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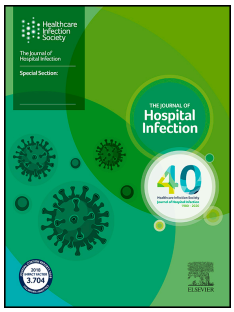

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Comparison of multiple definitions for Ventilator-Associated Pneumonia in patients requiring mechanical ventilation for non-pulmonary conditions: preliminary data from PULMIVAP, an Italian multicentre cohort study

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Abstract

Objectives: Compare intensivist-diagnosed VAP (iVAP) with four established definitions, assessing their agreement in detecting new episodes.

Methods: Analysis from multicentric prospective study on pulmonary microbiota 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 Diseases 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%CI=30.0%-44.0%), with an incidence rate of 4.64/100 patient-MVdays, 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 was not identified and 9% of patients were identified as VAP against intensivist diagnosis. VAP proportion differed among different criteria (25.2-30.1%).

Conclusions: Caution is needed 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.

Keywords: ventilator-associated pneumonia; healthcare-associated infections; mechanical ventilation; diagnosis; critically ill patients; critical care

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:5 June 2019). The study aimed to investigate a potential association between lung microbiota and VAP. All adult patients admitted to 9 ICUs in Northern Italy between September 2020 and June 2022 were considered for enrollment and followed up to 15 days of MV. Inclusion criteria were MV for non-pulmonary conditions; expected duration of MV>48 hours; and no antibiotic administration in the previous 72 hours.

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: a) PULMIVAP; b) European Centre for Disease Control and Prevention (ECDC) definition for intubation-associated pneumonia, which describes a subset of patient with pneumonia onset after 48 hours of MV [4]; c) modified ECDC for leucocytosis and leukopenia thresholds (ECDC-L); and d) 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 (95% CI).

Further details on methods were reported in **Supplementary material**.

Results

A total of 186 patients were included, most intubated for neurological reasons (159/186, 85%). Overall, the median age was 64 years (Q1-Q3:50-73 years) and APACHEII at ICU admission was 16 (Q1-Q3:11-21)(**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-MVdays. The first iVAP occurred at a median of 6 days (Q1-Q3:4-7 days), with 92% of episodes diagnosed within day 9 of MV (**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 (**Table S1**).

Microbiological tests were performed in 31/68 (46%) iVAP patients: in 25/31 (80.6%) at least one microorganism was identified. Of note, only 2/47 (4.2%) isolates were multidrug-resistant. *Klebsiella* spp., *Staphylococcus aureus* and *Pseudomonas* spp. accounted for more than half of isolates (25/47, 53.1%) (**Figure S2**).

Eighty-seven patients (46.7%) were identified as having VAP by at least one criterion, and in 6 patients VAP was diagnosed earlier by any criterion than by the intensivist. The median day at VAP was five for all criteria (Q1-Q3:4-7 days, except for ECDC-L, Q3=6 days). PULMIVAP, ECDC, ECDC-F, and ECDC-L definition did not identify 21, 20, 15, and 12 iVAP, respectively (**Figure 2**). Agreement between intensivist 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 8 to 15 cases not diagnosed as iVAP, so 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 (**Table S2**). The inflammation criterion (i.e., fever and leukocyte count) was not met in most of the iVAPs not recognised by the different definitions, accounting for 22.1% (PULMIVAP), 27.9% (ECDC-L),

133 29.4% (ECDC-F) and 35.3% (ECDC) of discordant cases (**Tables S3-S6**). Overall survival for
134 patients identified as VAP by the criteria differed slightly, and was higher than for those diagnosed by
135 the intensivist, 88.5-89.4% vs 79.1%. (**Table S7**).

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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 study. In contrast, 9% of patients were identified as VAP contrary to the intensivist's judgment. 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 multicentre 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 colonisation). Intriguingly, some authors suggested that misinterpretation of ventilator-associated tracheobronchitis (VAT) may explain these differences in incidence. In this case, recognising 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 generalisable. 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

likely affected our analysis, although this reflects the real-world scenario in most ICUs, especially those with limited resources.

Conclusions

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 standardise 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.

Conflict of interest: the authors declare no conflict of interest.

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Contribution: LA, EP, LC, and AB conceived the study. LA, EP, and LC wrote the first draft of the manuscript. All the authors reviewed the final version of the manuscript.

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Figure 1. Criteria analysed in the study.

	PULMIVAP criteria*	ECDC criteria (2022)α	Modified ECDC-L (leucocyte)β	Modified ECDC-F (fever)γ
Inflammation	Fever >38°C or hypothermia <35°C or Leukopenia (<4,500/mm³) or leucocytosis (≥10,000/mm³)	Fever >38°C or hypothermia <35°C or Leukopenia (≤4,000/mm³) or leucocytosis (≥12,000/mm³)	Fever >38°C or hypothermia <35°C or Leukopenia (<4,500/mm³) or leucocytosis (≥10,000/mm³)	Fever >38°C or hypothermia <35°C or T >37.5°C with concomitant NSAID or corticosteroid use or Leukopenia (≤4,000/mm³) or leucocytosis (≥12,000/mm³)
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, 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, 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			

Legend: CT computed tomography; NSAID Nonsteroidal anti-inflammatory drugs, ECDC European Centre for Disease Control and Prevention

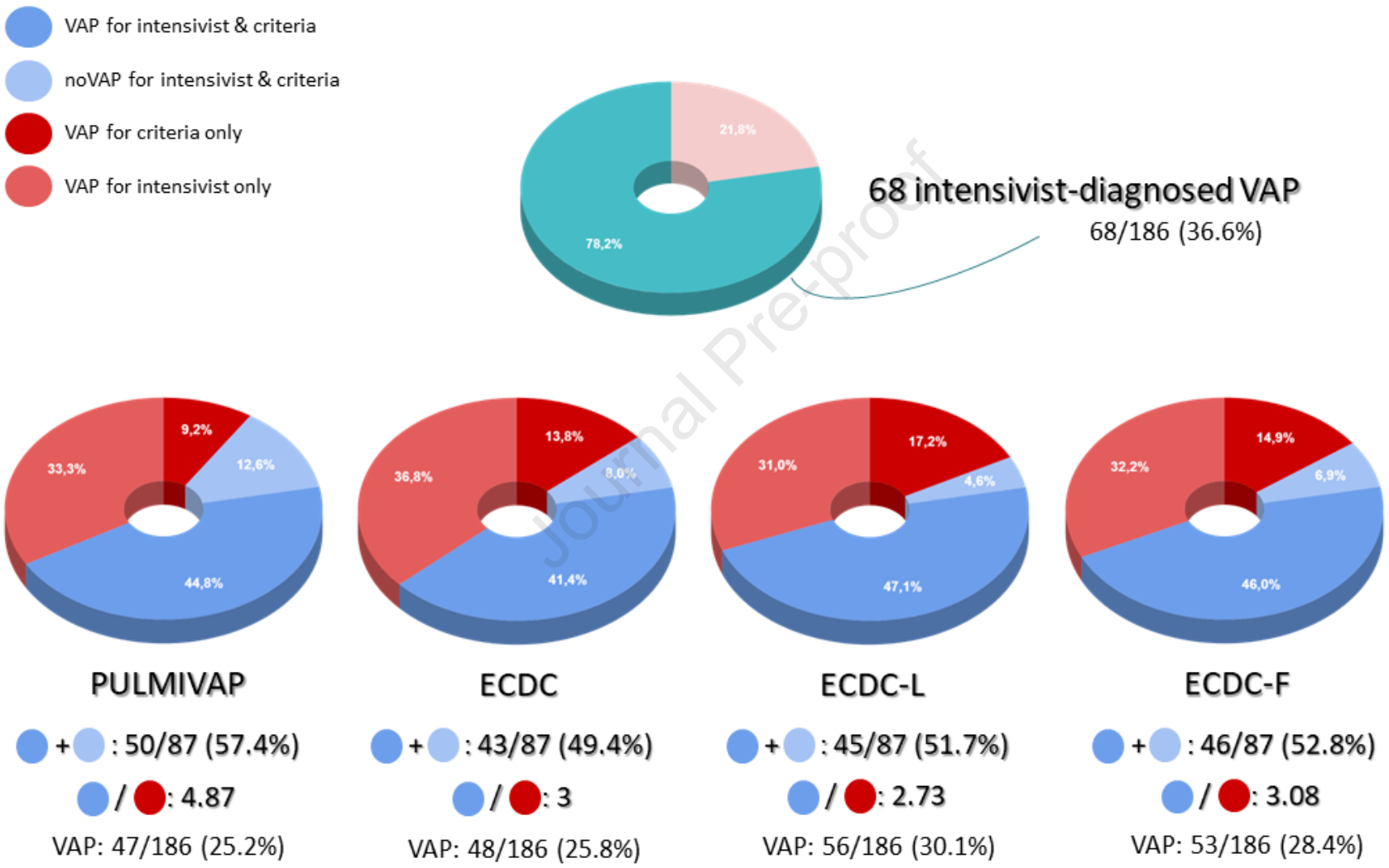
* Modified from Centers for Disease Control and Prevention definition of Infection-related Ventilator-Associated Complication and possibile ventilator-associated pneumonia (2016)

α ECDC definition for intubation-associated pneumonia, a subset of pneumonia case definition occurring in patients with invasive respiratory device in the 48 hours preceding the onset of infection. Tachypnoea and suggestive auscultation findings were not included since they are not usually applicable to intubated patients

β ECDC criteria with modified leucocyte count threshold according to CDC definition (2016)

γ ECDC criteria modified considering the impact of NSAIDs and corticosteroids on body temperature

Figure 2. Comparison between intensivist-diagnosed VAP and 4 established definitions in 87 patients with at least one hypothetical VAP event.



VAP: ventilator-associated pneumonia; PULMIVAP: study criteria; ECDC: European Centre for Disease Control and Prevention definition; ECDC-L: ECDC definition with modified leukocyte threshold; ECDC-F: ECDC definition modified for fever