], SARS-CoV-2 infection status, need for vasopressor support, duration of invasive mechanical ventilation (IMV) up to the onset of VAP, IMV duration post-VAP treatment, and total length of hospital stay following VAP development.

Bacterial isolates were identified using standard methods, with antibiotic susceptibility testing performed using the VITEK 2 system by Biomerieux (Marcy l'Etoile, France) [37]. Results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) breakpoints. However, CLSI guidelines no longer recommend susceptibility testing for tigecycline in respiratory samples, as tigecycline fails to achieve therapeutic levels in pulmonary tissue. Our institution implemented this recommendation in July 2023. Reported tigecycline susceptibilities are based on previously established CLSI breakpoints [38], with Enterobacterales, *Acinetobacter* spp., and *Staphylococcus aureus* isolates deemed susceptible at MIC values ≤ 2 μg/mL and resistant above this threshold for the WISCA model.

Extrapolations were applied for agents without established breakpoints or MIC values, such as *Pseudomonas aeruginosa* for tigecycline and Gram-negative organisms for linezolid. These extrapolations are detailed in Table S1 of the supplementary material. Empiric or directed antimicrobial therapy was classified as appropriate when the regimen effectively covered the isolated organism from lower respiratory tract cultures; if coverage was absent, it was classified as inappropriate.

WISCA development

The WISCA model was structured based on pathogens isolated from patients diagnosed with VAP. A VAP event was recorded if the patient fulfilled the ATS/IDSA criteria and had a positive lower respiratory culture with significant semi-quantitative growth (≥ 100,000 CFU). Organisms found to be susceptible to an antibiotic were marked as susceptible to the empirical antimicrobial regimen employed. For model purposes, any intermediate susceptibility was recorded as resistant. In cases where more than one culture of the same microorganism was available within a single episode, the most resistant culture was selected. If multiple organisms were present in a respiratory culture, both organisms were recorded, and the patient was classified as having VAP associated with multiple organisms, ensuring that clinical VAP symptoms and significant CFU counts were confirmed.

For patients with multiple subsequent cultures, clinical records were reviewed to confirm new VAP events and adherence to the ATS/IDSA description. Subsequent cultures not meeting VAP description were excluded to prevent results influenced by pharmacological pressure. However, if they met criteria for a new VAP event, they were included in the analysis.

We studied the coverage of antibiotic regimens in our institution according to local and international guidelines and for which automated sensitivity testing is routinely performed. These were as follows: meropenem (MEM), piperacillin/tazobactam (TZP), cefepime (FEP), and ceftazidime (CAZ); combination therapy: ceftazidime + linezolid (CAZ + LNZ) or vancomycin (CAZ + VA); meropenem + linezolid (MEM + LNZ) or vancomycin (MEM + VA); piperacillin/

tazobactam + linezolid (TZP + LNZ) or vancomycin (TZP + VA); and cefepime + linezolid (FEP + LNZ) or vancomycin (FEP + VA). Additionally, based on our local epidemiology, we studied ceftazidime + tigecycline (CAZ + TGC), meropenem + tigecycline (MEM + TGC), cefepime + tigecycline (FEP + TGC), and piperacillin/tazobactam + tigecycline (TZP + TGC).

Statistical analysis

Demographic data are reported as simple relative frequencies. The normality of the data distribution was assessed using the Shapiro–Wilk test. Pearson's chi-squared and Fisher's exact tests were used to compare proportions as appropriate. For comparisons of quantitative variables, Student's t tests and Wilcoxon-Mann–Whitney tests were used for normally and nonnormally distributed data, respectively.

In line with previous studies [30, 31], a Bayesian hierarchical logistic regression model was used to estimate the coverage of antibiotic regimens against pathogens linked to VAP. The model featured a hierarchical structure with varying intercepts for pathogens and empirical regimens, ensuring stable and reliable coverage estimates, especially for regimens with limited sensitivity testing. The detailed methodology can be found in the supplementary material. The Hamiltonian Monte Carlo (HMC) algorithm, implemented via Stan software, was used for Bayesian inference. Parameters and coverage estimates were summarized using the median and 95% Highest Density Intervals (HDIs), with wider HDIs indicating greater uncertainty. Covariates for age and sex were included to account for potential variability. Autocorrelation for the parameters was evaluated in distal lags (e.g., between Xt and Xt + h, $h \geq 2$), to ensure the samples were independent across iterations.

To evaluate the current impact of inadequate empirical or directed antibiotic regimens on clinical outcomes and justify the development of a WISCA tool for our population, we conducted univariate analyses using a Cox proportional hazards regression model. Each independent variable's association with in-hospital mortality was assessed, with variables showing a p-value < 0.1 in the univariate Cox models, as well as clinically relevant variables, included in multivariate Cox proportional hazards regression models. The multivariate analysis examined the effect of each variable on time to in-hospital death, considering both event occurrence and hospitalization duration post-VAP onset. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to quantify association strength. Model performance was evaluated using the concordance index (C-index), and overall model significance was assessed via the log-likelihood ratio test, with p-values < 0.05 deemed statistically significant. A stepwise method was applied for variable selection, and we present optimal models for the general population alongside stratified analyses, based on model concordance index (C-index) and goodness of fit.

The statistical analysis was implemented using Python for data analysis. The Bayesian hierarchical model was fitted using the CmdStanPy package (version 0.9.76) with the underlying Stan framework (version 2.26.1). Model diagnostics and posterior analyses were conducted using the ArviZ package (version 0.11.2).

Results

According to the specified criteria, we documented 197 episodes of VAP in 129 patients, as depicted in Fig. 1.

The median age of the patients included was 44 years (IQR 35–56), 31% of the subjects were women ($n = 40$), and the median Charlson comorbidity index was 1 (IQR 0–2). The median SOFA score was 5 (IQR 3–7), vasopressors were required for 40.60% of the VAP episodes ($n = 80$), and 26.39% of the episodes met the definition for ARDS ($n = 52$). The median hospital stay after VAP development was 12 days (IQR 6–21), the 90th percentile of days after VAP development was 29.4 days, and the in-hospital mortality rate for patients with VAP was 34.51% ($n = 68$). The remaining sociodemographic and clinical characteristics are shown in Table 1.

The diagnoses at hospitalization for the 129 patients who developed VAP episodes included COVID-19 and associated complications (16.3%, $n = 21$), ischemic stroke (15.5%, $n = 20$), status epilepticus (14%, $n = 18$), Guillain-Barré syndrome (7.8%, $n = 10$), and diabetic ketoacidosis (5.4%, $n = 7$). The primary indications for initiating IMV were airway protection due to altered mental status (42.6%, $n = 55$), respiratory failure (42.6%, $n = 55$), airway management for status epilepticus (14%, $n = 18$), and airway management for upper gastrointestinal bleeding (0.8%, $n = 1$). The remaining admission diagnoses and reasons for IMV in patients who developed VAP are detailed in Table S2 of the supplementary material.

In terms of local epidemiology and antibiotic resistance, the most frequently isolated organisms were *Acinetobacter baumannii* (36.04%, $n = 71$), Enterobacterales (26.90%, $n = 53$), *Pseudomonas aeruginosa* (18.27%, $n = 36$), *Staphylococcus aureus* (10.15%, $n = 20$), and *Stenotrophomonas maltophilia* (8.12%, $n = 16$). In 41.12% of the episodes, more than one organism was isolated ($n = 81$). The remaining isolated organisms can be found in Table 1.

According to standardized international terminology for describing acquired resistance profiles [39], 87.32% of *Acinetobacter baumannii* isolates were classified as XDR (extensively drug-resistant) *Acinetobacter baumannii* (XDR-AB) ($n = 62$). For Enterobacterales, 28.30% of the isolates were MDR (multidrug resistant) Enterobacterales ($n = 15$), and 7.54% were carbapenem-resistant

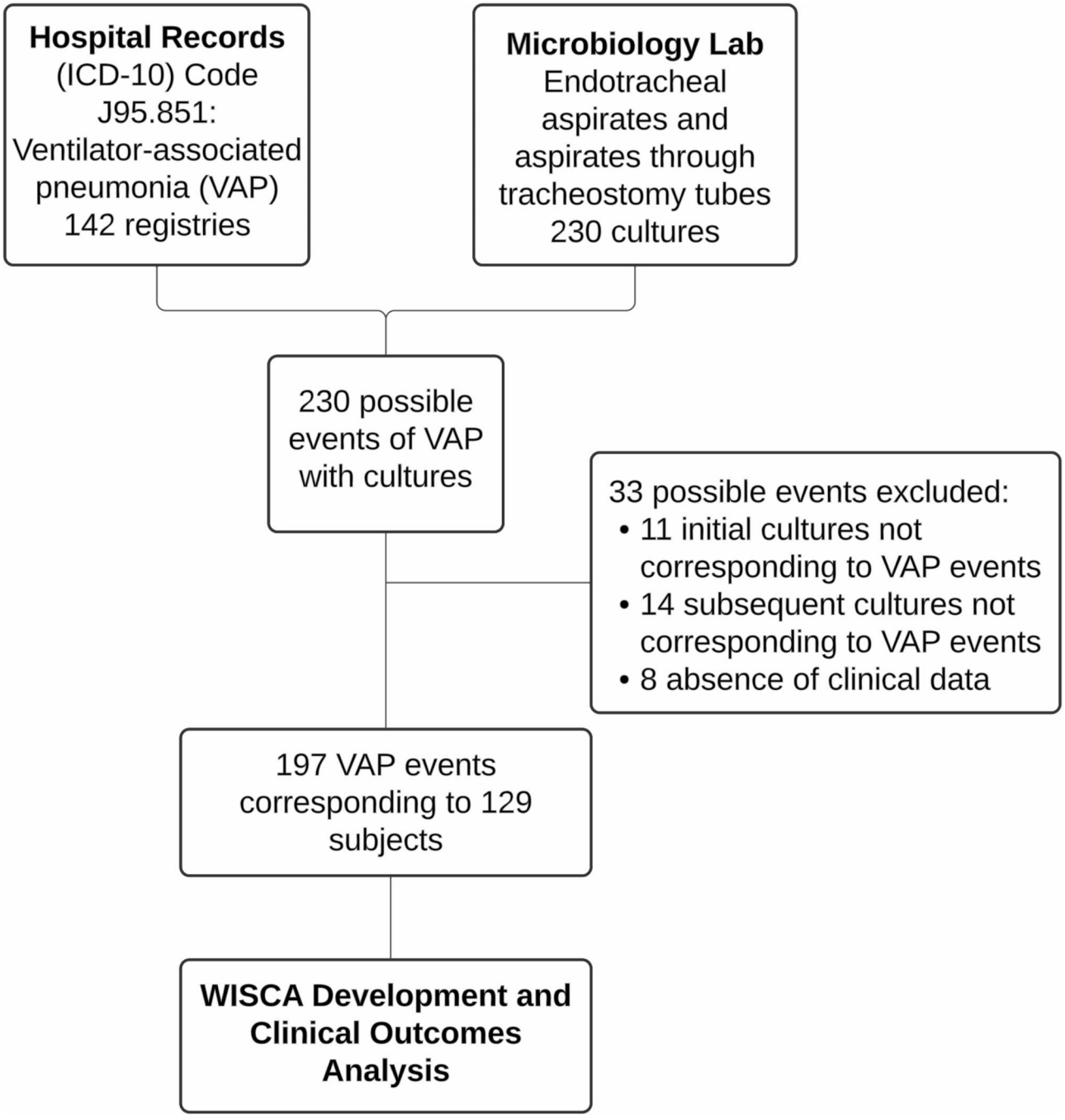

Fig. 1 Flowchart of case selection. ICD, International Classification of Diseases. VAP, Ventilator-Associated Pneumonia. WISCA, Weighted-Incidence Syndromic Combination Antibiogram

Enterobacterales ($n=4$). For *Pseudomonas aeruginosa*, 19.44% of the isolates were MDR, and 5.55% were XDR. Only 10% of the *Staphylococcus aureus* isolates were MRSA ($n=2$). The rest of the resistance profiles can be found in Table 2.

The most frequently used initial empiric therapy regimens were meropenem (24.87%, $n=49$), colistin + tigecycline (18.27%, $n=36$), piperacillin/tazobactam (13.7%, $n=27$), and meropenem + linezolid (7.61%, $n=15$). Other regimens were used in 35.53% ($n=70$) of the patients. The remaining antimicrobial regimens are listed in Table S3 of the supplementary material. Initial empiric therapy was inappropriate for 45.18% of VAP episodes ($n=89$). However, in 85.79% of the events, patients eventually received an appropriate regimen during the entire VAP episode. The median number of days to correct the initial

Table 1 Sociodemographic and clinical characteristics of patients with VAP and isolated organisms

Variable	Total VAP events (*n* = 197)	VAP events in men (*n* = 140)	VAP events in women (*n* = 57)	*p* value
Age (median, IQR)	44.0 (35.0–56.0)	47.5 (36.0-56.5)	40.0 (30.0–54.0)	**0.037**
Charlson comorbidity Index (median, IQR)	1.0 (0.0.0–2.0)	1.0 (0.0–2.0)	1.5 (0.25–3.75)	0.145
Clinical variables				
Initial Inappropriate Empiric Treatment - n (%)	89 (45.18)	59 (42.14)	30 (52.63)	0.236
Days to Correct Empiric Treatment - Median (IQR)	3.0 (1.0–5.75)	3.0 (1.0–6.25)	3.0 (2.0–5.0)	0.063
Inappropriate Directed Treatment for VAP- n (%)	28 (14.21)	18 (12.86)	10 (17.54)	0.529
Days from IMV to VAP development (median, IQR)	8.0 (4.0–15.0)	10.0 (4.0–16.0)	6.0 (4.0–12.0)	**0.049**
Days of IMV after VAP development (median, IQR)	9.0 (3.0–14.0)	10.0 (3.75-15.0)	8.0 (3.0–13.0)	0.579
Need for vasopressors - n (%)	80 (40.60)	57 (40.71)	23 (40.35)	1
SOFA score (median, IQR)	5.0 (3.0–7.0)	5.0 (3.0–7.0)	4.0 (2.0–6.0)	**0.047**
PaO2/FiO2 ratio (median, IQR)	232.5 (176.5–303.0)	232.0 (185.5–283.0)	233.0 (168.0-356.0)	0.280
ARDS diagnosis - n (%)	52 (26.39)	35 (25.00)	17 (29.82)	0.593
SARS-CoV-2 infection - n (%)	21 (10.65)	16 (11.43)	5 (8.77)	0.695
Multiple organisms isolated in VAP event - n (%)	81 (41.11)	63 (45.00)	18 (31.58)	0.109
Days of hospitalization after VAP event (median, IQR)	12.0 (6.0–21.0)	12.0 (6.0–21.0)	12.0 (7.0–23.0)	0.980
Post-VAP hospital stays over 30 days - n (%)	28.0 (21.71)	21 (23.08)	7 (18.42)	0.725
In-hospital mortality - n (%)	68 (34.51)	49 (35.00)	19 (33.33)	0.869
Isolated organisms - n (%)				
Acinetobacter baumannii	71 (36.04)	43 (30.71)	28 (49.12)	**0.023**
Burkholderia gladioli	1 (0.51)	0 (0.00)	1 (1.75)	0.641
Klebsiella aerogenes	1 (0.51)	1 (0.71)	0 (0.00)	1
Enterobacter cloacae complex	10 (5.08)	8 (5.71)	2 (3.51)	0.778
Escherichia coli	2 (1.02)	2 (1.43)	0 (0.00)	0.902
Hafnia alvei	1 (0.51)	1 (0.71)	0 (0.00)	1
Klebsiella oxytoca	2 (1.02)	1 (0.71)	1 (1.75)	0.496
Klebsiella pneumoniae	32 (16.24)	25 (17.86)	7 (12.28)	0.454
Proteus mirabilis	1 (0.51)	1 (0.71)	0 (0.00)	1
Providencia stuartii	1 (0.51)	1 (0.71)	0 (0.00)	1
Pseudomonas aeruginosa	36 (18.27)	28 (20.00)	8 (14.04)	0.436
Serratia marcescens	3 (1.52)	3 (2.14)	0 (0.00)	0.637
Staphylococcus aureus	20 (10.15)	13 (9.29)	7 (12.28)	0.711
Stenotrophomonas maltophilia	16 (8.12)	13 (9.29)	3 (5.26)	0.516

SOFA, Sequential Organ Failure Assessment score. ARDS, Acute Respiratory Distress Syndrome. SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2. VAP, Ventilator-Associated Pneumonia. IMV, Invasive Mechanical Ventilation.

Bold values are for statistically significant variables.

inappropriate empiric treatment was 3 days (IQR 1-5.75) (Table 1).

Four antibiotics were tested as monotherapies, and twelve combination regimens were evaluated in the WISCA model for the overall pool of pathogens. The median estimated coverages ranged from 19.42% (ceftazidime, CAZ) to 87.85% (cefepime + tigecycline, FEP + TGC). Compared to traditional WISCA models, the Bayesian model estimated lower coverage rates for some antibiotics, such as ceftazidime, with 31.47% coverage in the traditional model versus 19.42% (95% HDI 6.07–37.36) in the Bayesian model. Conversely, for some antibiotic combinations, the Bayesian WISCA model estimated higher coverage rates than traditional models, particularly for those combinations involving tigecycline. The complete set of median posterior distributions and the associated 95% HDIs, as well as the comparisons with the traditional WISCA model, are presented in Fig. 2 and Table S4 of the supplementary material.

WISCA with Bayesian hierarchical modeling, Dots represent the median of the posterior distribution, and the lines represent the associated 95% Highest Density Intervals (HDIs).

The algorithm used to sample from the posterior distributions showed optimal convergence, with R^ values close to 1 and well-mixed chains (Table S5, Figure S1). Autocorrelation plots (Figure S2) demonstrate minimal autocorrelation at distal lags ($h \geq 2$), supporting parameter reliability. Full Monte Carlo Markov Chain (MCMC) trace, density, and autocorrelation plots are available in Figures S1 and S2 of the supplementary material.

Table 2 Comparison of VAP-associated bacterial pathogens regarding the onset of VAP and resistance profiles

	Total Cases (*n* = 197)	VAP development within 5 days of IMV (*n* = 61)	VAP development after 5 days of IMV (*n* = 136)	*P* value
Organism - n (%)				
Acinetobacter baumannii	71 (36.04)	8 (13.33)	63 (45.99)	**< 0.001**
Enterobacterales	53 (26.90)	24 (39.34)	29 (21.32)	**0.014**
Pseudomonas aeruginosa	36 (18.27)	11 (18.33)	25 (18.25)	1
Staphylococcus aureus	20 (10.15)	13 (21.67)	7 (5.11)	**0.001**
Stenotrophomonas maltophilia	16 (8.12)	5 (8.33)	11 (8.03)	1
Burkholderia gladioli	1 (0.51)	0 (0.00)	1 (0.73)	1
Resistance Pattern - n (%)				
XDR - *Acinetobacter baumannii*	62.0 (87.32)	7.0 (11.29)	55.0 (88.70)	**< 0.001**
MDR - *Acinetobacter baumannii*	4.0 (5.63)	1.0 (25)	3.0 (75)	1.0
Carbapenem resistant Enterobacterales	4.0 (7.54)	0.0 (0)	4.0 (100)	0.419
MDR - Enterobacterales	15.0 (28.3)	6.0 (40)	9.0 (60)	0.619
Methicillin Resistant *Staphylococcus aureus*	2.0 (10)	0.0 (0)	2.0 (100)	0.854
MDR - *Pseudomonas aeruginosa*	7.0 (19.44)	0.0 (0)	7.0 (100)	0.165
XDR - *Pseudomonas aeruginosa*	2.0 (5.55)	1.0 (50)	1.0 (50)	1.0

Bold values are for statistically significant variables.

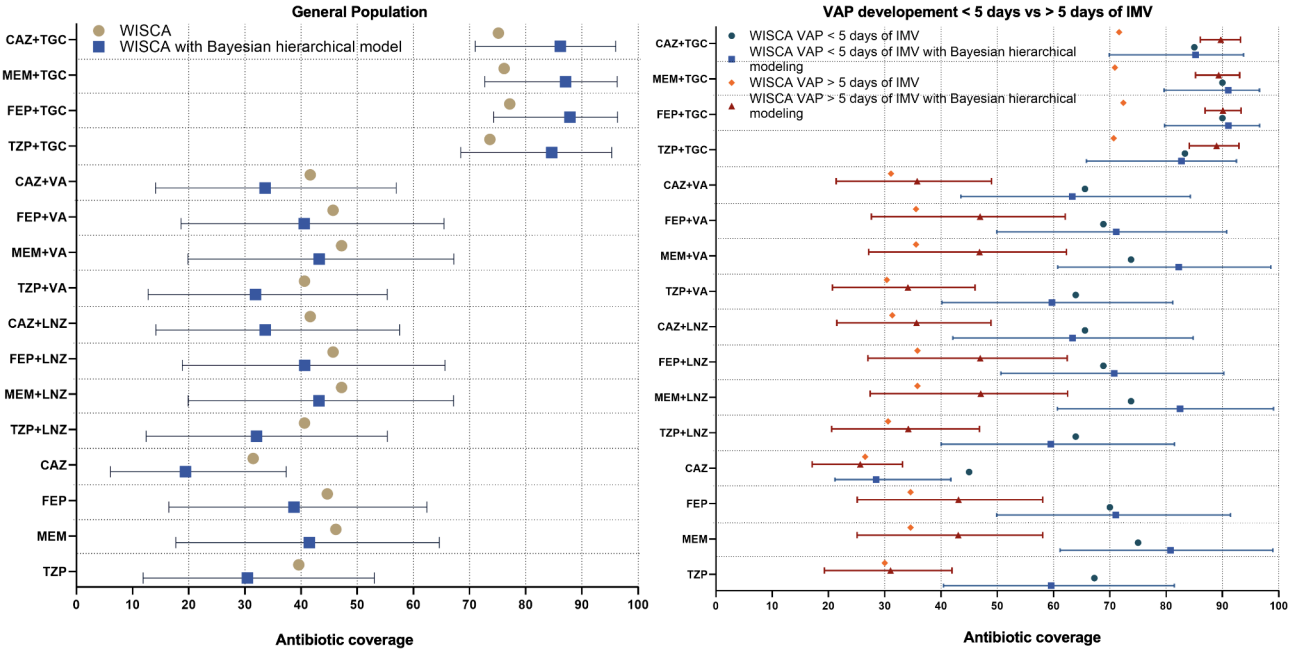

Fig. 2 WISCA estimated coverage for all evaluated antibiotic regimens in the general population who developed VAP, as well as in those who developed VAP before or after 5 days of IMV

We found significant differences in the distributions of VAP-causing microorganisms according to the days of IMV prior to the development of VAP. Specifically, Enterobacterales and *Staphylococcus aureus* were more frequently isolated within the first 5 days of IMV, whereas *Acinetobacter baumannii* was more frequently isolated after 5 days of IMV ($p < 0.02$), as shown in Fig. 3; Table 2.

Due to variations in the distribution of isolated microorganisms, we developed a WISCA model with a hierarchical Bayesian structure and calculated the posterior distributions for antibiotics tested as monotherapies and in combination regimens for both time periods, as shown in Fig. 2. These posterior distributions offered insights into the coverage of each regimen across different pathogen distributions and time frames. The median estimated coverages ranged from 28.47% (Ceftazidime, CAZ) to 91.04% (Cefepime + Tigecycline, FEP + TGC) for the group of patients who developed VAP within the first 5 days, while for the group of patients who developed VAP after 5 days, coverages ranged from 25.65% (Ceftazidime,

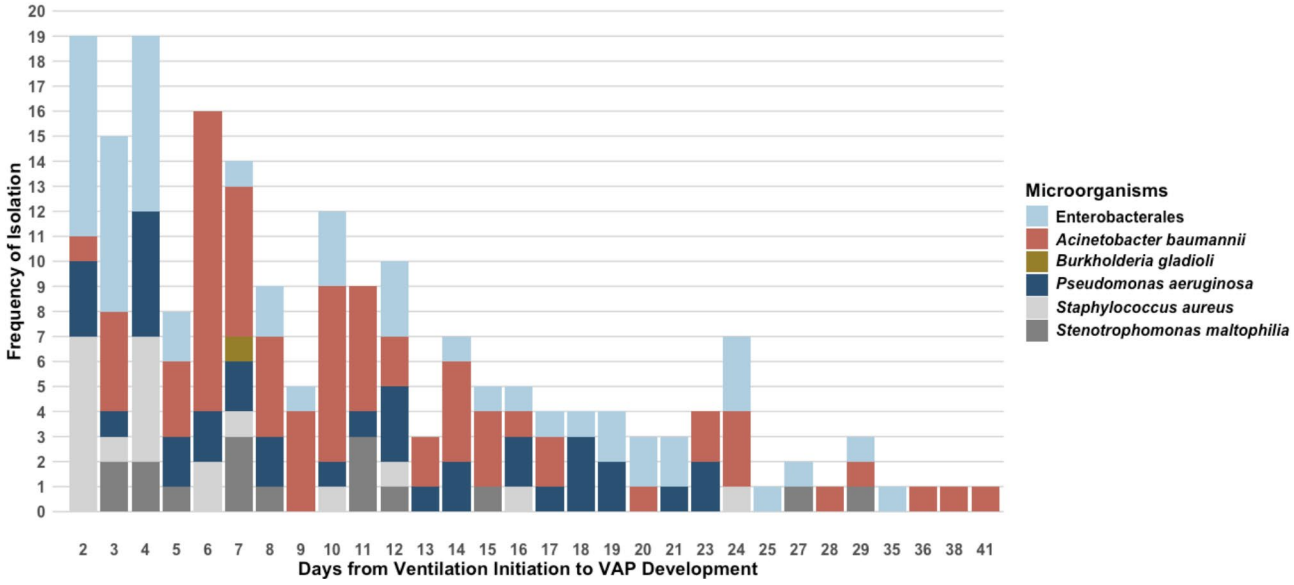

Fig. 3 Distribution of isolated microorganisms over time of IMV from patients who developed VAP

CAZ) to 90.09% (Cefepime + Tigecycline, FEP + TGC). Overall, the coverages were higher in patients who developed VAP within the first 5 days. Similarly, the algorithm used to sample from the posterior distributions of the parameters for the regimens in both time periods achieved optimal convergence, with R^ index values consistently near 1 and good mixing across all chains. The complete set of medians of the posterior distribution and the associated 95% HDIs for these antibiotic regimens during these time periods are shown in Table S6, as well as the R^ index values of the WISCA models parameters in Table S7 of the supplementary material.

According to the univariate analyses, inappropriate treatment for VAP, a low PaO2/FiO2 ratio, a high SOFA score, the need for vasopressors, the development of ARDS, and *Acinetobacter baumannii* infection were all positively associated with in-hospital mortality. In contrast, an increase in the number of days on IMV after VAP development was negatively associated with in-hospital mortality. Detailed findings on the remaining sociodemographic and clinical variables can be found in Table S8 of the supplementary material.

In the multivariate Cox proportional hazards regression analysis, several variables were identified as independently and significantly associated with in-hospital mortality. Inappropriate directed treatment for VAP, a higher SOFA score, and the presence of ARDS were all associated with an increased risk of mortality. Conversely, a longer duration of IMV following VAP development was linked to a reduced risk of mortality. Additionally, the onset of VAP within the first five days of IMV was associated with a lower mortality risk. The model demonstrated good predictive accuracy, with a concordance index of 0.878. The model's goodness of fit was further confirmed by a significant log-likelihood ratio test ($p < 0.001$). The complete set of variables is presented in Table 3.

Table 3 Cox proportional hazards regression analysis for In-hospital mortality

Variable	HR	95% CI HR	*p*-value
Charlson Comorbidity Index (CCI)	1.27	0.99–1.63	0.060
Days of IMV Post-VAP development	0.86	0.82–0.90	< 0.001
Inappropriate directed treatment for VAP	2.37	1.31–4.27	0.004
Sequential Organ Failure Assessment (SOFA) score	1.34	1.22–1.47	< 0.001
Acute Respiratory Distress Syndrome (ARDS)	3.09	1.77–5.39	< 0.001
VAP development during first 5 days of IMV	0.48	0.25–0.89	0.020

Concordance index: 0.878. Log-likelihood ratio test: 130.718 on 6 degrees of freedom, p-value = < 0.001

Finally, a stratified subgroup analysis was conducted using multivariate Cox proportional hazards regression, with the optimal models selected based on their concordance index and goodness of fit. Inappropriate directed treatment for VAP, elevated SOFA scores, and ARDS diagnosis were independently associated with in-hospital mortality in distinct age subgroups. In patients with SOFA scores above 6, both inappropriate directed treatment and advanced age were associated with in-hospital mortality, whereas in those with SOFA scores below 6, ARDS diagnosis and inappropriate directed treatment remained significant mortality predictors. Additionally, in patients with shock requiring vasopressor support, inappropriate directed treatment and high SOFA scores were also associated to increased in-hospital mortality.

Detailed variable associations and subgroup models are presented in Table S9 of the supplementary material.

Discussion

In our study, we developed a WISCA tool that expands the framework of classic hospital combined antibiograms by providing weighted coverage estimates based on the frequency of the pathogens identified. Similar to previous WISCA designs, we specified a Bayesian hierarchical logistic regression with random effects structures on the pathogens and the treatment regimens. Our study contributes to the limited knowledge concerning WISCA design for VAP in middle-income countries. To our knowledge, this is the first WISCA design for VAP in a Latin American country; previous studies have been conducted in high-income countries, specifically in Europe [28–33].

Based on the WISCA design, we observed that the most commonly used therapies in our hospital, where automated sensitivity testing is routinely conducted, exhibited reduced coverage rates. This finding highlights the specificity of our local microbiology, notably the high prevalence of colistin-based regimens—particularly the combination of colistin and tigecycline—which represents the second most frequently used initial therapy in our patient population (Table S3). Based on the time distribution of VAP-causing microorganisms during IMV, the presented WISCA model could support the use of colistin- and tigecycline-free combinations within the first 5 days of IMV in our institution. This approach has the potential to improve outcomes by reducing the likelihood of resistance development and minimizing the adverse effects associated with colistin or tigecycline therapy [40, 41].

In the group of patients with more than 5 days on invasive mechanical ventilation, we observed reduced coverage rates for most antimicrobial regimens, further underscoring the high use of colistin and tigecycline in our institution. Although tigecycline regimens are frequently used in our population of patients with extensively drug-resistant *Acinetobacter baumannii* (XDR-AB), it is important to note that tigecycline is not FDA-approved for the treatment of VAP. Nevertheless, it remains widely utilized in VAP cases caused by XDR-AB due to limited treatment alternatives [42–47]. Recent studies suggest that higher doses of tigecycline may enhance clinical outcomes without additional safety concerns [45–47]. However, its use in VAP is associated with lower cure rates and a higher risk of mortality compared to other treatments [48]. Despite these findings, the overall efficacy and safety profile of tigecycline in VAP remain concerning, necessitating careful consideration and further research.

Although the non-Bayesian WISCA design produced coverage rates similar to the Bayesian hierarchical WISCA model—with most rates of the traditional WISCA design falling within the 95% HDI of the Bayesian hierarchical WISCA —some discrepancies were observed in specific scenarios, such as ceftazidime coverage in VAP cases occurring within the first five days of IMV and tigecycline regimens in VAP cases beyond five days of IMV. The Bayesian hierarchical model in WISCA offers several advantages over traditional models, notably by accounting for variability across patient subgroups and providing more realistic uncertainty intervals. Unlike conventional models, it incorporates prior information and probabilistic distributions, which enhance coverage estimates in settings with limited data. This method is particularly advantageous in managing complex infections like VAP, where factors such as mechanical ventilation duration and local microbiology resistance patterns impact pathogen susceptibility. As a result, Bayesian hierarchical modeling yields more adaptive, subgroup-specific estimates, which may contrast with the 'fixed' coverage rates generated by traditional WISCA models.

Interestingly, our study revealed that initial inappropriate empirical treatment was not associated with increased mortality. However, inappropriate directed treatment throughout the entire VAP event was significantly related to increased mortality in our multivariate model. This finding may be explained by the rapid adjustment of the antimicrobial regimen in most patients who initially received inappropriate empirical treatment, and the fact that our study population had fewer comorbidities, as reported in previous studies [32, 49]. In contrast, some studies have suggested that improper initial empiric antibiotic therapy is associated with higher mortality in patients with VAP [50, 51]. These discrepancies may be attributed to differences in population characteristics, resource availability, and the level of specialized care provided in ICUs [52, 53]. Other variables associated with mortality included a high Charlson Comorbidity Index (CCI), a high Sequential Organ Failure Assessment (SOFA) score, and the presence of Acute Respiratory Distress Syndrome (ARDS), which is consistent with findings from other studies [54].

Notably, the development of VAP within the first 5 days of IMV (from day 2 to day 5) was independently associated with a lower risk of in-hospital mortality, possibly related to the increased incidence of highly resistant organisms (particularly XDR-AB) after 5 days of mechanical ventilation (Table 2 and Fig. 3). Similarly, an increase in the number of IMV days after VAP development was associated with reduced mortality, potentially due to a slow weaning process combined with a lower incidence of VAP as the duration of IMV increased in our population (Fig. 3).

The limitations of our study are primarily due to its retrospective nature. First, during data collection, some variables were missing and had to be excluded from the analyses. Additionally, certain variables that were intended for inclusion were unavailable in the hospital records. Systematic susceptibility testing for colistin was not performed at our institution at the time of this report, and testing for tigecycline in respiratory samples ended in July 2023 in our institution, in accordance with CLSI guidelines. Similarly, susceptibility testing for combinations of new beta-lactams with new beta-lactamase inhibitors only began this year, and as a result, these combinations were not included in the analysis. It should also be noted that, due to the retrospective nature of the study, we cannot fully exclude the possibility that some isolates, particularly in infections involving more than one organism where a non-fermenting Gram-negative was present, may represent colonization. Furthermore, the findings of this study are limited to a single hospital center, which may limit the generalization of the data.

This study underscores several critical insights. Our hospital unit, a reference center for uninsured populations in western Mexico, has a higher incidence of patients requiring IMV and developing VAP than commonly reported. Currently, inappropriate directed treatment in VAP is independently associated with in-hospital mortality at our institution, highlighting the potential utility of this WISCA model in guiding appropriate antibiotic regimens for this condition. Developing additional WISCA models for various infectious syndromes would further support empirical therapy tailored to our local epidemiology. A key strength of this study was the development of a WISCA model with a Bayesian hierarchical design, which promotes a more rational and standardized approach to empiric therapy, helping align antibiotic use with regional epidemiological patterns.

Conclusions

In conclusion, the development of a WISCA tailored for ventilator-associated pneumonia in our hospital has the potential to serve as a valuable tool for improving empirical antibiotic coverage, aligning with the unique microbiological profile and resistance patterns of our institution. By employing a hierarchical Bayesian model, we have achieved more precise coverage estimates, specific to various patient subgroups, emphasizing the importance of adjusting empirical therapies based on local epidemiological data. This approach aims to optimize VAP treatment in critically ill patients and may provide a framework for creating customized WISCA models in other settings, promoting more rational and effective antibiotic management in medium-income hospital environments.

Abbreviations

AMR	Antimicrobial Resistance
ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar Lavage
CAZ	Ceftazidime
CCI	Charlson Comorbidity Index
CLSI	Clinical and Laboratory Standards Institute
COPD	Chronic Obstructive Pulmonary Disease
FEP	Cefepime
HDIs	Highest density intervals
ICD-10	International Classification of Diseases 10th Edition
ICU	Intensive Care Unit
IDSA/ATS	American Thoracic Society and the Infectious Diseases Society of America
IMV	Invasive mechanical ventilation
LNZ	Linezolid
MCMC	Monte Carlo Markov c.hain
MDR	Multidrug resistant
MDROs	Multidrug-resistant organisms
MEM	Meropenem
MRSA	Methicillin-resistant Staphylococcus aureus
MDRO	Multidrug-Resistant Organisms
PaO2/FiO2 ratio	Partial pressure of oxygen in arterial blood to Fraction of inspired oxygen ratio
SOFA	Sequential Organ Failure Assessment
TZP	Piperacillin/tazobactam
TGC	Tigecycline
VAN	Vancomycin
VAP	Ventilator-associated pneumonia
WISCA	Weighted-incidence syndromic combination antibiogram
XDR	Extensively drug-resistant
XDR-AB	Extensively drug-resistant Acinetobacter baumannii

Supplementary Information

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Supplementary Material 1

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Author contributions

JB-R: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Software, Writing–original draft. AG-Q: Investigation, Data curation, Writing–original draft. BBA-C Investigation, Data curation, Writing– original draft. JCA-J Investigation, Data curation, Writing– original draft. LP-G Methodology, Investigation, Writing– original draft. JFA-V Investigation, Supervision, Project administration, Writing– review & editing. PM-A Investigation, Supervision, Project administration, Writing– review & editing, Validation.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Ethics statement

This study involving humans was approved by the "Comité de Ética en Investigación en Ciencias de la Salud del Centro Universitario de Tlajomulco, Universidad de Guadalajara" (ethical approval number CUTLAJO/DS/CEICS/018/24) and conducted in accordance with the Helsinki declaration, national legislation, and institutional requirements. As the study was performed retrospectively and only deidentified data were used, informed consent was waived.

Author details

[1]Department of Internal Medicine, Hospital Civil de Guadalajara "Fray Antonio Alcalde", Guadalajara, Mexico
[2]Microbiology Laboratory, Hospital Civil de Guadalajara "Fray Antonio Alcalde", Guadalajara, Mexico
[3]Laboratory of Microbiological, Molecular, and Biochemical Diagnostics (LaDiMMB), CUTlajomulco. University of Guadalajara, Tlajomulco de Zuñiga, Mexico
[4]HIV Unit Hospital Civil de Guadalajara "Fray Antonio Alcalde", Guadalajara C.P. 44670, Mexico
[5]Health Division, Tlajomulco University Center, University of Guadalajara, Tlajomulco de Zuñiga, Mexico

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