Journal of Hospital Infection 140 (2023) 90—95

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Comparison of multiple definitions for ventilator-associated pneumonia in patients requiring mechanical ventilation for non-pulmonary conditions: preliminary data from PULMIVAP, an Italian multi-centre cohort study

L. Alagna [a,†], E. Palomba [a,b,*,†], L. Chatenoud [c], R. Massafra [a], F. Magni [d], L. Mancabelli [e,f], S. Donnini [g], F. Elli [g], A. Forastieri [h], G. Gaipa [j], C. Abbruzzese [k], R. Fumagalli [l], M. Munari [m], A. Panacea [n], E. Picetti [o], L. Terranova [p], F. Turroni [f,q], R. Vaschetto [r], T. Zoerle [b,s], G. Citerio [d,t,u], A. Gori [b,v], A. Bandera [a,b]

[a] *Infectious Diseases Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[b] *Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*
[c] *Laboratory of Clinical Epidemiology, Department of Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy*
[d] *Neurointensive Care Unit, ASST-Monza, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy*
[e] *Department of Medicine and Surgery, University of Parma, Parma, Italy*
[f] *Interdepartmental Research Centre 'Microbiome Research Hub', University of Parma, Parma, Italy*
[g] *Department of Anaesthesia and Intensive Unit, Spedali Riuniti Livorno ATNO ESTAR, Livorno, Italy*
[h] *Department of Anaesthesia and Intensive Care, A. Manzoni Hospital, ASST Lecco, Lecco, Italy*
[j] *Tettamanti Research Centre, M.Tettamanti Foundation, Department of Paediatrics, University of Milano-Bicocca, Monza, Italy*
[k] *Department of Anaesthesia, Critical Care and Emergency, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[l] *Intensive Care, ASST GOM Niguarda, Milan, Italy*
[m] *Anaesthesia and Intensive Care Unit, University Hospital of Padova, Padova, Italy*
[n] *Università degli Studi di Brescia, Brescia, Italy*
[o] *Department of Anaesthesia and Intensive Care, Parma University Hospital, Parma, Italy*
[p] *Internal Medicine Department, Respiratory Unit and Adult Cystic Fibrosis Centre, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy*
[q] *Laboratory of Probiogenomics, Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy*
[r] *Department of Anaesthesia and Intensive Unit, Ospedale Maggiore della Carità, Novara, Italy*
[s] *Neuroscience Intensive Care Unit, Department of Anaesthesia and Critical Care, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

* Corresponding author. Address: Infectious Diseases Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, via Francesco Sforza 35, 20122 Milan, Italy.
E-mail address: emanuele.palomba@unimi.it (E. Palomba).
† These authors contributed equally to this work and should be considered co-first authors.

https://doi.org/10.1016/j.jhin.2023.07.023

[t] School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
[u] Neurointensive Care Unit, Department of Neuroscience, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[v] Department of Infectious Diseases, ASST Fatebenefratelli-Sacco University Hospital, Milan, Italy

ARTICLE INFO

Article history:
Received 11 June 2023
Accepted 31 July 2023
Available online 9 August 2023

Keywords:
Ventilator-associated pneumonia
Healthcare-associated infections
Mechanical ventilation
Diagnosis
Critically ill patients
Critical care

SUMMARY

Objectives: To compare intensivist-diagnosed ventilator-associated pneumonia (iVAP) with four established definitions, assessing their agreement in detecting new episodes.

Methods: A multi-centric prospective study on pulmonary microbiota was carried out in patients requiring mechanical ventilation (MV). Data collected were used to compare hypothetical VAP onset according to iVAP with the study consensus criteria, the European Centre for Disease Control and Prevention definition, and two versions of the latter adjusted for leukocyte count and fever.

Results: In our cohort of 186 adult patients, iVAPs were 36.6% (68/186, 95% confidence interval 30.0–44.0%), with an incidence rate of 4.64/100 patient-MV-days, and median MV-day at diagnosis of 6. Forty-seven percent of patients (87/186) were identified as VAP by at least one criterion, with a median MV-day at diagnosis of 5. Agreement between intensivist judgement (iVAP/no-iVAP) and the criteria was highest for the study consensus criteria (50/87, 57.4%), but still one-third of iVAP were not identified and 9% of patients were identified as VAP contrary to intensivist diagnosis. VAP proportion differed between criteria (25.2–30.1%).

Conclusions: Caution is needed when evaluating studies describing VAP incidence. Pre-agreed criteria and definitions that capture VAP's evolving nature provide greater consistency, but new clinically driven definitions are needed to align surveillance and diagnostic criteria with clinical practice.

Introduction

Ventilator-associated pneumonia (VAP) represents the most common healthcare-associated infection in the intensive care unit (ICU) [1]. VAP diagnosis has challenged clinicians for over half a century since it was first defined by Johanson *et al.* [2]. The international centres for disease control and prevention have introduced surveillance-based definitions [3,4], but the debate remains open. Indeed, accurate detection of VAP onset is critical both for epidemiological studies and clinical decision making.

We compared intensivist-diagnosed VAP (iVAP) with European surveillance-based definitions in a cohort of patients requiring mechanical ventilation (MV) for non-pulmonary conditions to assess their agreement in detecting new episodes.

Methods

Ancillary analysis of data collected in an ongoing multicentre prospective cohort study on pulmonary microbiota of patients undergoing MV (PULMIVAP-study, clinicaltrial.gov#NCT04849039, registered by Milan Area 2 Ethical Committee, #533_2019, approval: 5th June 2019). The study aimed to investigate a potential association between lung microbiota and VAP. All adult patients admitted to nine ICUs in Northern Italy between September 2020 and June 2022 were considered for enrolment and followed up to 15 days of MV. Inclusion criteria were MV for non-pulmonary conditions; expected duration of MV >48 h; and no antibiotic administration in the previous 72 h.

Following a consensus conference involving the nine participating centres, a study criterion (PULMIVAP) was defined for VAP to achieve comparable diagnoses between the centres (Figure 1), however, iVAP remained the one considered for patient management. Data collected from each day of MV were used to identify hypothetical VAP onset according to iVAP and four VAP definitions: (1) PULMIVAP; (2) European Centre for Disease Control and Prevention (ECDC) definition for intubation-associated pneumonia, which describes a subset of patient with pneumonia onset after 48 h of MV [4]; (3) modified ECDC for leukocytosis and leukopenia thresholds (ECDC-L); and (4) modified ECDC for the definition of fever in patients receiving corticosteroids or non-steroidal anti-inflammatory drugs (ECDC-F) (Figure 1).

Continuous variables were expressed as median with the first and last quartile (Q1–Q3), while categorical variables were expressed as frequencies and proportions. Appropriate tests made comparisons between VAP and no-VAP patients. We calculated the first VAP incident rate (IR), accompanied by the 95% confidence intervals (CIs).

Further details on methods are reported in the supplementary material.

Results

A total of 186 patients were included, most intubated for neurological reasons (159/186, 85%). Overall, the median age

	PULMIVAP criteria*	ECDC criteria (2022)[a]	Modified ECDC-L (leukocyte)[b]	Modified ECDC-F (fever)[c]
Inflammation	Fever >38°C or hypothermia <35°C or Leukopenia (<4500/mm^3) or leukocytosis (≥10,000/mm^3)	Fever >38°C or hypothermia <35°C or Leukopenia (≤4000/mm^3) or leukocytosis (≥12,000/mm^3)	Fever >38°C or hypothermia <35°C or Leukopenia (<4500/mm^3) or leukocytosis (≥10,000/mm^3)	Fever >38°C or hypothermia <35°C or T >37.5°C with concomitant NSAID or corticosteroid use or Leukopenia (≤4000/mm^3) or leukocytosis (≥12,000/mm^3)
Radiology	Lung consolidation • Chest X-ray • Chest CT-scan • Lung ultrasound	Lung consolidation • Chest X-ray • Chest CT-scan	Lung consolidation • Chest X-ray • Chest CT-scan	Lung consolidation • Chest X-ray • Chest CT-scan
Respiratory	New onset of purulent sputum, or change in character of sputum or Decrease in PaO2/FiO2 >100 or need for increased FiO2 or need for increased PEEP	New onset of purulent sputum, or change in character of sputum or Worsening gas exchange (e.g. O2 desaturation or increased oxygen requirements or increased ventilation demand)	New onset of purulent sputum, of change in character of sputum or Worsening gas exchange (e.g. O2 desaturation or increased oxygen requirements or increased ventilation demand)	New onset of purulent sputum, or change in character of sputum or Worsening gas exchange (e.g. O2 desaturation or increased oxygen requirements or increased ventilation demand)
Antibiotic	Decision to start a new antimicrobial			

Figure 1. Criteria analysed in the study. CT, computed tomography; ECDC, European Centre for Disease Control and Prevention; NSAID, non-steroidal anti-inflammatory drug; PEEP, positive end-expiratory pressure; PULMIVAP, study criteria. * Modified from Centers for Disease Control and Prevention (CDC) definition of infection-related ventilator-associated complication and possible ventilator-associated pneumonia (2016). [a] ECDC definition for intubation-associated pneumonia, a subset of pneumonia case definition occurring in patients with invasive respiratory device in the 48 h preceding the onset of infection. Tachypnoea and suggestive auscultation findings were not included as they are not usually applicable to intubated patients. [b] ECDC criteria with modified leukocyte count threshold according to CDC definition (2016). [c] ECDC criteria modified considering the impact of NSAIDs and corticosteroids on body temperature.

was 64 years (Q1—Q3: 50—73 years) and APACHEII at ICU admission was 16 (Q1—Q3: 11—21) (Supplementary Table S1). iVAP was diagnosed in 68/186 (36.6%) patients (95% CI = 30.0—44.0%), corresponding to an incidence rate of 4.64/100 patient-MV-days. The first iVAP occurred at a median of six days (Q1—Q3: four to seven days), with 92% of episodes diagnosed within day 9 of MV (Supplementary Figure S1).

No significant differences emerged between iVAP and no-VAP patients except for gender (female: no-VAP = 50% versus iVAP = 32%) and MV duration, that was significantly longer in iVAP patients (18 vs 10 days). Overall survival at ICU discharge was 79% (147/186), with no marked difference between the two groups (Supplementary Table S1).

Microbiological tests were performed in 31/68 (46%) iVAP patients: in 25/31 (80.6%) at least one micro-organism was identified. Of note, only two of 47 (4.2%) isolates were multi-drug-resistant. *Klebsiella* spp., *Staphylococcus aureus* and *Pseudomonas* spp. accounted for more than half of isolates (25/47, 53.1%) (Supplementary Figure S2).

Eighty-seven patients (46.7%) were identified as having VAP by at least one criterion, and in six patients VAP was diagnosed earlier by any criterion than by the intensivist. The median day at VAP was five for all criteria (Q1—Q3: four to seven days, except for ECDC-L, Q3 = six days). PULMIVAP, ECDC, ECDC-F and ECDC-L definitions did not identify 21, 20, 15 and 12 iVAPs, respectively (Figure 2). Agreement between intensivist

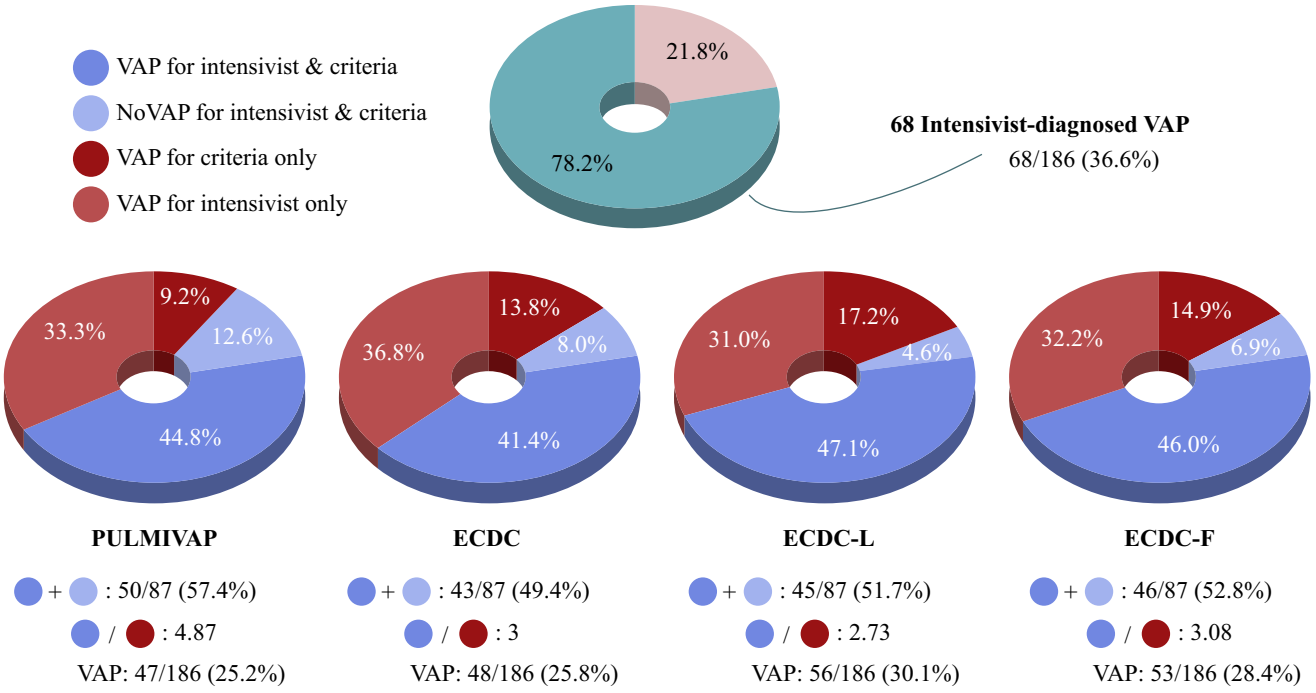

Figure 2. Comparison between intensivist-diagnosed ventilator-associated pneumonia (VAP) and four established definitions in 87 patients with at least one hypothetical VAP event. ECDC, European Centre for Disease Control and Prevention definition; ECDC-F, ECDC definition modified for fever; ECDC-L, ECDC definition with modified leukocyte threshold; PULMIVAP, study criteria.

diagnosis (iVAP/no-iVAP) and the criteria was highest for PULMIVAP (57.4%), followed by ECDC-F (52.8%), ECDC-L (51.7%) and ECDC (49.4%). The different criteria identified patients with VAP in eight to 15 cases not diagnosed as iVAP, thus the proportion of VAP differed depending on the criteria used, and was 25.2% (47/186) for PULMIVAP, 25.8% (48/186) for ECDC, 28.4% (53/186) for ECDC-F, and 30.1% (56/186) for ECDC-L (Supplementary Table S2). The inflammation criterion (i.e., fever and leukocyte count) was not met in most of the iVAPs not recognized by the different definitions, accounting for 22.1% (PULMIVAP), 27.9% (ECDC-L), 29.4% (ECDC-F) and 35.3% (ECDC) of discordant cases (Supplementary Tables S3—S6). Overall survival for patients identified as VAP by the criteria differed slightly, and was higher than for those diagnosed by the intensivist, 88.5—89.4% vs 79.1% (Supplementary Table S7).

Discussion

In our cohort of patients requiring MV for non-pulmonary conditions, iVAP and the criteria did not fully overlap in identifying VAP, with a proportion of discordant evaluation of 40% up to 51%, depending on the criterion. iVAP was reported in more than one-third of patients. When available (less than half of the episodes), respiratory cultures were positive in 80% of iVAP. As expected, being the study consensus criteria, PULMIVAP showed the highest concordance, but one-third of iVAP was still not identified, despite the definition being agreed by participants during a meeting at the start of the study. In contrast, 9% of patients were identified as VAP contrary to the intensivist's judgement. The other criteria analysed varied slightly in their ability to identify VAP, with ECDC-F showing the highest agreement. Nevertheless, 31—36% of iVAP were not identified, and 13.8—17.2% of episodes were defined as VAP in disagreement with the intensivist diagnosis. The discrepancy between iVAP and the various definitions was mainly due to cases diagnosed by the intensivist that did not meet the inflammation criterion, which includes thresholds for fever and leukopenia/leukocytosis that may not be met in many clinical scenarios. Contrarily, the respiratory and radiological criteria were present in almost all iVAPs.

Data comparing different diagnostic algorithms for VAP are lacking. A multi-centre study in 13 ICUs involving 244 patients showed that a quarter of VAP was not diagnosed according to the Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC/NHSN) 2008 and 2013 definitions [5]. Similarly, a study on 168 MV patients compared the CDC/NHSN definition with the Clinical Pulmonary Infection Score (CPIS) and found a much lower incidence rate of VAP, 5.2/1000 vs 13.1/1000 days of MV [6]. A recent prospective observational study of 85 ICU patients [7] compared the ECDC definition with the Johanson criteria, the CPIS and the CDC/NHSN definition. Using the ECDC as the reference standard, the sensitivity and specificity of each diagnostic algorithm were evaluated: CPIS had the highest diagnostic accuracy. In contrast, the sensitivity of the CDC/NHSN was only slightly better than the clinical criteria.

There is even less evidence comparing physician diagnosis with defined criteria. The only available study is a retrospective analysis of 66 ICU patients [8] comparing physician diagnosis with the CDC/NHSN definition, the local protocol and an Australasian VAP definition [9]. The physician-diagnosed arm showed significant disagreement with the definitions, both in identifying additional VAP cases and in classifying as VAP a portion of episodes diagnosed by the protocols as no-VAP.

Surveillance definitions are primarily designed to ensure comparability of results rather than to support clinical diagnosis. They must therefore be reproducible to serve additional purposes, such as informing public health policy and interventions. Such definitions should not be misinterpreted by clinicians as diagnostic criteria, as this could both lead to under diagnosis or overuse of antibiotics (e.g., treatment of respiratory colonization). Intriguingly, some authors suggested that misinterpretation of ventilator-associated tracheobronchitis (VAT) may explain these differences in incidence. In this case, recognizing VAT as a clinical disease may reduce length of antibiotic exposure and the consequent development of resistance, as well as the increased risk of adverse events [10,11]. Our findings may suggest that the disagreement between clinical diagnosis and surveillance definitions in the assessment of VAP is driven by different interpretations of indices such as white blood cell count or fever, which are often ambiguous in the critical patient.

A strength of our study is that we collected data prospectively, which ensures 'blind' use of prevalence criteria and shows how strict application of definitions can lead to underestimation of the complexity of the patient's clinical picture. Our cohort was restricted to patients without underlying pulmonary disease before MV, which may be a strength, as this is the population in which healthcare-associated infectious complications such as VAP could have the greatest impact. However, this may make our findings less generalizable. Another limitation is that the PULMIVAP study was designed to describe lung microbiota and not to evaluate diagnostic criteria for VAP or outcome measures; therefore, statistical inferences could not be made. In addition, the lack of microbiological sampling probably affected our analysis, although this reflects the real-world scenario in most ICUs, especially those with limited resources.

In conclusion, given the controversial and volatile nature of VAP diagnosis, pre-agreed criteria, and definitions that capture its evolving nature (i.e., flexible thresholds) ensure the greatest consistency with intensivist diagnosis. Exploring more complex definitions may standardize diagnosis and align surveillance criteria with clinical practice. However, greater flexibility may lead to inconsistencies and classification errors. When evaluating studies describing VAP incidence, care should be taken to consider the definition used for its diagnosis. Prospective studies need consensus criteria to warrant consistent data collection.

Acknowledgements

Preliminary results of the study were presented as an oral presentation at ECCMID 2023 in Copenhagen, Denmark. The authors wish to thank the PULMIVAP Study Group: Alice Rizzo; Valeria Pastore (Infectious Diseases Unit, Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy); Giulia Alessandri, Gabriele Andrea Lugli (Laboratory of Progenomics, Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy); Matteo Filippini, Nicola Latronico, Lorenzo Pilati (Università degli Studi di Brescia; ASST Spedali Civili, Brescia, Italy); Italo Calamai, Rosario Spina, Romano Giuntini (Anaesthesiology and Intensive Care Unit, AUSL Toscana Centro; S. Giuseppe Hospital, Empoli, Italy); Eleonora Simoncini (Clinical Trials Task Force, Ethics and Care Unit, AUSL Toscana Centro, Piero Palagi Hospital, Florence, Italy); Martina Viganò, Cristina Panzeri, Alberto Steffanoni (Department of Anaesthesia and Intensive Care, A. Manzoni Hospital, ASST Lecco, Lecco, Italy); Lara Vegnuti, Romilda Tucci, Baldassarre Ferro (Department of Anaesthesia and Intensive Care, Spedali Riuniti Livorno ATNO ESTAR, Livorno, Italy); Ilaria Beretta (Infectious Diseases Unit, ASST di Monza, Monza, Italy); Riccardo Giudici (Intensive Care, ASST GOM Niguarda, Milan, Italy); Anna Zeduri (School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy); Alessandro De Cassai, Federico Geraldini, Marzia Grandis (Anaesthesia and Intensive Care Unit, University Hospital of Padova, Padova, Italy); Francesca Grossi, Stefania Guido, Nello De Vita (Ospedale Maggiore della Carità, Novara, Italy); Marco Di Lecce, Bianca Maria Mainini (Department of Anaesthesia and Intensive Care, Parma University Hospital, Parma, Italy); Nino Stocchetti, Marco Carbonara (Neuroscience Intensive Care Unit, Department of Anaesthesia and Critical Care, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy); Antonio Pesenti, Giacomo Grasselli (Department of Anaesthesia, Critical Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy).

Author contributions

L.A., E.P., L.C. and A.B. conceived of the study. L.A., E.P. and L.C. wrote the first draft of the manuscript. All of the authors reviewed the final version of the manuscript.

Conflict of interest statement

The authors declare no conflicts of interest.

Funding sources

This work was supported by the Italian Ministry of Health (RF GR-2018-12365988), and the Associazione Nazionale per la Lotta control'AIDS (ANLAIDS) Sezione Lombarda.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2023.07.023.

References

[1] Magill SS, O'Leary E, Janelle SJ, Thompson DL, Dumyati G, Nadle J, et al. Changes in prevalence of health care-associated infections in U.S. hospitals. N Engl J Med 2018;379:1732—44.

[2] Johanson WG, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with Gram-negative bacilli. The significance of colonization of the respiratory tract. Ann Intern Med 1972;77:701—6.

[3] Centers for Disease Control and Prevention (CDC). National healthcare safety Network (NHSN) patient safety component manual. Ventilator-associated event. (VAE). Atlanta, GA: CDC; 2023.

[4] European Centre for Disease Prevention and Control (ECDC). Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/antimicrobial-use-healthcare-associated-infections-point-prevalence-survey-version6-1.pdf [last accessed July 2023].

[5] Ramírez-Estrada S, Lagunes L, Peña-López Y, Vahedian-Azimi A, Nseir S, Arvaniti K, et al. Assessing predictive accuracy for outcomes of ventilator-associated events in an international cohort: the EUVAE study. Intensive Care Med 2018;448:1212—20.

[6] Waltrick R, Possamai DS, De Aguiar FP, Dadam M, De Souza Filho VJ, Ramos LR, et al. Comparison between a clinical diagnosis method and the surveillance technique of the Center for Disease Control and Prevention for identification of mechanical ventilator-associated pneumonia. Rev Bras Ter Intensiva 2015;27:260—5.

[7] Rahimibashar F, Miller AC, Yaghoobi MH, Vahedian-Azimi A. A comparison of diagnostic algorithms and clinical parameters to diagnose ventilator-associated pneumonia: a prospective observational study. BMC Pulm Med 2021;21:1—11.

[8] Sieben NA, Dash S. A retrospective evaluation of multiple definitions for ventilator associated pneumonia (VAP) diagnosis in an Australian regional intensive care unit. Infect Dis Heal 2022;27:191—7.

[9] Elliott D, Elliott R, Burrell A, Harrigan P, Murgo M, Rolls K, et al. Incidence of ventilator-associated pneumonia in Australasian intensive care units: use of a consensus-developed clinical surveillance checklist in a multisite prospective audit. BMJ Open 2015;5:e008924.

[10] Colombo SM, Palomeque AC, Li Bassi G. The zero-VAP sophistry and controversies surrounding prevention of ventilator-associated pneumonia. Intensive Care Med 2020;46:368.

[11] Loeches IM, Povoa P, Nseir S. Ventilator associated tracheobronchitis and pneumonia: one infection with two faces. Intensive Care Med 2023:9—12.