

Interrater Variability in Identifying Ventilator Associated Pneumonia Using Six Different Definitions

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ABSTRACT

OBJECTIVE: There is no widely accepted standard definition for Ventilator Associated Pneumonia (VAP). The reliability of the current definitions in use remains controversial. Our objective was to assess the reliability of six commonly used VAP definitions: The Loose, The Rigorous, The Modified Clinical Pulmonary Infection Score (CPIS), The Canadian Critical Care Trials Group (CCCTG), The International Sepsis Forum Consensus (ISFC) and The Center for Disease Control and Prevention (CDC).

DESIGN: We examined the electronic health records of all the consecutively admitted adult patients at our institution who received invasive mechanical ventilation (IMV) for ≥ 48 hours, from January 2006 through December 2006. Patients were excluded if they developed pneumonia within the first 48 hours or if they had a tracheostomy before IMV. Two expert intensivists independently reviewed the following data for each patient: indications and duration of IMV, vital signs, oxygen requirements, the frequency of respiratory suctioning, amount, color and consistency of secretion, ventilator settings, leukocyte count, microbiologic and radiographic data. Interreviewer reliability in diagnosing VAP independently were compared using Cohen's-Kappa statistics.

RESULTS: A total of 115 patients met the initial inclusion criteria of which 47 patients were excluded (40 had pneumonia on presentation, 6 developed pneumonia within 48 hours and 1 had a tracheostomy on admission). The inter-reviewer agreement Kappa for the Loose, the Rigorous, CPIS, CCCTG, ISFC and CDC definitions for VAP were 0.22, 0.49, 0.33, 0.41, 0.38 and 0.68 respectively.

CONCLUSION: The CDC definition of VAP proved to be statistically more reliable than other tested definitions of VAP, as demonstrated by the lowest interrater variability between two independent reviewers.

KEYWORDS

Ventilator associated pneumonia; VAP; definition; interrater variability; intensive care unit

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in mechanically ventilated intensive care unit (ICU) patients.¹ The data collected by National Healthcare Safety Network (NHSN) from 2006 and 2008 revealed an incidence of VAP that ranged from approximately 3 per

1000 ventilator days in medical/surgical teaching ICUs to almost 11 per 1000 ventilator days in burn units.² Using the same definition, subsequent data from 2011 demonstrated VAP rates of 1.1 per 1000 ventilator days in medical/surgical teaching ICUs and approximately 5 per 1000 ventilator days in burn units.³ Various institutions have traditionally used the CDC definition to identify VAPs for reporting

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nosocomial infections to the NHSN, however, several other definitions have been used for both clinical and research applications. There exists no consensus for a gold standard definition for VAP and the reliability of currently used definitions remains in question.⁴⁻⁷ There are six definitions that are commonly used for VAP: the Loose,⁸ the Rigorous,⁸ the Modified Clinical Pulmonary Infection Score (CPIS),^{8,9} the Canadian Critical Care Trials Group (CCCTG),¹⁰ the International Sepsis Forum Consensus (ISFC)¹¹ and the Center for Disease Control and Prevention (CDC).¹² Despite the abundance of literature on VAP, there is a paucity of studies that compare the difference in VAP incidence using different clinical definitions of VAP in the same patient population.^{7,13}

Therefore, we conducted a population-based study to test the interrater variability of six commonly used VAP definitions; the Loose, the Rigorous, CPIS, CCCTG, ISFC and CDC.

METHODS

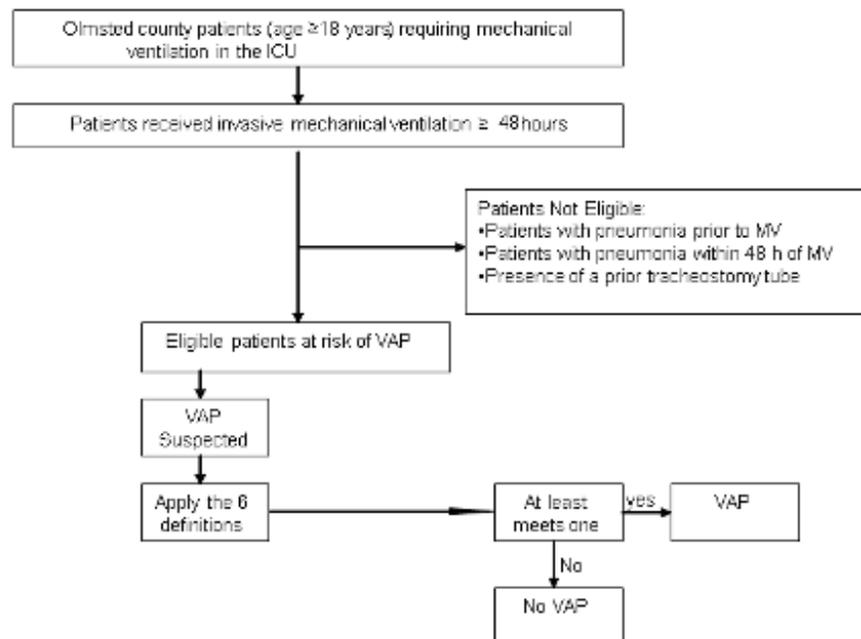
We conducted a retrospective electronic medical record (EMR) chart review of all the adult patients (≥ 18 years) from Olmsted County who were admitted to the Intensive Care Units (ICU) at our center, and required invasive mechanical ventilation (IMV) for > 48 hours, from January 1, 2006 through December 31, 2006. The Institutional Review Board (IRB) approved the study (#10-006656). After receiving the IRB approval, we identified patients who gave consent for the use of their EMR for research, and met the inclusion criteria. Patients who had pneumonia on presentation, developed pneumonia within 48 hours from admission or had a tracheostomy upon admission were

excluded. Two expert intensivists (Reviewers A and B) independently screened the EMRs of all the included patients to make a diagnosis of VAP (figure 1). The reviewers discussed the different definitions at the beginning of the study to assure mutual understanding of the definitions. The reviewers screened patients' records for changes in temperature, change in oxygen requirements, change in WBC count, and sputum cultures. If any change was detected, the reviewers would subject the case to the various definitions of VAP to determine which definitions applied. During the review process there was no direct discussion between the reviewers pertinent to any case in the study.

In addition to the clinical, microbiological, radiographic data, and laboratory reports, patients' demographics, baseline conditions, comorbidities, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE III] score, organ

FIGURE 1. The flowchart showing the method for diagnosing ventilator associated pneumonia.

Footnote: ICU=intensive care unit, MV=mechanical ventilation; VAP= ventilator associated pneumonia



dysfunction (Sequential Organ Failure Assessment [SOFA] score, reasons for MV, intubation type, infection severity (sepsis, severe sepsis or septic shock),¹⁴ modified CPIS score,¹⁵ documented witnessed aspiration, prescription of appropriate initial antimicrobial treatment, and compliance with Institute of Health Care Improvement ventilator bundle were abstracted from the EMR. Other important variables that were abstracted included date of admission, admission diagnosis, date and location of intubation, indication for IMV, duration of IMV, vital signs, oxygen requirements, frequency of respiratory suctioning, amount, color and consistency of secretion, ventilator settings, leukocytes, potential sources of infection, date of extubation and date of dismissal or expiration and nutritional status. Whenever the constellation of clinical, laboratory, microbiologic and radiographic data suggested the development of pneumonia the reviewers independently would apply the six definitions to determine whether or not a given patient met the criteria for one or more definition.

A patient identified as having VAP by any definition is considered as a positive case of VAP. The detailed explanation about the six VAP definitions is given in the online supplement.

STATISTICAL ANALYSIS

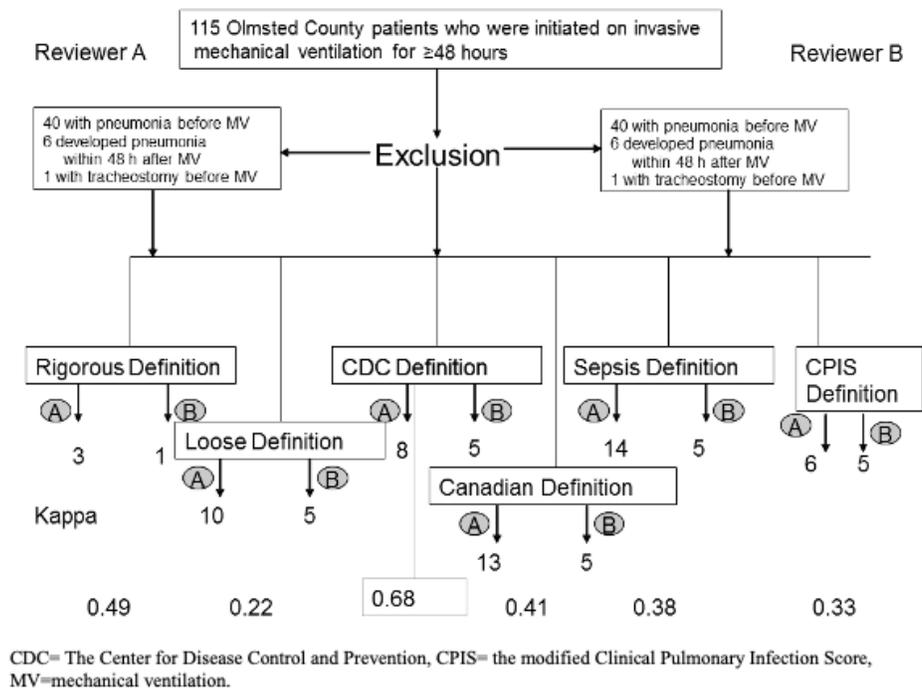
The categorical data was summarized as counts and percentage, whereas, continuous data was summarized as median (interquartile range [IQR]). Student's-t test and Mann-Whitney U test were used to compare the continuous variables with normal distribution and skewed distribution, respectively, whereas Chi-square and Fisher's exact test were used to compare the categorical variables, depending on the size of the variable in the contingency table. Cohen's kappa statistics were used

to estimate the inter-reviewer variability for each one of the six definitions for VAP between the two reviewers.¹⁶ A kappa value of <0.2 was considered to reflect poor inter-reviewer agreement, 0.21-0.40 was considered fair, 0.41-0.60 was considered moderate, 0.61-0.80 was considered good and >0.80 was considered excellent.¹⁶ For this study, we defined "reliability" as the VAP definition with the lowest level of interrater variability between two independent observers. It is important to know that reliability does not imply "accuracy" of VAP diagnosis (whether a patient has or does not have VAP) – only that observers using a particular definition arrived at the same diagnostic conclusion. All of the analyses were performed using JMP 9.0 software (SAS Institute; Cary, NC).

RESULTS

During the study, 115 patients met the initial inclusion criteria. After thorough independent revision by both reviewers, the reviewers excluded 47 patients (40 had pneumonia on presentation, 6 developed pneumonia within 48 hours and 1 had a tracheostomy on admission) (Figure 2).

FIGURE 2. The interrater variability of different ventilator associated pneumonia definitions.



The table shows the differences in baseline characteristics, causes for mechanical ventilation, comorbidities, and outcomes between the patients with VAP (all the possible cases identified by both the authors) and without VAP. There was no difference in the baseline characteristics and severity of illness between the VAP and non-VAP patients. Most of the patients with VAP were admitted in the surgical ICU (81%) as compared to the patients without VAP (55%), $p=0.06$. The most common antecedent documented conditions in VAP patients were coma (43%), postoperative state (19%), cardiogenic pulmonary edema (10%) and acute respiratory distress syndrome (ARDS) (10%) (Table).

VAP patients were re-intubated more often than non-VAP patients (29% vs. 6%, respectively) $p=0.02$. There was no difference in the mortality at hospital discharge among the VAP and non-VAP patients

TABLE: Differences in baseline characteristics, causes, comorbidities, and outcomes between ventilator associated pneumonia (VAP) and non-VAP patients

Demographics	VAP (n=21)	Non-VAP (n=47)	P-value
Age (y)	67 (49-81)	67 (46-77)	0.87
Sex: male	13 (62)	28 (60)	0.86
Race: Caucasian	17 (81)	42 (89)	0.44
Body mass index	27 (24-32)	24 (20-32)	0.67
APACHE III score	76 (68-98)	76 (53-94)	0.91
SOFA score on day one	7 (5-9)	6 (4-8)	0.27
ICU type: Medical	4 (19)	21 (45)	0.06
Surgical	17 (81)	26 (55)	
Cause for mechanical ventilation			
Cardiogenic pulmonary edema	2 (10)	3 (6)	0.64
Acute respiratory distress syndrome	2 (10)	5 (11)	0.99
Trauma	1 (5)	4 (9)	0.99
Coma	9 (43)	8 (17)	0.02
Cardiac arrest	1 (5)	4 (9)	0.99
Post-Surgery	4 (19)	8 (17)	0.99
COPD exacerbation/acute asthma	1 (5)	6 (13)	0.42
Comorbid conditions			
Pulmonary diseases	4 (19)	15 (32)	0.38
Congestive heart failure	5 (24)	7 (15)	0.37
Diabetes	8 (38)	11 (23)	0.21
Moderate to severe renal disease	3 (14)	6 (13)	0.99
Malignancy	5 (24)	10 (21)	0.82
Lymphoma			
Outcomes			
Reintubation	6 (29)	3 (6)	0.02
ICU length of stay (d)	13.6 (10.1-15.7)	6.6 (5.1-8.8)	<0.01
Hospital length of stay (d)	20.1 (15.8-27.9)	12.3 (8.9-18.6)	0.3
IMV days	7.2 (1.6-11.3)	3.5 (2.1-5.4)	0.01
Hospital mortality	6 (29)	10 (21)	0.51

*Data are presented as No. (percentage) or median (interquartile range). APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary diseases; ICU = Intensive Care Unit; IMV = Invasive mechanical ventilation; SOFA = Sequential Organ Failure Assessment score

($p=0.51$), however, VAP patients were mechanically ventilated for a longer duration ($p=0.01$) and had longer length of stay in the ICU ($p < 0.01$) as compared to non-VAP patients.

For cases that were suspected to have developed VAP, reviewer A determined that 10, 3, 6, 13, 14 and 8 cases met the Loose, the Rigorous, CPIS, CCCTG, ISFC and CDC Definition, respectively. Whereas, the reviewer B determined that 5, 1, 5, 5 and 5 met The Loose, The Rigorous, CPIS, CCCTG, ISFC and CDC Definition, respectively. The kappa value for the Loose, the Rigorous, CPIS, CCCTG, ISFC and CDC definitions between the two reviewers was 0.22, 0.49, 0.33, 0.41, 0.38 and 0.68 respectively (Figure 2).

DISCUSSION

We evaluated the interrater/reviewer variability of six common definitions used to identify VAP in the ICU. We observed large inter-reviewer variability when diagnosing VAP from medical record review. Out of six definitions of VAP, only the CDC definition demonstrated interrater variability between the two reviewers. The Rigorous and CCCTG definitions were the most reliable, whereas, the Loose, CPIS and ISFC definitions were only fairly reliable in identifying VAP. To the best of our knowledge, this is the first study that measured the interrater variability in VAP definitions.

Physicians rely on integrating clinical findings, laboratory and microbiologic data to establish a diagnosis. The clinical findings can be in part subjective and hence, vulnerable to variability in interpretation. Radiographs are documented and interpreted. Radiographic changes can be due to normal physiological processes other than, but resembling pneumonia, ranging from lung contusion in trauma to pulmonary edema and pleural effusions in heart failure patients. The matter is complicated by the fact that some of the radiographic changes can persist for weeks, potentially masking pneumonia. Previous studies support the finding that the interpretation of chest radiographs can vary significantly.^{17,18} Treating physicians and intensivists may also interpret chest radiographs differently.¹⁹ Furthermore, microbiologic data can be difficult to interpret, as mechanically ventilated



patients' airways invariably become colonized with hospital flora. ICU patients commonly receive prophylactic, empiric or therapeutic antimicrobials, which can result in change in patients' flora and select out for resistant opportunistic and pathogenic bacteria. They can also suppress bacterial growth and decrease the yield of cultures. All of these issues have to be taken in consideration when processing microbiologic information in this patient population. Some authorities have proposed that respiratory cultures obtained invasively via bronchoscopy should be the gold standard in making the diagnosis of VAP. This notion is impractical to apply in clinical practice. The invasive nature of the procedure, the time it takes to perform, and the cost of procedure, are certainly barriers to its utility in investigating VAP. Furthermore, the level of training and expertise of the reviewer can affect the processing of data necessary to diagnose VAP. In one study looking at these two variables, inter-observer agreement was moderate at best when applying the CDC definition.²⁰ Relying on objective data to diagnose VAP may be a better way to standardize reviewers and institutions reporting for epidemiologic purposes, however, from a clinical perspective it may be difficult, due to the need for assessing various parameters to diagnose VAP.

Several governing bodies are interested in institutional VAP rates. The mandate for public reporting is on the horizon. The way Centers for Medicare and Medicaid Service will consider VAP rates in the reimbursement process remains unclear. In addition, it remains unclear if these governing bodies will use epidemiologic criteria, i.e. NHSN reports, or administrative data, i.e. ICD-9 coding, to compare different institutions in quality of care performance measures. The major concern with the use of administrative databases to measure VAP incidence rates is the underreporting of VAP cases in these databases,¹⁹ which falsely lowers the incidence of VAP in the community. For this reason, the CDC introduced new possible/probable VAP definitions that address various events that could affect patients while on mechanical ventilation.²¹ The new definition is rather a group of definitions that are meant to distinguish ventilator associated events that are not necessarily infectious in nature from those that are infectious in nature. Those that are infectious in nature are then further classified into possible and probable VAP. In the most simple way to understand

the new definitions: for a patient to be considered to have a possible or probable VAP, he or she would have to have at least two days of invasive mechanical ventilation with stable fraction of inspired oxygen (FiO₂) and positive end-expiratory pressure (PEEP) for at least two days. He or she would have to then develop a change in either FiO₂ or PEEP (>20% increase or >3 cm H₂O respectively) and the change be sustained for at least two days, and accompanied by evidence of inflammatory response (leukocytosis and/or fever) or clinical suspicion of infectious process for which antibiotics are initiated and continued along with purulent respiratory secretions and/or positive respiratory secretions cultures for a bacterial pathogen. The new definition focuses on changes in oxygenation as a trigger to investigate a possible VAP. It aims to distinguish between infectious and non-infectious complications of mechanical ventilation, and acknowledges the fact that VAP diagnosis is not always clear-cut and can be possible or probable. The new definitions are expected to be more objective and less susceptible to individual variation in interpretation, but will need to be studied further. At the time we conducted our study, the new CDC definitions were not available.

Our study has both strengths and weaknesses. Major strengths are 1) the population-based nature of the study, designed specifically to study the interrater variability of the VAP definitions eliminates the referral and sampling biases seen in the observational studies; 2) we used a comprehensive approach to diagnose the VAP cases and used a standardized operating protocol throughout the study, which enhanced the quality of our study. This study also has limitations. Only two observers participated and there was a wide variability between each observer collectively using any definition of VAP. It is retrospective which may lend to confounding and unmeasured bias. To account for these biases we used quality measures like a standardized protocol for data gathering, diagnosis of the VAP and data extraction. Although the study was conducted at a single center, which raises some concerns regarding the generalizability of the results, Mayo Clinic is the only center providing critical care services in the Olmsted County.²² Furthermore, findings from the Olmsted County population have shown to be generalizable to the Upper Midwest population and provide invaluable



information regarding various diseases, which are consistent with the national data.^{23,24}

CONCLUSION

The CDC definition of VAP proved to be statistically more reliable than other tested definitions of VAP as demonstrated by the lowest interrater variability between two independent reviewers.

SUPPLEMENT

The six definitions used in this study:

1. Loose definition: chest x-ray infiltrate (unilobar, unilateral, or bilateral) with 2 of the following 3 findings: temperature, $>38^{\circ}\text{C}$ or $<35.5^{\circ}\text{C}$; white blood cell count, $>10,000/\mu\text{L}$ or $<4000/\mu\text{L}$; or purulent respiratory secretions.
2. Rigorous definition: chest x-ray infiltrate (unilobar, unilateral, or bilateral) with all of the following 3 findings: temperature, $>38^{\circ}\text{C}$ or $<35.5^{\circ}\text{C}$; white blood cell count, $>10,000/\mu\text{L}$ or $<4000/\mu\text{L}$; or purulent respiratory secretions.
3. The modified clinical pulmonary infection score (CPIS) ≥ 6 .

The modified clinical pulmonary infection score

Criterion	Range	Score
Temperature,	≥ 36.5 and ≤ 38.4	0
	≥ 38.5 and ≤ 38.9	1
	≥ 39.0 and ≤ 36.0	2
Blood leukocyte, mm^3	$\geq 4,000$ and $\leq 11,000$	0
	$<4,000$ or $>11,000$	1
	+band forms ≥ 500	2
Tracheal secretions	Absence	0
	Presence and non-purulent (color: white or light-yellow)	1
	Presence and purulent (color: yellow, green or brown)	2
Oxygenation, $\text{PaO}_2/\text{FiO}_2$	>240 or ARDS	0
	≤ 240 and no evidence of ARDS	2
Pulmonary radiography	No infiltrate	0
	Diffused (or patchy) infiltrate	1
	Localized infiltrate	2
Culture of tracheal aspirate (semi-quantitative: 0-1-2 or 3+)	Pathogenic bacteria cultured $\leq 1+$ or no growth	0
	Pathogenic bacteria cultured $>1+$	1
	+same pathogenic bacteria seen on the Gram stain $>1+$	2

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CHF = congestive heart failure; $\text{PaO}_2/\text{FIO}_2$ = ratio of arterial oxygen pressure to fraction of inspired oxygen.

4. The Canadian Critical Care Trials Group classification

A. Definite bacterial pneumonia: at least one of the following three criteria was fulfilled:

1. Positive result of pleural fluid culture
2. Rapid cavitation of the lung infiltrate as determined by computed tomography or
3. Histopathologic demonstration of pneumonia (consolidation with intense polymorphonuclear leukocyte accumulation in bronchioles and adjacent alveoli involving several adjacent low-power microscopic, with or without tissue necrosis) during biopsy or autopsy.

B. Probable bacterial pneumonia: if none of the above criteria were met yet patient had cultures of specimens obtained using a bronchoalveolar lavage which grew at least one organism in significant concentration ($>10^4$ cfu/ml).

C. Possible pneumonia: if none of the above criteria were met yet patient's chest radiograph, sputum culture, temperature, white blood cell count and clinical course were consistent with pneumonia.



- D. **No pneumonia:** if in the opinion of the study investigator, the patient's course was not compatible with pneumonia.
5. The International Sepsis Forum Consensus definition
1. **Microbiologically confirmed:** if fulfilled one of the following criteria
 - a. The patient must have a new or progressive radiographic infiltrate, along with a high clinical suspicion of pneumonia (or a CPIS of ≥ 6 , using a Gram stain of a lower respiratory tract sample) plus a definite cause established by the recovery of a probable etiologic agent from a) an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate);
 - b. The recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *Mycobacterium tuberculosis*, *Legionella* species, influenza virus, or *Pneumocystis jirovecii* (carinii));
 - c. Recovery of a likely/possible respiratory pathogen in high concentrations using quantitative cultures of a lower respiratory tract sample (endotracheal aspirate, BAL, or protected specimen brush)
 - d. Positive serology.
 2. **Probable:** The patient must have a new or progressive radiographic infiltrate along with a high clinical suspicion of pneumonia (or a CPIS of ≥ 6 , using a Gram stain of a lower respiratory tract sample) plus detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, endotracheal or bronchoscopic aspirate, or quantitatively cultured bronchoscopic BAL fluid or brush catheter specimen), but in concentrations below the diagnostic threshold, or the presence of a negative lower respiratory tract culture if collected within 72 hours after starting a new antibiotic regimen.
 3. **Possible:** Abnormal chest radiograph of uncertain cause, in a patient with a low or moderate clinical suspicion of pneumonia, but with microbiological or serological

evidence of definite or probable pneumonia (as defined above).

6. The Center for Disease Control and Prevention (CDC).

Clinical diagnosis of VAP was defined as the presence of new or progressive and persistent infiltrates, or consolidation, or cavitations on the chest radiograph, and at least 1 of the following: fever $>38^{\circ}\text{C}$ with no other recognized cause, leukocytosis ($\geq 12.0 \times 10^9/\text{L}$) or leukopenia ($<4.0 \times 10^9/\text{L}$), or altered mental status with no other cause in ≥ 70 years old; and at least 2 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 sound, worsening gas.

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