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Original Article

The CDC PNU-1 criteria for diagnosis of ventilator-associated pneumonia

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Abstract

Background Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in the pediatric intensive care unit (PICU), with mortality rates of up to 50%. Post-mortem pulmonary examination is considered to be the gold standard for diagnosis of VAP, but is impossible for routine application. The sensitivity and specificity of *Clinical Pulmonary Infection Score* (CPIS) are considered to be similar to the those of the gold standard, but the *Centers for Disease Control and Prevention* PNU-1 (CDC PNU-1) is simpler and not invasive, compared to the CPIS.

Objective To evaluate the level of agreement between CDC PNU-1 and CPIS criteria in diagnosing VAP.

Methods This cross-sectional study was conducted in the PICU at Dr. Soetomo Hospital, Surabaya from June to October 2018. Subjects were children aged 1 month–18 years who had been intubated for more than 48 hours. The VAP diagnoses were made by CDC PNU-1 and CPIS criteria. The level of agreement between the two methods was evaluated by Cohen's Kappa test using SPSS Statistics Base 21.0 software.

Results Thirty-six subjects were evaluated using CDC PNU-1 and CPIS criteria. Subjects' mean age was 3.5 (SD 4.7) years. Amongst 19 patients with VAP, 14 were diagnosed by CPIS criteria and 17 were diagnosed by CDC PNU-1 criteria. The level of agreement between the CDC PNU-1 and CPIS criteria was good (Kappa 0.61; 95%CI 0.31 to 0.83). The CDC PNU-1 had sensitivity 0.85, specificity 0.77, positive predictive value (PPV) 0.70, and negative predictive value (NPV) 0.89.

Conclusion The CDC PNU-1 criteria has a good level of agreement with CPIS criteria in diagnosing VAP. **[Paediatr Indones. 2019;59:195-201; doi: http://dx.doi.org/10.14238/pi59.4.2019.195-201]**.

Keywords: *ventilator-associated pneumonia; VAP; criteria pulmonary infection score; CPIS; CDC PNU-1*

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in the PICU. The definition of VAP is pneumonia that develops in the patient who has been intubated and received mechanical ventilation for 48 hours or more.[1,2] Mechanical ventilation may increase the risk of hospital-acquired pneumonia (HAP) in the PICU by 6-21 times, with mortality rate of 33-50%. Variations may be associated with the patients' underlying diseases. A surveillance study by the *International Nosocomial Infection Control Consortium* (INICC) in several countries used clinical, radiological, and microbiological criteria and concluded that more VAP cases occurred in low-middle-income countries, such as India (36.2%), compared to upper-middle-income countries, such as Italy (6.6%).[3]

Post-mortem pulmonary histology and microbiological examination performed immediately after death is the gold standard in establishing a diagnosis of

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VAP. However, this examination is impossible to apply to the management of VAP patients. Several studies have been conducted to determine the best method for diagnosing VAP, the most common of which is the *Clinical Pulmonary Infection Score* (CPIS), which uses clinical, radiological, and microbiological criteria. Although the CPIS criteria require rather invasive methods, CPIS has a good diagnosis value (sensitivity 72% and specificity 85%).[4] A more recently-developed diagnostic tool that is simpler and non-invasive compared to CPIS is the *Centers for Disease Control and Prevention* (CDC) PNU-1. It has never been used in Indonesia. This CDC criteria is non-invasive and only uses clinical criteria, without microbiological examination. Since 2009, these criteria have been used in various institutions with specific advantages for certain age groups.[5]

Guidelines for diagnosis and management of VAP in pediatric patients is very limited.[6,7] The choice of simple, inexpensive, non-invasive, and fast diagnostic tools is needed, especially in low-income countries.

This study aimed to evaluate the level of agreement between CDC PNU-1 and CPIS criteria in diagnosing VAP.

Methods

A cross-sectional study was conducted in the PICU of Dr. Soetomo General Hospital, Surabaya, from June to October 2018. Subjects were children aged 1 month–18 years who were intubated and had mechanical ventilation for 48 hours or longer. The observations for 48 hours were carried out by assessing each item in each criteria (**Table 1** and **2**). Diagnoses of VAP were made by both CDC PNU-1 and CPIS criteria (VAP or no VAP). Ventilator-associated pneumonia was considered to be established for CPIS score >6. Exclusion criteria were the presence of pneumonia prior to ventilation, immunocompromised status (absolute neutrophil count or total white blood cell count < 500/mm^3), leukemia, lymphoma, HIV with CD4 < 200 cells/mm^3, or those who had a history of solid organ or hematopoietic stem cell transplant, splenectomy, cytotoxic chemotherapy, or steroid use (excluding inhaled steroids) daily for > 2 weeks on the date of VAP established.

This study was approved by the Ethics Committee at Dr. Soetomo Hospital. Characteristic data collected included age, gender, length of PICU stay, duration of mechanical ventilation, frequency of intubation, difficulty intubating, PRISM 3 score, and main disease. Subjects were evaluated for VAP by both criteria (**Tables 1** and **2**).

The level of agreement was analyzed by Cohen's Kappa statistic (κ), which is a robust tool for measuring observational correlation, taking into account the variation due to chance. Standard error for κ was calculated using the original equation proposed by Cohen.[10] Kappa values (κ) of <0.20 show poor agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good, and 0.81-1.00 very good agreement. Statistical analysis was performed using *IBM SPSS statistics version 20* software. Chi-square test was used to compare

Table 1. Clinical pulmonary infection score (CPIS) criteria[8]

CPIS	Skor
Temperature (°C)	
> or equal to 36.5 and < or equal to 38.4	0
> or equal to 38.5 and < or equal to 38.9	1
> or equal to 39 and < or equal to 36	2
Blood leukocytes, mm3	
> or equal to 4,000 and < or equal to 11,000	0
< 4,000 or > 11,000	1
+ band forms > equal to 50%	Add 1 point
Tracheal secretions	
Absence of tracheal secretions	0
Presence of non-purulent tracheal secretions	1
Presence of purulent tracheal secretions	2
Oxygenation: PaO2/FIO2, mmHg	
> 240 or ARDS	0
< or equal to 240 and no ARDS	2
(ARDS defined as PaO2/FIO2 , < or equal to 200, pulmonary arterial wedge pressure < or equal to 18 mmHg and acute bilateral infiltrates)	
Pulmonary radiography	
No infiltrate	0
Diffuse (or patchy) infiltrate	1
Localized infiltrate	2
Progression of pulmonary infiltrate	
No radiographic progression	0
Radiographic progression (after CHF and ARDS excluded)	2
Culture of tracheal aspirate	
Pathogenic bacteria cultured in rare or light quantity or growth	0
Pathogenic bacteria cultured in moderate or heavy quantity	1
Same pathogenic bacteria seen on Gram stain	Add 1 point

Table 2. CDC PNU-1 criteria[9]

Signs/symptoms/laboratory
For ANY PATIENT, at least one of the following: • Fever (>38.0°C or >100.4°F) • Leukopenia (≤4000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3) • For adults >70 years old, altered mental status with no other recognized cause And at least two of the following: • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (for example: O_2 desaturations (for example: PaO_2/FiO_2 < 240), increased oxygen requirement, or increased ventilator demand) ALTERNATE CRITERIA, for infants < 1 years old : Worsening gas exchange (for example : desaturation (for example oximetry < 94%), increased oxygen requirements, or increased ventilator demand) And at least three of the following : • Temperature instability • Leukopenia (< 4000 WBC/mm^3) or leukocytosis (> 15,000 WBC/mm^3) and left shift (>10% band forms) • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements • Apnea, tachypnea, nasal flaring with retraction of chest wall or nasal flaring with grunting • Wheezing, rales, or rhonchi • Cough • Bradycardia (<100 beats/min) or tachycardia (170 beats/min) ALTERNATE CRITERIA, for child >1 year old or ≤12 years old, at least three of the following: • Fever (>38. 0°C or >100. 4°F) or hypothermia (< 36. 0°C or <96.8°F) • Leukopenia (≤4000 WBC/mm^3) or leukocytosis (≥15,000 WBC/mm^3) • New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements • New onset or worsening cough, or dyspnea, apnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange (for example: O_2 desaturations [for example pulse oximetry < 94%), increased oxygen requirements, or increased ventilator demand)
Imaging test evidence
Two or more serial chest imaging test results with at least one of the following: New and persistent or Progressive and persistent • Infiltrate • Consolidation • Cavitation • Pneumatoceles, in infants ≤1 year old Note: In patients without underlying pulmonary or cardiac disease (for example: respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive imaging test result is acceptable

proportion and Mann-Whitney U test was used to compare quantitative variables.

Results

Of 50 mechanically-ventilated PICU patients during the study period, 36 met the inclusion criteria. Fourteen patients were excluded, 10 because of pneumonia prior to ventilation, 2 due to their immunocompromised status, and 2 because they died before a VAP diagnosis was established. The study flow chart is shown in **Figure 1**. Characteristics of subjects are listed in **Table 3**.

Nineteen patient were diagnosed as VAP with both criteria. Fourteen were diagnosed with VAP by CPIS and 17 patients by the CDC PNU-1 criteria. The most common bacterial cause of VAP was Acinetobacter baumanii, which was found in 6/36 children.

The CDC PNU-1 criteria showed a good level of agreement with CPIS (Cohen's κ=0.61; 95%CI 0.31 to 0.83; P<0.001). The CDC PNU-1 criteria had a sensitivity of 0.86 and a specificity of 0.77.

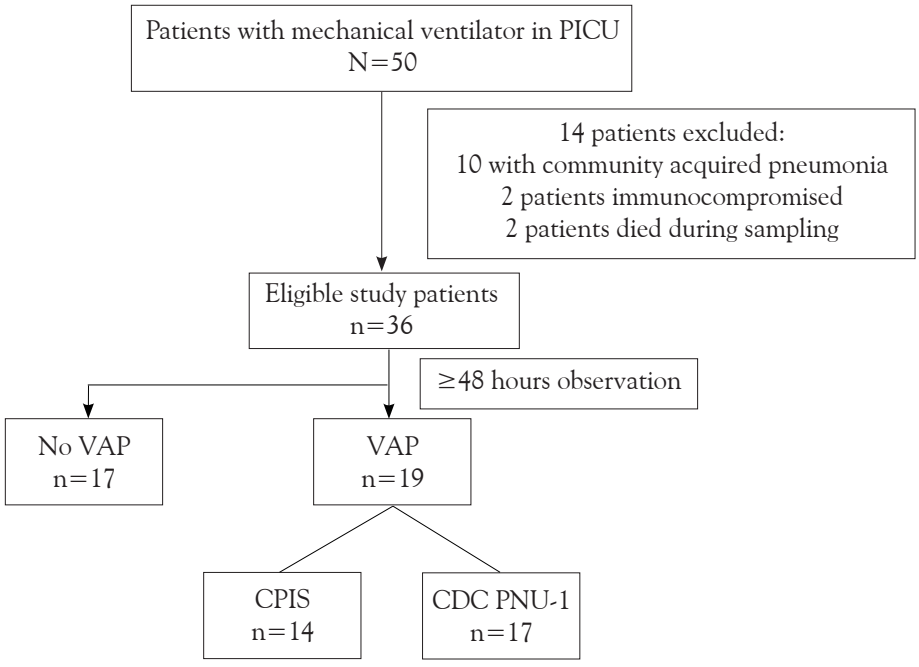

Figure 1. Study flow chart

Table 3. Characteristics of subjects

Characteristics	VAP		P value
	CPIS n=14	CDC PNU-1 n=17	
Gender			
Male	9	9	0.738
Female	5	8	
Mean age (SD), years	3.5 (4.7)		
Nutritional status			
Normal	8	9	0.431
Moderate malnutrition	3	5	
Severe malnutrition	3	3	
Mean PRISM 3 score (SD)	6 (5.2)		
Frequency of intubation			
< 3 times	13	15	0.906
>3 times	1	2	
Difficulty of intubation			
Yes	3	4	0.114
No	11	13	
Mean length of stay (SD), days	14 (15.9)		
Mean duration of ventilation (SD), days	12 (13.7)		
Main Disease			
Neurology	4	5	0.171
Cardiology	4	5	
Nephrology	1	3	
Hematology	2	2	
Gastroenterology	2	1	
Endocrinology	0	0	
Respirology	1	1	
Outcomes			
Survived	9	11	0.813
Died	5	6	

The positive likelihood ratio was 1.12 and negative likelihood ratio was 1.09.

Discussion

Pneumonia is the leading cause of nosocomial infections in the PICU, and the use of mechanical ventilators increases the risk of infection by 6-21 times. As many as 95% of pneumonia cases are nosocomial infections due to VAP, and about 20% die.[10,11] Ventilator-associated pneumonia is associated with increased morbidity, including longer durations of mechanical ventilation and PICU length of stay. Risk factors for developing VAP have been described in multiple studies. A previous study noted increased VAP rates in patients who had experienced witnessed aspiration, reintubation, prior antibiotic therapy, continuous enteral nutrition, and bronchoscopy.[12] Another study found that genetic syndromes, reintubation, and transport out of the PICU were independent predictors of VAP.[13] Srinivasan *et al.*[14] identified enteral nutrition, sedative/narcotic usage, presence of a gastric tube, female sex, prolonged mechanical ventilation, and post-surgical admission as independent risk factors for VAP or healthcare-associated pneumonia in PICUs. Other reported risk factors include immunodeficiency, neuromuscular blockade, blood product usage, or medications such as steroids, H_2 blockers, and metoclopramide.[5]

Guidelines for diagnosis and management of VAP in pediatric patients is currently very limited. Studies comparing assessments with CPIS and post-mortem pathological results showed no significant differences.[15,16] Similarly, a post-mortem study assessed the accuracy of VAP diagnoses by comparing clinical criteria to microbiology (CPIS), and reported sensitivity of 69% and specificity of 72%.[17] Most of researchers agree that pulmonary histological examination coupled with quantitative tissue culture can be an acceptable gold standard, but the method is considered too invasive and difficult for patients on mechanical ventilation.[17]

In developing countries, diagnosing VAP remains a problem, hence, a simple and accurate method is needed. Clinical criteria are still required for early diagnosis of VAP. Biopsy is accurate, but not applicable to small children, so the most widely-used diagnostic tool is CPIS (a gold standard). The Kappa agreement test was performed on data with categorical variables. Both of these criteria have the same ability if the value of agreement between the two variables was high. The kappa value between the CPIS and CDC PNU-1 was 0.61, indicating a good level of agreement. Hence, the CDC-PNU 1 criteria can be used as a diagnostic tool for VAP.

In contrast, Waltrick *et al.*[18] reported that the CDC method could not be used as a surveillance method (kappa value 0.47, sensitivity 37%, and specificity 100%, compared to CPIS). This low sensitivity of the CDC criteria in detecting VAP may have been related to several factors, such as age (subjects were >18 years of age), as well as inability of researchers to observe changes in ventilator settings and clinical changes in all VAP patients, other than the cut-off value. The cut-off CPIS score was also different in their study, at >7. In addition, their inclusion criteria were different as was their treatment protocol which included 30o patient elevation position, gastric ulcer prophylaxis, sedation, and the use of clorhexidin for oral hygiene.

Another study compared CDC surveillance method with CPIS and showed that only 14.5% of cases diagnosed with VAP using CPIS were identified using CDC PNU-1.[19] Their study differed from ours in that they studied adult patients and used a retrospective study design while we diagnosed prospectively in real time. They also had limitations in clinical observation, as they could not identify specific diagnostic criteria when compared with bedside clinical criteria (changes in mental status, purulent secretion), as well as possible false positive data.

In the absence of a gold standard for diagnosing VAP, clinical assessment currently remains important as a substitute. However, Wallace *et al.*[20] found that the system of scoring individuals was poor by assessing VAP clinically using the 2008 CDC-NHSN algorithm, with a low suitability value of $\kappa=0.19$. Their study was not appropriate for evaluating risk factors, because some patients had undergone kidney or bone marrow transplantation, had immunosuppressive diseases or chronic lung disease, which can increase the risk of VAP.

The definition of VAP depends on the integration of clinical findings, as well as radiographic and microbiological data, to make a diagnosis. Clinical

findings can be partially subjective, and therefore, susceptible to variability in documentation and interpretation. In addition, radiographic changes in chest photos can be caused by pathological processes other than pneumonia, or can resemble pneumonia from pulmonary contusions in trauma patients, to pulmonary edema and pleural effusion in heart failure patients. This problem is further complicated by the fact that radiography at times does not detect changes for weeks, potentially masking new processes. A previous study also support the finding that interpretation of chest radiographs can vary between clinicians.[21] The CDC definition of VAP is more subjective and clinical. Although there are many shortcomings such as high subjectivity and low specificity, our findings may have a significant impact if a combination of clinical and objective criteria are evaluated.[21]

Safdar *et al.*[22] studied 73 patients on mechanical ventilators. A total of 36 patients were diagnosed with VAP by the CDC criteria and 35 patients were diagnosed with VAP by the CPIS criteria. They found that the CPIS criteria had very good agreement with the CDC PNU-1 criteria (Cohen's κ 0.81; 95%CI 0.67 to 0.94). Comparison of the CDC criteria to CPIS had sensitivity 0.89 and specificity 0.91, with a positive likelihood ratio of 10.96 and a negative likelihood ratio of 0.12. They used the same exclusion criteria as our study, namely, the exclusion of patients suffering from pneumonia before ventilation and suspected pneumonia during the incubation period while intubated. They also used the same CPIS value cut-off of >6.

The subjects of this study were 14 children suffering from VAP with positive sputum culture results, where the results of the most bacterial culture were *Acinetobacter baumanii* found in 6/36 children. Gadappa *et al.*[23] reported that the most common organisms in early VAP are Acinetobacter baumannii and MRSA, whereas Pseudomonas aeruginosa is the most common organism in late VAP. They noted a no significant association between positive culture and death in VAP (P=0.067). Other studies also reported that Acinetobacter was the most common isolate in VAP.[24-26]

The limitation of this study was that the CDC PNU-1 criteria, while a good early diagnosis tool, did not take into account sputum culture examination, so determination of antibiotic therapy is empirical. Thus, culture examination is still recommended in order to determine the most appropriate subsequent antibiotic therapy.

In conclusion, CDC PNU-1 criteria can be used as an initial diagnostic tool to establish VAP diagnosis, followed by confirmation using other criteria that are close to the gold standard.

Conflict of Interest

None declared.

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