

Microbiological Etiology and Detection of Drug-Resistant Bacteria in Pneumonia in Patients with Organophosphate Poisoning in the Intensive Care Unit

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Purpose: Organophosphate (OP) poisoning, a frequent method of suicide in the Asia-Pacific region and rural areas, inhibits cholinesterase (ChE), causing an acute cholinergic crisis. Pneumonia occurs in 20–50% of these cases, contributing to disease severity and mortality. However, data on the causative pathogens and the risk of drug-resistant bacteria in this patient population are limited. Thus, our study aimed to address these gaps.

Patients and Methods: This retrospective cohort study (April 2011–March 2023) investigated patients admitted to the intensive care unit (ICU) or emergency medical center at Niigata University Medical & Dental Hospital with acute OP poisoning. Data on patient demographics, pneumonia diagnosis, sputum culture results, prior antibiotic use, and risk factors for drug-resistant bacteria were collected. We also analyzed the detection rates of methicillin-resistant *Staphylococcus aureus* and SPICE (*Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*) organisms.

Results: Among the 21 patients with OP poisoning, 13 (62%) developed pneumonia and received antibiotic treatment. They had a longer ICU stay, higher Sequential Organ Failure Assessment scores on admission, and lower serum ChE activity (<100 IU/L). Gram-negative bacilli (GNB) were observed in five sputum cultures from 12 patients with pneumonia, with *Pseudomonas aeruginosa* isolated from three cases. None of the patients had known risk factors for drug-resistant bacteria.

Conclusion: Pneumonia in patients with OP poisoning was predominantly caused by GNB, particularly *P. aeruginosa*. Thus, despite the absence of known risk factors for drug-resistant bacteria, clinicians should consider the possibility of resistant pathogens when selecting empirical antibiotic therapy for pneumonia in these patients.

Keywords: pesticide poisoning, pulmonary infection, drug-resistant pathogens, *Pseudomonas aeruginosa*

Introduction

Organophosphate (OP) compounds are widely used as pesticides, and ingestion (accidental and intentional) can lead to poisoning. Due to their low cost and easy accessibility, OP poisoning is a common method of suicide in the Asia-Pacific region and rural areas.^{1,2} Severe pesticide poisoning is rare in developed countries, except for Japan, where cases peaked in the 1980s.^{3,4} Although the rate of pesticide-related suicides has declined, OP poisoning is a serious medical concern, often leading to critical illness and death.⁵

OP compounds inhibit esterases, including cholinesterase (ChE). This results in excess acetylcholine, causing an acute cholinergic crisis characterized by a toxidrome with muscarinic and nicotinic features.⁶ Loss of consciousness and bronchorrhea lead to pneumonia in 20–50% of cases, which is associated with disease severity.^{5,7,8} The causes of this pneumonia

include aspiration of excessive secretions and improper gastric lavage or ventilator management. However, unlike ventilator-associated pneumonia (VAP), which develops against a background of airway colonization and biofilm formation, it may occur at an earlier stage.⁹ Such a difference in onset timing can influence the microorganisms causing the pneumonia.

Community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and VAP are recommended to be empirically treated based on the risk of bacteria developing drug resistance.^{10,11} However, each predictive performance has its limitations, and uniform empirical broad-spectrum therapy may result in excessive or insufficient treatment.^{12,13} To ensure timely initiation of appropriate treatment, methods that enable earlier identification of causative bacteria and strategies tailored to individual patient risk are warranted.¹⁴

Prevention and prompt treatment of pneumonia in patients with OP poisoning is crucial. However, the causative pathogens of pneumonia in cases of OP poisoning have not been investigated, and there is no evidence-based guidance for empirical therapy. Thus, this study aimed to investigate the microbiological profiles of patients with OP poisoning who developed pneumonia and assess the risk of antimicrobial-resistant bacteria.

Materials and Methods

Study Design

We performed a retrospective cohort study on patients with acute OP poisoning admitted to the intensive care unit (ICU) or emergency medical center at Niigata University Medical & Dental Hospital between April 2011 and March 2023. Acute OP poisoning was diagnosed based on the exposure history, characteristic clinical symptoms, and decreased serum ChE activity. In each case, detailed notes were taken from all relatives regarding the circumstances surrounding the poisoning. The specific OP compounds involved were not analyzed due to the limited availability of such information in the medical records.

Data Collection

We used the patients' electronic medical records to collect clinical and demographic data, including age, sex, medical history, use of pralidoxime iodide or atropine, Sequential Organ Failure Assessment (SOFA) score and serum ChE activity at admission, length of stay in the ICU, pneumonia, A-DROP (advanced age, dehydration, respiratory failure, orientation disturbance, and low blood pressure) score at pneumonia onset, antibiotics and duration of administration, and mortality. Pneumonia was diagnosed by the attending physician based on clinical symptoms and chest X-ray findings. All cases were retrospectively confirmed by an independent physician by identifying new infiltrates on chest X-rays and reviewing the medical records for accompanying signs of lower respiratory tract infection (eg fever, cough, sputum production, dyspnea, and desaturation). HAP is defined as pneumonia that develops more than 48 h following admission. VAP is defined as pneumonia that develops more than 48 h following endotracheal intubation. No exclusion criteria have been established.

In cases of OP poisoning where pneumonia developed, additional data were recorded, including the timing of sputum culture collection, Gram stain results, identified microorganisms, and antimicrobial use. A polymicrobial Gram stain pattern was defined as the presence of mixed bacteria (eg gram-positive cocci and gram-negative bacilli [GNB] with no predominant pathogen). Antimicrobial susceptibility testing was conducted in accordance with the Clinical and Laboratory Standards Institute guidelines available during the study period.

Risk of Drug-Resistant Bacteria

The study primarily focused on cases of pneumonia where the causative organism was identified as methicillin-resistant *Staphylococcus aureus* (MRSA) or a SPICE (*Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*) organism. *Klebsiella aerogenes* was reclassified from *Enterobacter* to *Klebsiella* in 2017.^{15,16} However, owing to its similarities with *Enterobacter*, it is considered a SPICE organism. These drug-resistant pathogens (DRP) often produce AmpC β -lactamases.¹⁷ We followed the 2024 Japanese Respiratory Society (JRS) guidelines for adult pneumonia management¹⁸ to assess the presence of known risks for DRP in patients with pneumonia, including prior antimicrobial use (within the past 90 days), hospitalization history (within the past 90 days), previous detection of drug-resistant bacteria (within the past year), immunodeficiency, use of a gastric acid-suppressive agent, chronic respiratory disease, tube feeding, and a nonambulatory status. Immunodeficiency was defined as any of the following: neutropenia

(<500/ μ L); use of steroids, immunosuppressants, or biologics; human immunodeficiency virus infection; hematopoietic stem cell transplantation; solid organ transplantation; or primary immunodeficiency. We calculated the CAP-DRP score based on these risk factors per a previous study on the risk of DRP in cases of CAP.¹⁹

Statistical Analysis

All statistical analyses were performed using JMP Pro 18 (SAS Institute Inc., NC, USA). The Shapiro–Wilk test was used to assess normality in continuous variables. Non-normally distributed data were reported as the median and interquartile range (IQR). Wilcoxon rank-sum tests were used for continuous variables and Fisher exact test for categorical variables. The Cochran–Armitage trend test was performed to evaluate the associations between sputum culture submission timing and culture results. P-values <0.05 were considered statistically significant.

Ethics Statement

This study complied with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Niigata University Medical and Dental Hospital (approval number: #2022-0307, approval date: 2023-3-20). The requirement for written informed consent was waived because this retrospective study analyzed the test results obtained from electronic medical records, and there was no need to perform additional invasive procedures. The study purpose and opportunities to opt out were posted on the hospital's website.

Results

Patient Characteristics

Among the 21 patients with OP poisoning, 13 (62%) received antimicrobial treatment for pneumonia (Table 1). Most of the patients with pneumonia (12/13, 92%) required intubation and mechanical ventilation due to impaired consciousness or bronchorrhea. Patients with pneumonia had significantly longer ICU stays [21 (13–38) vs 5 (2–10), $P = 0.0059$], higher SOFA scores on admission [5 (2–9) vs 2 (0–4), $P = 0.015$], and lower ChE activity [8 (3–30) vs 191 (7–271),

Table 1 Characteristics of Patients with OP Poisoning with and Without Pneumonia

Patient Characteristics	With Pneumonia (n = 13)	Without Pneumonia (n = 8)	P-value
Age (years), median (IQR)	76 (62–82)	70 (66–82)	0.78
Female, n (%)	7 (54)	1 (13)	0.085
Mental disorders, n (%)	6 (46)	3 (38)	1.00
Comorbidities, n (%)	2 (15)	3 (38)	0.32
SOFA score on admission, median (IQR)	5 (2–9)	2 (0–4)	0.015
Serum cholinesterase (U/L), median (IQR)	8 (3–30)	191 (7–271)	0.036
Mechanical ventilation, n (%)	12 (92)	4 (50)	0.048
Renal replacement therapy, n (%)	1 (8)	0	1.00
Use of pralidoxime iodide, n (%)	9 (69)	3 (38)	0.21
Use of atropine, n (%)	6 (46)	1 (13)	0.18
Gastric lavage, n (%)	11 (85)	5 (63)	0.32
Number of days in ICU, median (IQR)	21 (13–38)	5 (2–10)	0.0059
Mortality, n (%)	2 (15)	1 (13)	1.00

Note: P-values <0.05 were considered statistically significant.

Abbreviations: IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

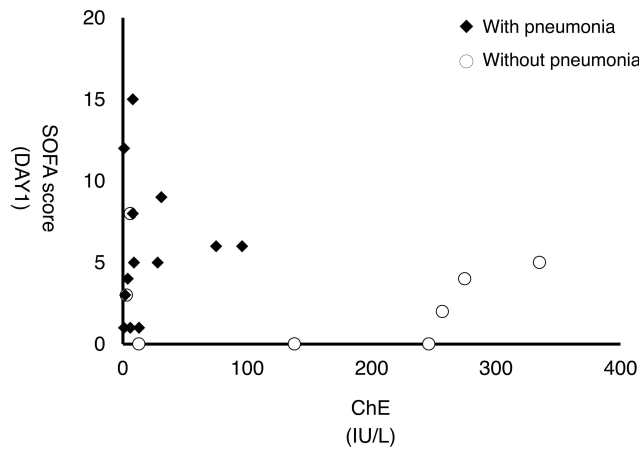


Figure 1 Relationship between SOFA scores and ChE levels. Among patients with organophosphate poisoning, those with pneumonia had higher SOFA scores and lower ChE levels.

Abbreviations: ChE, cholinesterase; SOFA, Sequential Organ Failure Assessment.

$P = 0.036$] than patients without pneumonia. The number of patients who underwent gastric lavage was higher in those with pneumonia than those without; however, this was not statistically significant [11(85) vs 5(63), $P = 0.32$]. Our findings revealed that the lower the serum ChE activity, the higher the SOFA score at admission and the more likely the patient was to have pneumonia (Figure 1).

Sputum Gram Stain and Culture Results

Sputum samples were collected from 12 patients with OP poisoning who developed pneumonia (Table 2). All samples were aspirated sputum or endotracheal aspirates. Bronchoalveolar lavage was not performed. Gram stains predominantly

Table 2 Bacteria Detected in Patients with Pneumonia (n = 13) and Details of Antimicrobial Therapy

Patient No.	Gram Stain	Culture		Initial Antibiotics	Antibiotic Escalation
		MRSA	SPICE Organism ^a		
1	Not identified	Not identified	<i>Citrobacter diversus</i>	A/S	No
4	GNB	Not identified	<i>Enterobacter cloacae</i> , <i>Pseudomonas aeruginosa</i>	A/S	Yes (P/T)
5	Polymicrobial ^b	Not identified	Not identified	A/S	No
6	Not tested	Not tested	Not tested	A/S	No
8	GNB	Not identified	<i>Pseudomonas aeruginosa</i>	A/S	Yes (MEPM)
9	Polymicrobial	Not identified	Not identified	A/S	No
10	GNB	Not identified	Not identified	A/S	No
14	GPC	Not identified	Not identified	A/S	No
15	GNB	Not identified	<i>Pseudomonas aeruginosa</i>	A/S	Yes (P/T)
16	Polymicrobial	Not identified	Not identified	A/S	No
17	GPC	Not identified	Not identified	P/T	No
18	Polymicrobial	Not identified	Not identified	A/S	No
19	Polymicrobial	Not identified	<i>Klebsiella aerogenes</i>	A/S	No

Notes: ^aSPICE organisms include the following: *Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*, including *Klebsiella aerogenes*.

^bMultiple staining or morphological patterns of bacteria detected by Gram staining.

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; A/S, ampicillin/sulbactam; GNB, gram-negative bacilli; P/T, piperacillin/tazobactam; MEPM, meropenem; GPC, gram-positive cocci.

showed GNB or polymicrobial patterns (GNB in 4/13 patients and polymicrobial patterns in 5/13). Although MRSA was not isolated, *P. aeruginosa* was identified in three cases, all of which showed GNB on Gram staining. Of the three *Pseudomonas aeruginosa* isolates, one demonstrated intermediate resistance to ceftazidime while remaining susceptible to other anti-*Pseudomonas* antibiotics. One isolate was malformed and could not undergo susceptibility testing. Other detected bacteria are listed in [Table S1](#). All patients initially received penicillin combined with a β -lactamase inhibitor (ampicillin/sulbactam, 11; piperacillin/tazobactam, 1), among whom three required escalation therapy.

Risk Factors for DRP

Besides a slightly older age, none of the patients with OP poisoning who developed pneumonia had known risk factors, including the CAP-DRP score ([Table 3](#)). SPICE organisms were more frequently identified in patients who developed pneumonia after hospital day 2 (median: 3 days; IQR: 2–4; [Figure 2](#)). Although not statistically significant, the patients

Table 3 Factors Influencing the Risk of Developing Pneumonia Caused by Drug-Resistant Bacteria Patients with Organophosphate Poisoning (n = 12^a)

Patient Characteristics	With SPICE Organism ^b (n = 5)	Without SPICE Organism (n = 7)	P-value
Age (years), median (IQR)	76 (60–81)	82 (62–87)	0.26
Female, n (%)	4 (80)	4 (57)	1.00
Mental disorders, n (%)	1 (20)	4 (57)	0.29
Comorbidities, n (%)	1 (20)	1 (14)	1.00
Admission SOFA score, median (IQR)	5 (2–6)	8 (3–12)	0.17
Onset of pneumonia (day), median (IQR)	3 (2–4)	1 (1–2)	0.034
HAP / VAP, n (%)	3 (60)	1 (14)	0.22
Number of days in ICU, median (IQR)	16 (9–32)	26 (20–42)	0.15
Duration of antimicrobial therapy (days), median (IQR)	9 (6–19)	11 (9–17)	0.52
A-DROP score at pneumonia onset (IQR)	2 (1–3)	2 (2–5)	0.79
Septic shock, n (%)	0	2 (29)	0.47
Antimicrobial use within the past 90 days, n (%)	0	0	1.00
Hospitalization for more than 2 days within the past 90 days, n (%)	0	0	1.00
Nonambulatory status before hospitalization, n (%)	0	0	1.00
Immunodeficiency ^c , n (%)	0	0	1.00
Enteral feeding, n (%)	0	0	1.00
Use of gastric suppressive agents before pneumonia onset, n (%)	0	1 (14)	1.00
CAP-DRP score ^d , median (IQR)	0 (0–0)	0 (0–0)	0.39
Chronic respiratory disease, n (%)	0	0	1.00
Gastric lavage, n (%)	5 (100)	5 (71)	0.46

Notes: ^aOne case was not submitted for culture and was excluded. ^bSPICE organisms include the following: *Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*, including *Klebsiella aerogenes*. ^cImmunodeficiency is defined as any of the following: neutropenia (<500/ μ L), use of steroids, immunosuppressive drugs, and biologics; HIV/AIDS; after hematopoietic stem cell transplant; after solid organ transplant; and primary immunodeficiency. ^dThe CAP-DRP score is the sum of the following risk factors: prior hospitalization, immunosuppression, previous use of antibiotics, use of gastric acid-suppressive agents, tube feeding, and nonambulatory status. P-values <0.05 were considered statistically significant.

Abbreviations: IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; A-DROP, advanced age, dehydration, respiratory failure, orientation disturbance, and low blood pressure; HAP, Hospital-acquired pneumonia; VAP, Ventilator-associated pneumonia.

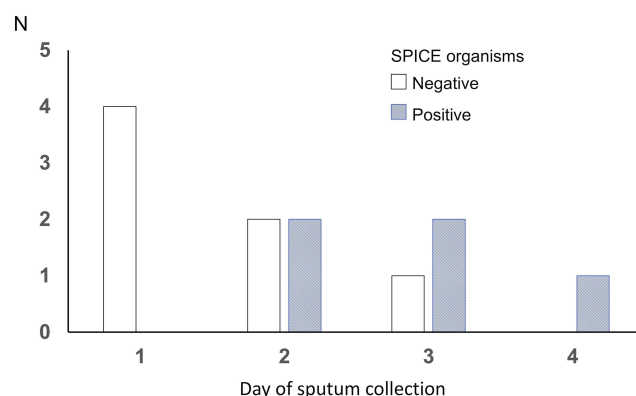


Figure 2 Relationship between the day of sputum collection and culture results. The Cochran–Armitage trend test revealed a significant correlation between the pattern of sputum culture (SPICE organisms) and the day of sputum collection ($p < 0.05$).

Abbreviations: SPICE, *Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*.

with detected SPICE bacteria had a higher incidence of HAP or VAP [3 (60) vs 1 (14), $P = 0.22$]. The detection of SPICE organisms was not associated with the SOFA score on admission, A-DROP score, or septic shock.

Discussion

We investigated the clinical characteristics, microbiological profiles, and risk factors for drug-resistant bacteria in patients with OP poisoning who developed pneumonia. There was a statistically significant association between pneumonia and longer ICU stays, higher SOFA scores on admission, and lower ChE activity. Furthermore, although all patients lacked known risk factors for drug-resistant bacteria, SPICE organisms, including *Pseudomonas aeruginosa*, were frequently detected in those with pneumonia.

OP poisoning causes respiratory failure due to central and peripheral cholinergic symptoms, leading to pneumonia and acute respiratory distress syndrome. The major causes of mortality are respiratory and circulatory failure,^{7,20,21} and the SOFA score may act as a predictor of patient outcomes.^{22,23} Wang et al identified pneumonia as a key risk factor for mortality in OP poisoning.²⁴ In our patient cohort, those with pneumonia had higher SOFA scores and lower serum ChE activity; however, 2 out of 13 cases had low mortality, which was likely due to effective empirical antimicrobial therapy. Alternatively, pneumonia may have not influenced mortality in this study as the course of OP poisoning itself was favorable. In cases of *P. aeruginosa* pneumonia, antimicrobial agents were appropriately escalated to antipseudomonal ones. The reason why the presence of SPICE organisms did not affect the treatment period or ICU stay may be attributed to appropriate escalation therapy. In VAP, the onset and inappropriate antimicrobial therapy are poor prognostic factors;^{25,26} however, OP poisoning-associated pneumonia may not affect the prognosis if the pneumonia and poisoning are effectively managed. Thus, early recognition of pneumonia and appropriate treatment are crucial in patients with OP poisoning.

The 2019 American Thoracic Society and Infectious Diseases Society of America guidelines removed the classification of healthcare-associated pneumonia (HCAP), which was once considered a high risk for drug-resistant bacteria.¹⁰ Instead, factors such as prior MRSA or *Pseudomonas* detection, recent hospitalization, and recent intravenous antibiotics were emphasized. A large Japanese study by Shindo et al identified additional CAP/HCAP risk factors, including prior hospitalization, immunosuppression, previous antibiotic use, gastric acid suppressants, tube feeding, and a nonambulatory status.²⁷ The validation study performed by Kobayashi et al¹⁹ revealed that the presence of three or more of the six risk factors identified by Shindo et al²⁷ predicted DRP. The JRS guidelines continue to recognize nursing/healthcare-associated pneumonia (equivalent to HCAP) and recommend empirical therapy based on the risk of drug resistance.¹⁸ Although the patients with OP poisoning who developed pneumonia in our study did not have any known risk factors for resistant bacteria, SPICE organisms, including *P. aeruginosa*, were detected in their sputum cultures. Chronic respiratory disease is a risk factor for resistant bacteria in CAP.^{28–30} However, none of the patients in our study had a history of respiratory disease. Additionally, no association was observed between the other comorbidities and pneumonia or culture results. Altuwaijri et al reported that only *P. aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae* were isolated from the culture specimens of patients who experienced

organophosphate poisoning.³¹ This suggests that OP poisoning may be one of the risks of pneumonia caused by SPICE organisms.

Except for one patient with pneumonia, the remaining 12 required mechanical ventilation due to disturbance of consciousness or bronchorrhea. Thus, mechanical ventilation may have increased the risk of infection with SPICE organisms. However, the early onset of pneumonia in these patients suggests classification as CAP or early-onset VAP. VAP is categorized as early- or late-onset VAP, and a high frequency of isolation of MRSA and *P. aeruginosa* was reported in cases of late-onset VAP.³² However, other studies have contradicted this finding, reporting the isolation of drug-resistant bacteria in early-onset VAP.^{33,34} In our study, SPICE organisms were detected in pneumonia cases occurring from hospital day 2 onward, underscoring the need for vigilant monitoring for DRP. Although not statistically significant, 3/5 patients with detected SPICE bacteria had HAP or VAP. In patients with OP poisoning, if the severity of respiratory failure worsens after admission, the involvement of drug-resistant bacteria must be considered, even if a few days have not yet elapsed, particularly in intubated patients.

In cases of bacterial pneumonia, Gram staining of sputum samples is crucial for the rapid identification of potential pathogens. Pathogen-targeted therapy for CAP and VAP based on Gram staining results does not negatively impact clinical outcomes.^{35,36} Gram staining is particularly effective for detecting *Streptococcus pneumoniae* and *Haemophilus influenzae*, but its diagnostic accuracy for other bacterial species is unclear.³⁷ Yoshimura et al reported the specificity of Gram staining of GNB for predicting culture results as 60.7%.³⁶ In all three cases of *P. aeruginosa* pneumonia in our study, GNB were identified by Gram staining before culture confirmation, indicating that OP poisoning can cause *P. aeruginosa* pneumonia. Thus, Gram staining may serve as a predictive tool for *P. aeruginosa* pneumonia following OP poisoning. Although the optimal empirical antimicrobial therapy for pneumonia in OP poisoning cases remains unclear, Gram staining could help with appropriate treatment selection.

This study has several limitations. First, it was a single-center, retrospective observational study with a limited sample size, comprising 13 pneumonia cases over a 12-year period. Thus, the trends observed in this study cannot be ruled out as potential outcomes of random error. There is a potential for selection bias, and the findings may not be generalizable to other institutions or regions where OP poisoning is less prevalent. Second, OP poisoning was diagnosed based on clinical presentation and exposure history, introducing the possibility of over- or underdiagnosis. Third, pneumonia was diagnosed by the attending physician, raising the possibility of misclassification. Additionally, this study lacked a comparator group of ICU patients with pneumonia unrelated to OP poisoning, limiting the study's ability to determine whether the microbiological etiology or clinical associations observed are unique to this population. Thus, larger prospective, multicenter (ideally multinational) studies involving appropriate control groups are warranted to validate our findings and determine whether OP poisoning independently contributes to the risk of pneumonia caused by resistant pathogens.

Conclusion

Despite the absence of known risk factors for drug-resistant bacteria, GNB, including *P. aeruginosa*, were frequently identified in early-stage pneumonia in patients with OP poisoning. The need for mechanical ventilation in most patients may have contributed to the early onset of drug-resistant infections. Therefore, clinicians should take into consideration the potential presence of resistant pathogens when selecting empirical antimicrobial therapy for pneumonia in these patients, even in the absence of classic risk factors.

Abbreviations

CAP, Community-acquired pneumonia; ChE, cholinesterase; DRP, Drug-resistant pathogens; GNB, Gram-negative bacilli; GPC, Gram-positive cocci; HAP, Hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; ICU, Intensive care unit; IQR, interquartile range; JRS, Japanese Respiratory Society; MRSA, Methicillin-resistant *Staphylococcus aureus*; SOFA, Sequential Organ Failure Assessment; SPICE, *Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter*; VAP, Ventilator-associated pneumonia.

Data Sharing Statement

The authors confirm that the data supporting the study's findings are available in the article and its [supplementary material](#). Raw data were generated at Niigata University. Derived data supporting the findings of this study are available from the corresponding author, Yuuki Bamba, on request.

Ethics Approval and Informed Consent

This study complied with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Niigata University Medical and Dental Hospital (approval number: #2022-0307, approval date: 2023-3-20). As this retrospective study analyzed test results obtained from electronic medical records and no additional invasive procedures were required, the Ethics Committee waived the requirement for written informed consent. The study purpose and opportunities to opt out were posted on the hospital's website.

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Author Contributions

All authors made a significant contribution to this work, whether that is in the conception, study design, execution, as well as data acquisition, analysis, and interpretation or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and have agreed to be accountable for all aspects of the work.

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Disclosure

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