A Comparison of Diagnostic Algorithms and Clinical Parameters to Diagnose Ventilator-Associated Pneumonia: A Prospective Observational Study

Farshid Rahimibashar
Hamadan University of Medical Sciences
Andrew Carl Miller
Nazareth Hospital https://orcid.org/0000-0001-8474-5090
Mojtaba H. Yaghoobi
Alborz University of Medical Sciences
Amir Vahedian-Azimi (Amirvahedian63@gmail.com)
https://orcid.org/0000-0002-1678-7608

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Abstract

BACKGROUND: Suspicion and clinical criteria continue to serve as the foundation for ventilator-associated pneumonia (VAP) diagnosis, however the criteria used to diagnose VAP vary widely. Data from head-to-head comparisons of clinical diagnostic algorithms is lacking, thus a prospective observational study was performed to determine the performance characteristics of the Johanson criteria, Clinical Pulmonary Infection Score (CPIS), and Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC/NHSN) criteria as compared to Hospital in Europe Link for Infection Control through Surveillance (HELICS) reference standard.

METHODS: A prospective observational cohort study was performed in three mixed medical-surgical ICUs from one academic medical center from 1 October 2016 to 30 April 2018. VAP diagnostic criteria were applied to each patient including CDC/NHSN, CPIS, HELICS and Johanson criteria. Tracheal cultures and serum procalcitonin values were obtained for each patient.

RESULTS: Eighty-five patients were enrolled (VAP 45, controls 41), mean age 46.94±18.9 years with a male predominance (72.94%). Using HELICS as the reference standard, the true positive (TP; sensitivity) and false negative (FN; miss rate) rates were CDC/NHSN (TP 44%; FN 0%), CPIS (TP 43%; FN 1%), Johnson (TP 43%; FN 1%). The highest true negative rate was seen with CPIS. CPIS had the highest Youden index; CDC/NHSN had the lowest. The positive tracheal culture rate was 81.2%. The sensitivity for positive tracheal culture *with* the serum procalcitonin level >0.5 ng/ml was 51.8%. CDC/NHSN had the highest false positive correlation with tracheal aspirate cultures.

CONCLUSION: VAP remains a considerable source of morbidity and mortality in modern ICUs. The optimal diagnostic method remains unclear. Using HELICS criteria as the reference standard, CPIS displayed greater diagnostic accuracy compared to CDC/NHSN and Johanson criteria. Accuracy was improved with the addition of serum procalcitonin >0.5 ng/ml, but not positive quantitative endotracheal aspirate culture.

TRIAL REGISTRATION: Not indicated for this study type.

Background

The incidence of nosocomial infections (NI) amongst intensive care unit (ICU) patients is 2-5 times that of general admissions [1]. Amongst the most prevalent and threatening ICU NIs is ventilator-associated pneumonia (VAP), which may develop in patients receiving invasive mechanically ventilated (MV) for ≥48 hours [2–6]. VAP has a cumulative incidence of 10%-45%, and an attributable risk of 5%-27% [7–12]. VAP-associated comorbidities include prolonged duration of MV, delayed MV weaning, increased antibiotic consumption, prolonged ICU and hospital length-of-stay (LOS), increased treatment-related expenditures, and increased crude and attributed mortality [2–6,13–15].

Attributable mortality is defined as the percentage of deaths that would not have occurred in the absence of the infection. One-third to one-half of all VAP-related deaths are directly attributable to the infection, with Pseudomonas aeruginosa and Acinetobacter spp. exacting higher tolls [16–18]. Recent studies have reappraised the impact of VAP on mortality to be 10% [19,20], with surgical patients and those with mid-range illness severity presenting the highest associated risk [21], and trauma status being associated with a lower mortality than non-trauma status [22]. Accordingly, VAP prevention has emerged as a high priority [23,24]. Since 2004, the *Institute for Healthcare Improvement* has recommended that all ICUs implement a ventilator bundle to reduce the VAP rate as part of its' *5 Million Lives* campaign [23,24]. In line with this effort, one bundle component is the accurate diagnosis and determination of VAP incidence [23–25]. To this end, great effort has been expended to generate standardized diagnostic algorithms. Some examples (**Table 1**) include: Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC/NHSN) [26], Clinical Pulmonary Infection Score (CPIS) [27], Hospital in Europe Link for Infection Control through Surveillance (HELICS) [28], Johanson criteria [29], and others [30,31]. However, the criteria used to diagnose VAP vary widely, which impacts reports of incidence and outcomes. Moreover, the standard diagnosis comparator to which algorithms are compared as well as and inter-algorithm agreement varies significantly (**Table 2**), making inter-study comparisons difficult [32]. Even with strict criteria, the interpretation of some factors, such as the radiographs or the aspect of tracheal secretions, can be very subjective. Additionally, VAP identification via diagnostic scoring tools may underperform in select patient sub-populations (eg. Burns [33], surgical [34]) and has been shown to correlate poorly with International Classification of Diseases coding data, thereby limiting large-scale epidemiologic study [35,36].

Table 1
Ventilator-associated pneumonia diagnostic algorithms utilized in this study.

Published Criteria (citation)	Systemic Criteria	Chest Criteria	Chest Radiography Criteria	Microbiologic Criteria
CDC/NHSN (26)	- Inflammatory response - Temperature >38°C - WBC >12,000/mm^3 or <4,000/mm^3 - OR new antimicrobial agent is started for ≥4 days → Infection-related ventilator-associated complication	After a period of stability or improvement on the ventilator (≥2 calendar days of stable or ↓ F_iO_2 or PEEP): - Minimum daily F_iO_2 ↑ ≥0.20 lasting 2 days - Or minimum daily PEEP values ↑ ≥3 cm H_2O lasting 2 days → Ventilator-associated condition	—	Microbiologic quantitative (+), OR histologic (+), OR (+) for legionella, influenza, RSV, adenovirus, or parainfluenza virus AND Gram-stain evidence ≥25 neutrophils/lpf and ≤10 epithelial cells/lpf → Probable VAP
CPIS [a] (27)	Fever: - 38.5-38.9 (1 point) - ≥39 or <36.5 (2 points) WBC: - <4,000/mm^3 or >11,000/mm^3 (2 points)	- Secretions but not purulent (1 point) - Purulent secretions (2 points) - P_aO_2/ F_iO_2 <240 without ARDS (2 points)	Diffuse infiltrate (1 point) Localized infiltrate (2 points) Progressive infiltrate (without cardiac disease or ARDS) (+2)	Positive (1 point)
HELICS [b] (28)	At least 1 criterion: - Temperature >38°C (with no other cause) - WBC >12,000/mm^3 or <4,000/mm^3 - If age >70 years: AMS without other cause	At least 1 of following criteria (2 clinical pneumonia only = PN4 and PN5): 1. New onset purulent sputum or change in sputum character (color, odor, quantity, consistency) 2. Cough or dyspnea or tachypnea 3. Suggestive auscultation (rales or bronchial breath sounds, rhonchi, wheezing) 4. Worsening gas exchange (O_2 desaturation, increasing F_iO_2 requirements or ventilation demands)	Image suggestive of pneumonia. (≥2 serial chest X-rays or CT scans with suggestive imaging for patients with underlying cardiac or pulmonary disease)	1. PN1 – (+) quantitative Cx from minimally contaminated LRT specimen [c] 2. PN2 – (+) quantitative Cx from possibly contaminated LRT specimen [d] 3. PN3 – Alternative methods: [e] (+) blood or pleural Cx, pleural or pulmonary abscess, histology, or pathogen antigen or antibody testing. 4. PN4 – (+) sputum Cx or non-quantitative LRT specimen Cx 5. PN5 – No positive results
Johanson (29)	Temperature >38.5°C WBC >12,000/mm^3	Purulent secretions	New or progressive consolidation	—

[a] Score >6 is suggestive of VAP.

[b] VAP diagnosis if criteria met and invasive respiratory device (even intermittently) in the 48 hours preceding the onset of infection.

[c] Either: (1) Broncho-alveolar lavage (BAL) with a threshold of ≥ 104 cfu/mL or ≥ 5 % of BAL obtained cells contains intracellular bacteria on direct microscopic exam; (2) Protected brush (PB Wimberley) with a threshold of ≥ 103 cfu/mL; (3) Distal protected aspirate (DPA) with a threshold of ≥ 103 cfu/mL.

[d] Quantitative culture of LRT specimen (e.g., endotracheal aspirate) with a threshold of 106 cfu/mL.

[e] Either: (1) positive blood culture not related to another source of infection; (2) positive growth in culture of pleural fluid; (3) pleural or pulmonary exam shows evidence of pneumonia; (4) positive exams for pneumonia with virus or particular germs (Legionella, Aspergillus, mycobacteria, Mycoplasma, Pneumocystis carinii) . The latter may include: (A) positive detection of viral antigen or antibody from respiratory secretions (e.g., EIA, FAMA, shell vial assay, PCR); (B) positive direct exam or positive culture from bronchial secretions or tissue; (C) seroconversion (ex: influenza viruses, Legionella, Chlamydia); or (D) detection of antigens in urine (Legionella).

AMS = altered mental status; ARDS = acute respiratory distress syndrome; CDC/NHSN = centers for disease control and prevention national health safety network; CPIS = clinical pulmonary infection score; Cx = culture; F_iO_2 = fraction of inspired oxygen; HELICS = hospital in Europe link for infection control through surveilance; LRT = lower respiratory tract; P_aO_2 = partial pressure of oxygen in arterial blood; RSV = respiratory syncytial virus; VAP = ventilator associated pneumonia; WBC = white blood cell

Table 2
Performance characteristics of ventilator-associated pneumonia diagnostic algorithms.

Criteria Studied	Year, (citation)	Population	Comparator	Sample Size	Sensitivity	Specificity	PPV	NPV	(+) LR	(-) LR	ROC AUC	Kappa (κ) index, agreement level [a]
CDC/NHSN	2015, (66)	Mixed [b]	CPIS	38	0.37	1.0	1.0	0.84				κ = 0.47, moderate
CPIS	1999, (52)	Mixed [b]	Pathology	23	0.77	0.42						
CPIS [c]	2004, (72)	Mixed [b]	Quantitative Cultures	69	0.41	0.77	0.8	0.36			0.64	
CPIS	2004, (73)	Mixed [b]	Quantitative Cultures	88	0.89	0.47	0.57	0.84				κ = 0.33, fair
CPIS	2007, (33)	Burn	Quantitative Cultures	28	0.30	0.80	0.70	0.50				
CPIS	2010, (49)	Mixed [b]	Pathology	142	0.46	0.60			1.13	0.96		
CPIS	2015, (34)	Surgical (mixed)	Quantitative Cultures	497	0.633	0.644	0.61	0.674			0.60	
CPIS	2018, (74)	Surgical (acute care)	Quantitative Cultures	198	0.611	0.781	0.64	0.759				
HELICS	2013, (45)	Mixed [b]	Not clearly specified	57 [d]	0.86	0.99	0.77	0.995				κ = 0.80, substantial
Johansen [e]	1999, (52)	Mixed [b]	Pathology	23	0.69	0.75						
Johansen	2018, (74)	Surgical (acute care)	Quantitative Cultures	198	0.828	0.59	0.564	0.843				
NTDB/NTR	2015, (75)	Trauma	CDC/NHSN	279	0.864	0.578	0.74	0.74				κ = 0.47, moderate

[a] Agreement based on score: ≤ 0 (no agreement); 0.01–0.20 (slight); 0.21–0.40 (fair); 0.41– 0.60 (moderate); 0.61–0.80 (substantial); and 0.81–1.00 (almost perfect agreement).

[b] A mixed population containing both medical and surgical patients. Studies that did not specify ICU type were by default classified as mixed.

[c] For CPIS threshold of >7, rather than current standard of >6. The AUC using threshold CPIS >6 was 0.54, other values not reported.

[d] Data from sub-population of a larger study assessing various types of ICU-acquired infections.

[e] The presence of all three criteria increased the specificity to 92% at the cost of a high beta error (sensitivity 23%).

CDC/NHSN means centers for disease control and prevention national health safety network; ICU means intensive care unit; MV means mechanical ventilation; NR means not reported; NTDB/NTR means national trauma data bank / national trauma registry; NPV means negative predictive value; PPV means positive predictive value; ROC AUC means receiver operating curve area under curve; (+) LR means positive likelihood ratio; (-) LR means negative likelihood ratio

Additionally, high serum procalcitonin level is an independent prognostic biomarker of mortality risk in critically ill VAP patients [37], and whereas some have advocated for its inclusion in diagnostic algorithms [38], guidelines have recommended against incorporating procalcitonin into diagnostic algorithms aimed to determine when to initiate treatment [39]. Rather, it's current utility lies in helping clinicians determine when to de-escalate or stop antibiotics [39–42]. As such, VAP diagnosis remains challenging as clinical signs and symptoms may be non-specific, and an agreed upon diagnostic microbiologic technique is lacking. Additionally, international guidelines disagree on their use for risk stratification to determine treatment [21,39]. Moreover, data comparing techniques head-to-head is lacking, thus we conducted a prospective non-randomized study to determine if in patients with VAP, does application

of the Johanson criteria [29], CPIS [27], or CDC/NHSN [26] criteria provide the greatest diagnostic performance characteristics as compared to HELICS [28] as the reference standard.

Materials And Methods

A prospective observational cohort study was performed in three mixed medical-surgical ICUs from one academic medical center from 1 October 2016 to 30 April 2018. The study was approved by the Investigational Review Board at Hamadan University of Medical Sciences, Hamadan, Iran (IR.UMSAHA.REC.1395.23). All study parts were reviewed according to the *Strengthening the Reporting of Observational Studies in Epidemiology 'STROBE'* guideline [43]. Consent was required and covered both study participation and publication of de-identified aggregate findings. Surrogate consent from the patient's legal guardian or designated health proxy was permitted in cases where the subject lacked decision-making capacity. All patients that survived and regained their faculties were informed of the project. All data generated or analyzed during this study are included in this article. De-identified individual subject data may be available from the corresponding author on reasonable.

Patients were eligible for study participation if: (1) age ≥18 years, (2) admitted to the ICU >48 hours, (3) receiving invasive MV >48 hours (any mode except high frequency percussive ventilation or high frequency oscillatory ventilation), (4) full-code status, and (5) informed consent obtained from the patient, legal guardian or healthcare surrogate upon ICU admission (prior to intubation). Patients with any limitation of code status including but not limited to *No Code, Do Not Resuscitate,* or *Do Not Intubate*, were excluded (**Figure 1**). Patients with known pregnancy were excluded.

Patient selection was performed by an enrollment team of two physicians (1 critical care, 1 infectious disease) not directly involved in the study. All consecutive patients identified at the participating ICUs with VAP according to the HELICS criteria were eligible. Each case patient was matched by the enrollment team, which was blinded to the outcome, with another ICU patient that did not have VAP. Matching was based on: (1) admission indication; (2) ICU LOS ≥48 hours; (3) receiving invasive MV >48 hours (any mode except high frequency percussive ventilation or high frequency oscillatory ventilation); (4) severity of illness at ICU admission as quantified by the Acute Physiology and Chronic Health Evaluation (APACHE) II score >15, (5) full code status, and (6) age ≥18 years.

VAP diagnosis was made independently by the treating clinical team. Diagnostic criteria were according to HELICS criteria [28] in accordance with in institutional standard and other published studies [2,44–47]. Chest radiograph interpretation was undertaken "off-line" and by a team of 3 physicians (1 radiology, 1 critical care, 1 pulmonology) who were independent of the treating team. Kendal agreement coefficient between the clinicians in chest radiograph interpretation was 0.99. Procalcitonin was measured at the time of initial VAP suspicion. A single value was used, and thresholds were in accordance with prior published studies [48].

Data Collection

Screening, data collection and reporting was undertaken by a trained, dedicated full-time nurse. The data collection tool was a two-part checklist including demographic variables, clinical and microbiological variables. The tool was developed during two 90-minute meetings by a consensus multidisciplinary panel consisting of 17 physicians representing critical care (n=5), anesthesia (n=3), pulmonology (n=5), internal medicine (n=3), and forensic medicine (n=1), and 10 critical care nurses. The Quantitative face validity was determined using Impact Score (2.5-4.5), and quantitative content validity was determined via 27 panelists. The measured content validity ratio and content validity index were 0.51 and 0.89 respectively. The internal validity of the questionnaire was determined by the Cronbach's alpha coefficient to be 0.91.

Statistics

Statistical analyses were performed using IBM® SPSS version 22.0 (IBM Corp, Armonk, USA). Data were summarized using mean ± standard deviation (SD) for quantitative variables and frequency (%) for qualitative variables. Study size was determined by *a prior* sample size calculation. Considering a VAP prevalence of 0.5, 95% confidence interval level, 80% power, and absolute error 10%, the necessary sample size was calculated to be 85 patients.

Normally distributed variables were compared using the Student's t-test. Categorical variables were compared using Chi-square (χ^2) test or Fisher's exact test when appropriate. Trend of change in distribution of relative frequencies between ordinal data were compared using χ^2 test for trend. The Youden index (or Youden's J Statistic) was calculated as: $J = sensitivity + specificity - 1$.

Results

One-hundred twenty-nine patients were screened, and 85 were included in the final analysis (**Figure 1**). The mean age was 46.94 ± 18.90 years with a male predominance (72.9%). Measures of illness severity and hospital course metrics are listed in **Table 3.** Positive tracheal culture was seen in 81.2% with cultures yielding Acinetobacter (37.6%), Staphylococcus aureus (22.4%), Escherichia coli (14.1%), Pseudomonas (10.6%), Klebsiella (10.6%), and Proteus (3.5%). Multiple drug resistant (MDR) organisms were identified in 36.5% of isolates. Using HELICS as the reference standard, the true positive (TP; sensitivity) and false negative (FN; miss rate) rates for the assessed diagnostic algorithms were: CDC/NHSN (TP 44%; FN 0%), CPIS (TP 43%; FN 1%), Johnson (TP 43%; FN 1%). The sensitivity for positive tracheal culture *with* the serum procalcitonin level > 0.5 ng/ml (51.8%). The highest Youden index was seen with CPIS, and the lowest was seen with CDC/NHSN (**Table 4**). The highest true positive and true negative was seen with CDC/NHSN and CPIS respectively.

Table 3
Patient demographic and clinical information.

Variable	All	VAP (n=45)	No VAP (n=41)	p-Value
Age, years, mean (SD)	46.9 (18.9)	44.2 (20.7)	49.9 (16.4)	0.159 [a]
Male, mean (SD)	62 (72.9)	33 (73.3)	29 (72.5)	0.931 [c]
Admission indication, N (%)				0.652 [c]
Trauma	54 (63.5)	30 (66.7)	24 (60)	
Post-operative	31 (36.5)	15 (33.3)	16 (40)	
Comorbidities, yes, N (%)				0.932 [b]
ARDS	7 (8.2)	3 (6.7)	4 (10)	
Cancer	13 (15.3)	6 (13.3)	7 (17.5)	
COPD	7 (8.2)	4 (8.9)	3 (7.5)	
CHF	24 (28.2)	13 (28.9)	11 (27.5)	
ESRD	14 (16.5)	9 (20)	5 (12.5)	
Multiple trauma	20 (23.5)	10 (22.2)	10 (25)	
Positive tracheal culture, N (%)	69 (81.2)	40 (88.9)	29 (72.5)	0.093 [c]
MDR organism, yes, N (%)	31 (36.5)	17 (37.8)	14 (35)	0.825 [c]
Procalcitonin, ng/mL, mean (SD)	4.03 (4.68)	3.53 (3.6)	4.6 (5.6)	0.308 [a]
APACHE II, mean (SD)	18.1 (2.84)	17.9 (3.43)	18.4 (1.98)	0.399 [a]
Duration of intubation, hours, mean (SD)	177.1 (39.61)	176.02 (38.7)	178.32 (41.09)	0.791 [a]
Reintubation, N (%)	32 (37.6)	14 (31.1)	18 (45)	0.262 [c]
MV duration prior to VAP, hours, median (IQR)	72 (54-87.5)	72 (52-87.5)	72 (64.5-88.5)	0.639 [a]
ICU duration prior to developing VAP, days, median (IQR)	7 (6-8)	7 (6-8.5)	7 (6-8)	0.118 [a]
VAP timing, mean (SD)	———		———	———
Early (< 5 days)		15 (33.3)		
Late (≥ 5 days)		30 (66.7)		
Length-of-stay, days, mean (SD)				
ICU	9.8 (3.0)	13.13 (3.27)	12.72 (2.75)	0.538 [a]
Hospital	15.4 (3.1)	12.67 (3.34)	11.96 (2.99)	0.320 [a]
Mortality, N (%)				
ICU	68 (80)	37 (82.2)	31 (77.5)	0.787 [c]
Hospital	63 (74.1)	33 (73.3)	30 (75)	0.861 [c]

VAP = ventilator-associated pneumonia; IQR = interquartile range; MDR = multiple drug resistant; APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; VAP = ventilator-associated pneumonia

[a] Independent sample t-test

[b] Fisher exact test

[c] Chi-square

Table 4
Sensitivity, specificity, and Youden index for assessed methods of ventilator-associated pneumonia diagnosis compared to the HELICS criteria as the reference standard.

Criteria	Ventilator-Associate Pneumonia			% Sensitivity	% Specificity	Youden index [a]
	Positive	Negative	Total			
CDC/NHSN						
Positive	44	39	83	100	4.9	0.049
Negative	0	2	2			
Total	44	41	85			
CPIS						0.49
Positive	43	20	63	97.7	51.2	
Negative	1	21	22			
Total	44	41	85			
Johnson						
Positive	43	22	65	97.7	46.3	0.44
Negative	1	19	20			
Total	44	41	85			

[a] A measure of the maximum diagnostic accuracy, where 1 signifies a perfect test and 0 signifies no diagnostic value.

CDC/NHSN = centers for disease control and prevention national health safety network; CPIS = Clinical Pulmonary Infection Score, HELICS = Hospital in Europe Link for Infection Control through Surveillance.

The Kappa agreement coefficient results between each method and either serum procalcitonin level or positive tracheal culture separately is highlighted in **Table 3**. The greatest correlation between positive VAP assessment and serum procalcitonin levels ≥0.5 ng/ml was observed with Johanson and CPIS (roughly 70%), with the CDC/NHSN method lagging at 58.7%. Additionally, CDC/NHSN showed the greatest false positive correlation with tracheal aspirate cultures (19.3%; **Table 4**).

The Kappa agreement coefficients between methods are depicted in **Table 5**. Although all coefficients were statistically significant, the greatest agreement was observed between Johanson and CPIS ($p<0.001$) and Johanson and CDC/NHSN ($p<0.001$), and the least correlation was observed between CPIS and CDC/NHSN ($p=0.015$; **Table 6**). **Table 7** shows the Kappa agreement coefficients between individual parameters and diagnostic algorithms.

Table 5
Correlation of serum procalcitonin and tracheal aspirate results with ventilator-associated pneumonia diagnostic algorithms.

Criteria	Serum Procalcitonin Level, ng/mL				Kappa (κ) index, agreement level [a] (p-Value)	Tracheal Culture			Kappa (κ) index, agreement level [a] (p-Value)
	< 0.25	0.25-0.5	> 0.5	Total		Positive	Negative	Total	
Johanson, n (%)									
Positive	10 (15.4)	9 (13.8)	46 (70.8)	65 (100)	0.47, moderate (<0.001)	61 (93.8)	4 (6.2)	65 (100)	0.579, moderate (<0.001)
Negative	18 (90)	0	2 (10)	20 (100)		8 (40)	12 (60)	20 (100)	
Total	28 (32.9)	9 (10.6)	48 (56.5)	85 (100)		65 (100)	20 (100)	85 (100)	
CDC/NHSN, n (%)									
Positive	26 (31.3)	9 (10.8)	46 (58.7)	83 (100)	0.06, slight (0.58)	67 (80.7)	16 (19.3)	83 (100)	0.04, slight (0.49)
Negative	2 (100)	0	0	2 (100)		2 (100)	0	2 (100)	
Total	28 (32.9)	9 (10.6)	48 (56.5)	85 (100)		69 (81.2)	16 (18.8)	85 (100)	
CPIS, n (%)									
Positive	11 (17.5)	8 (17.7)	44 (69.8)	22 (100)	0.42, moderate (<0.001)	61 (96.8)	2 (3.2)	63 (100)	0.663, substantial (<0.001)
Negative	17 (77.3)	1 (4.5)	4 (18.2)	85 (100)		8 (36.4)	14 (63.6)	22 (100)	
Total	28 (32.9)	9 (10.6)	48 (56.5)	83 (100)		69 (81.2)	16 (18.8)	85 (100)	

[a] Agreement based on score: ≤ 0 (no agreement); 0.01–0.20 (slight); 0.21–0.40 (fair); 0.41– 0.60 (moderate); 0.61–0.80 (substantial); and 0.81–1.00 (almost perfect agreement).

CDC/NHSN = centers for disease control and prevention national health safety network; CPIS = Clinical Pulmonary Infection Score, HELICS = Hospital in Europe Link for Infection Control through Surveillance.

Table 6
Kappa agreement coefficient among ventilator-associated pneumonia diagnostic methods.

Criteria	Kappa (κ) index, agreement level [a]	p-Value
CPIS and Johanson	0.874	<0.001
CDC/NHSN and Johanson	0.145	<0.001
CDC/NHSN and CPIS	0.129	0.015

[a] Agreement based on score: ≤ 0 (no agreement); 0.01–0.20 (slight); 0.21–0.40 (fair); 0.41– 0.60 (moderate); 0.61–0.80 (substantial); and 0.81–1.00 (almost perfect agreement).

CDC/NHSN = centers for disease control and prevention national health safety network; CPIS = Clinical Pulmonary Infection Score, HELICS = Hospital in Europe Link for Infection Control through Surveillance.

Table 7
Correlation of individual variables with ventilator-associated pneumonia diagnostic methods.

Parameter	Kappa agreement coefficient		
	CDC/NHSN	CPIS	Johanson
PCT >0.5 ng/ml	0.061	0.423	0.470
Infiltrate on radiograph	-0.045	0.874	0.738
Temperature	-0.044	0.529	0.579
WBC	-0.044	0.739	0.729
P_aO_2	-0.038	0.094	-0.139
Tracheal culture	0.044	0.663	0.579
Blood culture	-0.011	0.238	0.165

CDC/NHSN = centers for disease control and prevention national health safety network; CPIS = Clinical Pulmonary Infection Score, HELICS = Hospital in Europe Link for Infection Control through Surveillance, PCT = Serum procalcitonin; WBC = White blood cell; P_aO_2 = Partial pressure of O_2 in arterial blood.

Discussion

Suspicion and clinical criteria continue to serve as the foundation for VAP diagnosis, however the criteria used to diagnose VAP vary widely, impacting reports of incidence and outcomes. Numerous diagnostic algorithms have been proposed to standardize the diagnosis, allow for easier identification, and improve comparability across studies. Unfortunately, inter-algorithm agreement varies significantly (**Table 2**), making comparisons between studies difficult. Even with strict criteria, the interpretation of some factors (eg. radiographs) may be subjective. Additionally, diagnostic algorithms performance varies by patient population [33,34] and correlates poorly with coding data[35,36] and postmortem histology [49]. Even so, a need exists for an effective tool that may be utilized in the clinical environment to aid *real time* VAP diagnosis.

VAP diagnosis is usually based on 2 or 3 components: (1) systemic signs of infection, (2) new or worsening infiltrates seen on chest imaging, and (3) microbiologic evidence of pulmonary parenchymal infection when available [49]. However, the false positive rates are high for chest roentenograms (58%) [50], no single radiographic sign was shown to have a diagnostic accuracy greater than 68% [51]. Moreover, false positive rates are similarly high for clinical symptoms such as fever (42%) or purulent airway secretions (67%) [50]. Combining these criteria does little to improve diagnostic performance. In a post-mortem study, the combination of infiltrates on the chest radiograph with 2 of 3 clinical criteria (leukocytosis, purulent secretions, fever) had a sensitivity of 69% and a specificity of 75% [52]. This is significantly lower than the sensitivity and specificity for HELICS (mixed population) and CPIS (medical and mixed populations only; **Table 2**).

Patient characteristics in our cohort were largely similar to those of other published cohorts, including age [9,20,53–57], male gender predominance [9,54,58–61], and APACHE II score [54–57,60–62]. Also, MV duration [58,61–64], re-intubation rates [9,61,65], ICU LOS [56–59,61,63], and hospital LOS [56,59,61,63] were within the range of prior published studies. Moreover, the array of cultured pathogens, and incidence of MDR pathogens, was congruent with prior studies [60].

Direct comparisons of the performance characteristics of the CDC/NHSN, CPIS, HELICS, and Johanson criteria have not previously been reported. Moreover, only two studies were identified that compared VAP diagnostic algorithms [32,66]. HELICS was chosen as the reference standard due as it has been reported to have the best performance characteristics, is widely used internationally, and has been used as the reference standard for numerous other studies [2,44–47]. CDC/NHSN and CPIS criteria were chosen as the other two most widely recognized and used criteria. The Johanson criteria was selected as the third comparator for its historical significance. Whereas CDC/NHSN had the highest sensitivity for detecting VAP, the specificity was low. CPIS exhibited the best overall performance in terms of sensitivity and specificity when comparing to a HELICS reference standard. Similar to a prior study, the addition of microbiological data to the clinical definitions did not significantly improve the sensitivity or specificity [49].

Among the most studied biomarkers for VAP diagnosis and prognosis is serum procalcitonin. Serum procalcitonin concentration >0.5 ng/ml has been reported to have a diagnostic sensitivity and specificity of 68.25% and 89.83% respectively [67]. Others have reported that the optimal threshold value VAP diagnosis on day 1 was 5.0 ng/ml (sensitivity 91%, specificity 71%) [51]. Furthermore, procalcitonin levels may correlate with mortality (75% at level >10 ng/ml) [67], however others have disputed its impact [7,8,68]. The current study found that serum procalcitonin concentration >0.5 ng/ml correlated moderately with a diagnosis of VAP by CPIS and Johanson criteria, but only slightly with CDC/NHSN criteria.

Limitations

The non-randomized methodology and absence of histopathology confirmation of VAP diagnosis are limitations of this study. Moreover, culture results were based on endotracheal aspirate specimens. However, positive quantitative endotracheal aspirate cultures have been reported to have a high degree of correlation with broncho-alveolar lavage in VAP patients and are a useful minimally invasive diagnostic tool [69–71].

Conclusion

Ventilator-associated pneumonia remains a considerable source of morbidity and mortality in modern intensive care units. The optimal diagnostic method remains unclear. Using HELICS criteria as the reference standard, CPIS displayed greater diagnostic accuracy compared to CDC/NHSN and Johanson criteria. Accuracy was improved with the addition of serum procalcitonin >0.5 ng/ml, but not positive quantitative endotracheal aspirate culture.

Abbreviations

VAP	Ventilator-associated pneumonia
CPIS	Clinical Pulmonary Infection Score
CDC/NHSN	Centers for Disease Control and Prevention's National Healthcare Safety HELICS/Hospital in Europe Link for Infection Control through Surveillance
TP	True positive
FN	False negative
NI	Nosocomial infection
ICU	Intensive care unit
MV	Mechanical ventilation
LOS	Length-of-stay
APACHE	Acute Physiology and Chronic Health Evaluation
SD	Standard deviation
χ^2	Chi-square test
J	Youden's J Statistic, or Youden Index
MDR	Multiple drug resistant

Declarations

Ethics approval: The study was approved by the Investigational Review Board at Hamadan University of Medical Sciences, Hamadan, Iran (IR.UMSAHA.REC.1395.23).

Consent (participation & publication): Consent was required and covered both study participation and publication of de-identified aggregate findings. Surrogate consent from the patient's legal guardian or designated health proxy was permitted in cases where the subject lacked decision-making capacity. All patients that survived and regained their faculties were informed of the project.

Availability of data and material: All data generated or analyzed during this study are included in this article. De-identified individual subject data may be available from the corresponding author on reasonable.

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Author's Contributions: The original idea was conceived by FRB and AVA. Study design, implementation, and data acquisition was performed by FRB, MHY and AVA. Data analysis was performed by AVA and ACM. Manuscript writing and revision was performed by ACM and AVA. All authors read and approved the final manuscript.

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Figures

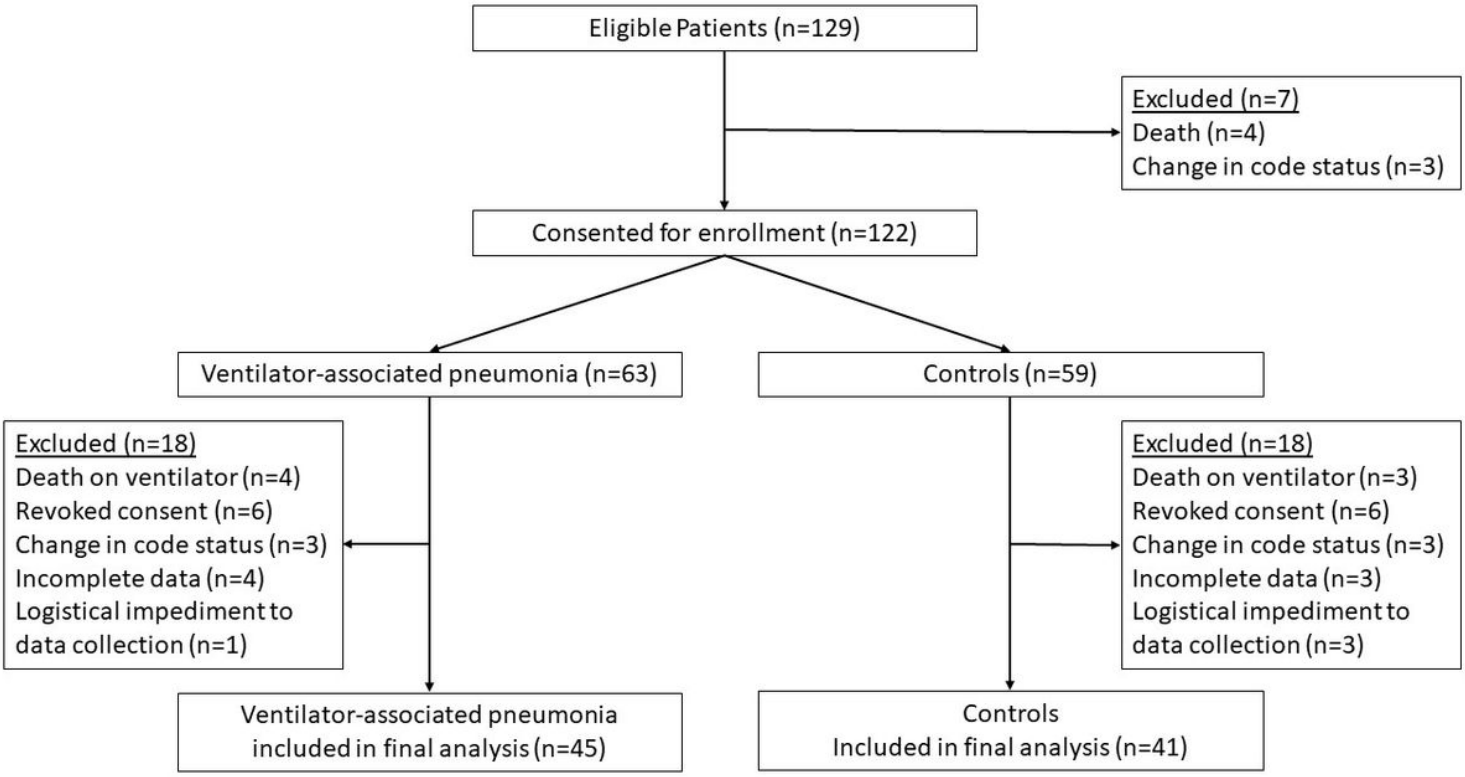

Figure 1

Patient flow diagram.