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Prediction of pathogen positive-culture results in acute poisoning patients with suspected aspiration

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Purpose: This study sought to compare the characteristics of patients with pathogen-positive and negative cultures, and to investigate factors predicting pathogen-positive culture results in patients of acute poisoning with suspected aspiration.
Methods: Consecutive patients with acute poisoning admitted to an intensive care unit between January 2016 and December 2018 were retrospectively studied. Respiratory specimens were collected from the enrolled patients at the time of the suspected aspiration. We compared the characteristics of patients with pathogen-positive and negative culture results and analyzed the causative pathogens.
Results: Among the 526 patients, 325 showed no clinical features that could be attributed to aspiration, and 201 patients had clinical features suggestive of aspiration. Of these, 113 patients had pathogen-positive culture, 61 were negative, and the specimens of 27 patients contained poor-quality sputum. In univariate analysis, patients with a positive culture showed a longer time to culture from ingestion (p=0.01), faster heart rate (p=0.01), and higher partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) (p=0.02) than patients with negative culture. Multivariate analysis demonstrated that PaO_2/FiO_2 (adjusted odd ratio, 1.005; 95% confidence interval [CI], 1.002-1.008; p=0.005) was a significant risk factor for pathogen-positive culture. The area under the receiver operating characteristic curve of PaO_2/FiO_2 was 0.591 (95% CI, 0.510-0.669, p=0.05). Gram-negative pathogens (GNPs) were predominant and at least one GNP was observed in 84 (73.3%) patients among those with pathogen positive culture.
Conclusion: We failed to find any clinical factors associated with positive culture results. Antibiotics that cover GNPs could be considered when deciding the initial antibiotic regimen at the time of suspected aspiration.

Key Words: Pneumonia, Aspiration, Drug overdose, Decision making, Anti-bacterial agents

INTRODUCTION

Aspiration is defined as the abnormal entry of oropharyngeal or gastric contents into the larynx and the lower airways, causing aspiration syndromes, including aspiration pneumonitis and aspiration pneumonia[1,2]. Both aspiration pneumonia and pneumonitis may subsequently develop acute respiratory distress syndrome, which are responsible for substantial morbidity and mortality[3-5].

Aspiration develops frequently in the poisoned patients and is associated with prolonged intensive unit stay and increased mortality[6,7]. Antibiotics are indicated if the patients have aspiration pneumonia, whereas antibiotic treatments are not recommended for aspiration pneumonitis. Distinguishing aspiration pneumonia from aspiration pneumonitis is necessary before antibiotics prescription in patients with suspected or confirmed aspiration because several studies have demonstrated that prophylactic antimi-

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crobial therapy at the time of a witnessed or suspected aspiration event did not prevent the development of aspiration pneumonia or reduce mortality[1,8-10].

However, in clinical practice, differentiation between these two diseases is difficult because their symptoms and signs overlap. In literature review, there are no established markers or methods to differentiate, and there were no studies that have focused on the question of whether or not to administer antibiotics when aspiration is suspected. Hence, the decision whether to give antibiotics made by physicians in charge, although based on risk factors of aspiration and clinical features of patients, may be relatively subjective.

Given the definition of aspiration pneumonia and pneumonitis, the main difference between these two diseases is the presence aspirated particles harboring colonizing pathogens[11]. Under this notion, it may be more reasonable to prescribe antibiotics to patients with pathogens in the respiratory tract cultures than those without pathogens. Accordingly, proving pathogen in respiratory tract cultures may be used to support decision making for the initiation of antibiotic treatment. Therefore, this study aimed to compare the characteristics of patients with pathogen positive and negative cultures, and to investigate factors predicting pathogen positive culture results in acute poisoning patients with suspected aspiration. We also investigated the causative organisms in the patients with pathogen positive cultures.

MATERIALS AND METHODS

1. Study design and patients

This retrospective observational study was conducted between January 2016 and December 2018 at a 1400-bed, tertiary care, university-affiliated hospital. The institutional review board of our hospital reviewed and approved this study (IRB approval No., 2106-006-103) and waived consent.

We reviewed the medical records of 526 consecutive adult patients (≥18 years old) who presented to the emergency department (ED) due to acute self-poisoning with antidepressants, antipsychotics, sedative-hypnotics, and pesticides. After reviewing the medical records, patients who had a clinical suspicion of aspiration within 48 h after arrival at the ED were included in the study. Aspiration induced lung injury was suspected when the patients had newly developed infiltration on the chest X-ray and met at least one of the following criteria: 1) body temperature ≥ 38.0°C or ≤36.0°C; 2) white blood cell (WBC) count 〉12,000/mm^3 or 〈4,000/mm^3; 3) increased C-reactive protein (CRP, 〉0.5 mg/dL); 4) respiratory distress (sputum, cough) or tachypnea (respiration rate ≥30 breaths/min)[12-15]. Patients in whom respiratory tract culture was performed 48 h after admission were excluded because of the possibility of hospital-acquired pneumonia. Cases of simple asphyxiants or gas poisoning with carbon monoxide, propane, methane, nitrogen, and other gases were also excluded.

2. Data collection

Variables including age, sex, the use of decontamination procedures, reason for substance ingestion (intentional or unintentional), alcohol co-ingestion, underlying diseases, and type of substance ingested were recorded during the first contact with the patients in the ED. Glasgow Coma Scale (GCS) score, vital signs (systolic blood pressure, heart rate [HR], peripheral oxygen saturation [SpO_2], and body temperature), laboratory variables including partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), WBC count, CRP, and lactic acid, and chest X-ray were routinely evaluated in the ED and every day, in the morning after admission. Therefore, in this study, we used the latest values of GCS, vital signs, and laboratory variables collected before suspicion of aspiration induced lung injury.

3. Respiratory tract cultures

Respiratory tract cultures were obtained at the time of suspicion of aspiration induced lung injury, before antibiotic use. Specimens consisted of sputum or closed endotracheal tube aspirates, and were considered acceptable when numerous polymorphonuclear neutrophils and rare squamous epithelial cells (〈10 per low power field; 10×objective) were observed[16-18].

Patients were grouped as having pathogen positive culture when predominant microorganisms were *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus dysgalactiae*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Nocardia* spp., *Moraxella catarrhalis*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *and gram-negative bacilli*. Patients were grouped as pathogen negative culture when normal throat flora, such as α- or γ-*streptococcus*, *Micrococcus* spp., *Neisseria* spp., *Corynebacterium* spp.,

coagulase-negative *Staphylococcus* were isolated or predominant infectious agents were not identified in the respiratory tract culture[19,20].

4. Statistical analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation, and non-normal distributions are shown as the median and interquartile range. Categorical variables are reported as frequencies (%). Between patients with pathogen positive culture and those with negative culture, categorical variables were compared using the chi-square test or Fisher' s exact test, and continuous variables were compared using the t-test or the Mann-Whitney U-test. We used backward stepwise logistic regression with age, sex and variables with p-value less than 0.1 on a univariate analysis to predict factors for pathogen positive culture, and significant risk factors were reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Each risk factor' s ability to predict positive culture was evaluated using the area under the receiver operating characteristic curve (AUROC). A *p*-value of less than 0.05 was considered statistically significant. PASW Statistics for Windows, version 18.0. (SPSS Inc., Chicago, Ill., USA) was used for statistical analyses.

RESULTS

A total of 526 patients presented to the ED with acute poisoning; of these patients, 325 showed no radiological or clinical signs suggestive of aspiration. The remaining 201 patients (38.2%) showed clinical features of aspiration, and respiratory tract specimens were collected. Twenty-seven patients had poor quality specimens and 174 patients had acceptable culture results. Of these, 61 (35.1%) patients had no isolated pathogen, and 113 (64.9%) had at least one bacterial pathogen (Fig. 1).

As shown in Table 1, the mean age and sex were not significantly different between culture positive and negative patients. There were no significant differences in systolic blood pressure, body temperature, SpO_2, and GCS between the two groups. Laboratory findings, including WBC count, CRP, and lactic acid levels, were not significantly different. Underlying diseases and substances ingested were not significant. However, time to culture from ingestion was longer in patients with positive culture than those with negative (20.8 [16.6-30.9] vs. 16.5 [10.1-23.8] hours, p=0.01). HR was faster in patients with culture positive patients than in those with negative culture (93.0 [82.0-108.5] vs 85.0 [76.0-103.0], p=0.01). Patients with positive culture had higher PaO_2/FiO_2 than those with negative culture (420.1±150.8 vs.

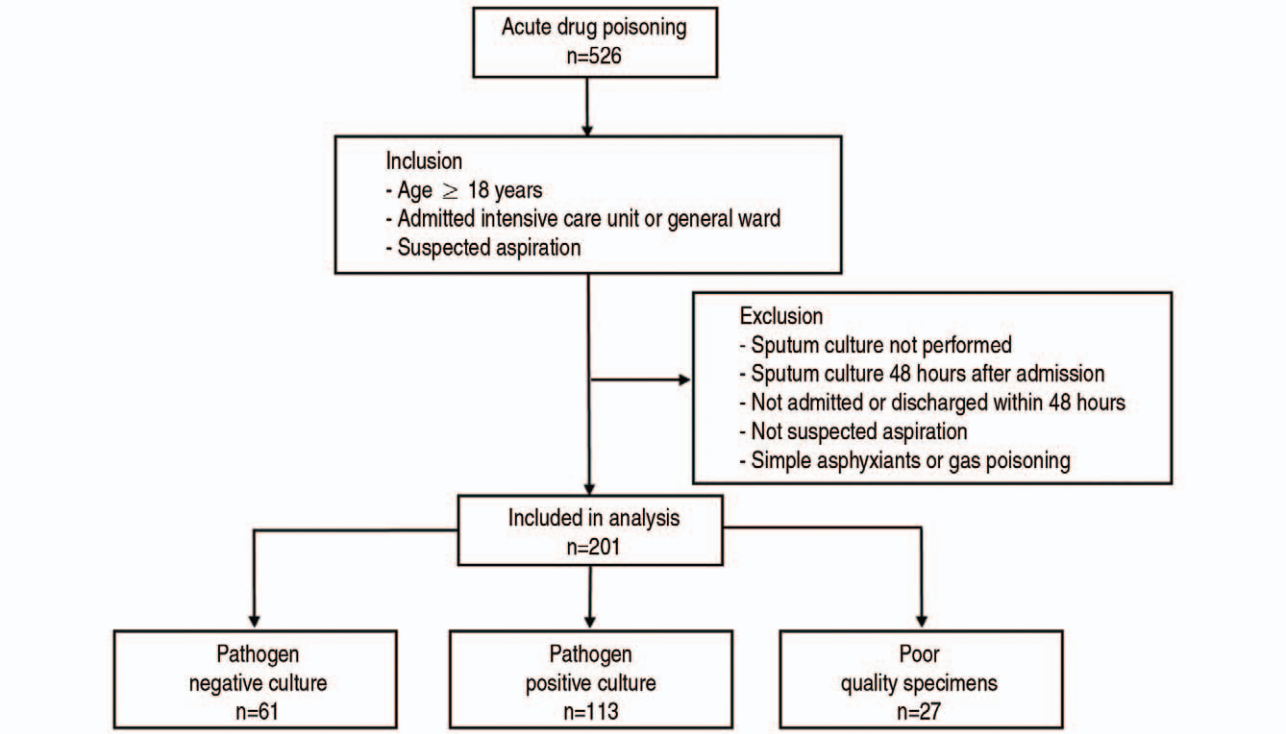

Fig 1. Flow chart of study

365.4±121.5, p=0.02) (Table 1).

Overall, the most commonly identified pathogens were *Klebsiella pneumoniae* (49, 43.4%), followed by *Staphylococcus aureus* (27, 23.9%), *Streptococcus pneumoniae* (18, 15.9%), and *Enterobacter* species (15, 13.3%). Of the 113 patients with positive culture, 29 patients had one gram-positive pathogen (GPP) and 64 had one gram-negative pathogen (GNP). Mixed pathogens (one GPP and one GNP) were isolated in 16 patients, and 4 had two GNPs. Therefore, 84 patients had at least one GNP, and 29 patients had no GNP. Likewise, 45 patients had at least one GPP, and 68 patients had no GPP (Table 2).

In the multivariate analysis using sex, age, time from ingestion to culture, HR, and PaO_2/FiO_2, PaO_2/FiO_2 FiO_2 (aOR,

Table 1. Baseline characteristics of the enrolled patients.

	Pathogen positive (n=113)	Pathogen negative (n=61)	*p*-value
Age, years	60.2±15.6	60.8±12.8	0.78
Age≥65 years, n (%)	47 (41.6)	25 (41.0)	1.00
Males, n (%)	69 (61.1)	38 (62.3)	0.87
Time from ingestion to culture, (hr)	20.8 (16.6-30.9)	16.5 (10.1-23.8)	0.01
Decontamination, n (%)			
Lavage	30 (26.5)	17 (27.9)	0.80
Charcoal	39 (34.5)	21 (34.4)	0.60
Intentional, n (%)	111 (98.2)	60 (98.4)	0.23
Alcohol ingestion, n (%)	58 (51.3)	32 (52.5)	0.79
Underlying diseases, n (%)			
Cardiac	22 (19.5)	13 (21.3)	0.84
Liver cirrhosis	4 (3.5)	1 (1.6)	0.66
CNS	8 (7.1)	2 (3.3)	0.50
DM	15 (13.3)	9 (14.8)	0.82
Neoplastic	4 (3.5)	4 (6.6)	0.45
Neuropsychiatric	25 (22.1)	16 (26.2)	0.58
Others	8 (7.1)	7 (11.5)	0.40
Substance, n (%)			
Analgesics	5 (4.4)	3 (4.9)	0.88
Antidepressant	13 (11.5)	8 (13.1)	0.76
Antipsychotics	8 (6.1)	2 (3.3)	0.30
Sedative-hypnotics	45 (39.8)	29 (47.5)	0.33
Pesticides	47 (41.6)	23 (37.7)	0.78
Miscellaneous	11 (9.7)	6 (9.8)	0.98
SBP (mmHg)	110.0 (95.0-130.0)	110.0 (100.0-140.0)	0.62
HR (beats/min)	93.0 (82.0-108.5)	85.0 (76.0-103.0)	0.01
HR (beats/min), n (%)			0.40
≤100	72 (63.7)	45 (73.8)	
101-150	39 (34.5)	15 (24.6)	
≥151	2 (1.8)	1 (1.6)	
Temperature (˚C)	36.4 (36.1-36.6)	36.3 (36.1-36.5)	0.42
GCS	9.5±3.9	9.7±4.1	0.78
SpO_2, %	92.3±13.4	93.1±9.8	0.68
PaO_2/FiO_2 (mmHg)	420.1±150.8	365.4±121.5	0.02
PaO_2/FiO_2, n (%)			0.14
≤100	2 (1.8)	0 (0.0)	
101-200	9 (8.0)	5 (8.2)	
201-300	15 (13.3)	16 (26.2)	
≥301	87 (77.0)	40 (65.6)	
White blood cell ($10^3/mm^3$)	11.9±6.9	12.0±6.2	0.99
CRP (mg/dL)	0.11 (0.04-0.55)	0.12 (0.04-0.69)	0.78
Lactic acid (mmol/L)	3.0 (1.8-5.7)	2.7 (1.5-4.0)	0.22
ICU admission, n (%)	113 (100.0)	60 (98.4)	0.35
Mechanical ventilation, n (%)	103 (91.2)	54 (79.7)	0.60

CNS: central nervous system, DM: diabetes mellitus, SBP: systolic blood pressure, HR: heart rate, GCS:Glasgow coma scale, PaO_2/FiO_2: partial pressure of arterial oxygen to the fraction of inspired oxygen, CRP: C-reactive protein, ICU: intensive care unit

1.005; 95% CI, 1.002-1.008; p=0.005) was significant risk factor for pathogen positive culture (Table 3). AUROC of PaO_2/FiO_2 was 0.591 (95% CI, 0.510-0.669, p=0.05) (Fig. 2).

DISCUSSION

We performed this study to identify the factors to predict pathogen positive results in acute poisoning patients with suspected aspiration. We found that pathogen positive culture and negative patients had similar characteristics excepting for time from ingestion to culture, HR and PaO_2/FiO_2 at the first time when they displayed clinical symptoms or signs of aspiration. However, given the AUROC of PaO_2/FiO_2, it would be inappropriate in differentiation between patients with pathogen positive culture and those with pathogen negative culture. In addition, in analysis of pathogen positive culture results, we found that GNPs were predominant causative organisms.

Differentiation aspiration pneumonia and aspiration pneumonitis is difficult because their signs and symptoms can overlap. Previous studies have examined the frequency, risk factors, and outcomes of aspiration pneumonia in patients with acute poisoning[21-24]. However, all these studies were performed without distinguishing aspiration pneumonia from aspiration pneumonitis. Therefore, the study population was heterogeneous and the study results have limitation in determining the patients who will be helped by antibiotic prophylaxis. Regrettably, comparing results of our study to those of previous studies were impossible, owing to absence of microbiologic evaluation in prior studies.

There are some differences in clinical characteristics between two disease entities: aspiration pneumonitis presents abruptly and immediate acute respiratory distress and hypoxia typically develop within hours of aspiration. Additionally, symptoms often rapidly improve within 48 hours of the initial insult. On the other hand, symptoms of aspiration pneumonia usually develop within hours to a few days after event. This gradual onset of symptoms in

Table 2. Microbial etiology of pathogen positive culture results.

Microorganisms	N=113
Single gram-positive (n=29, 25.7%)	
Staphylococcus aureus	19
Streptococcus pneumoniae	10
Single gram-negative bacteria (n=64, 56.6%)	
Enterobacter aerogenes	8
Enterobacter cloacae	1
Klebsiella pneumoniae	38
Escherichia coli	6
Pseudomonas aeruginosa	4
Acinetobacter baumanii	3
Proteus mirabilis	1
Hemophilus influenzae	1
Serratia marcescens	1
Stenotrophomonas maltophilia	1
Mixed gram-positive and negative bacteria (n=16, 14.2%)	
Acinetobacter baumanii+Stretococcus pneumoniae	1
Enterbacter aerogenes+Staphylococcus aureus	2
Enterbacter aerogenes+Streptococcus pneumoniae	3
Escherichia coli+Staphylococcus aureus	1
Klebsiella pneumoniae+Staphylococcus aureus	5
Klebsiella pneumoniae+Streptococcus pneumoniae	4
Double gram-negative bacteria (n=4, 3.5%)	
Acinetobacter baumanii+Klebsiella pneumoniae	1
Enterbacter aerogenes+Klebsiella pneumoniae	1
Klebsiella oxytoca+Proteus mirabilis	1
Pseudomonas aeruginosa+Serratia marcescens	1

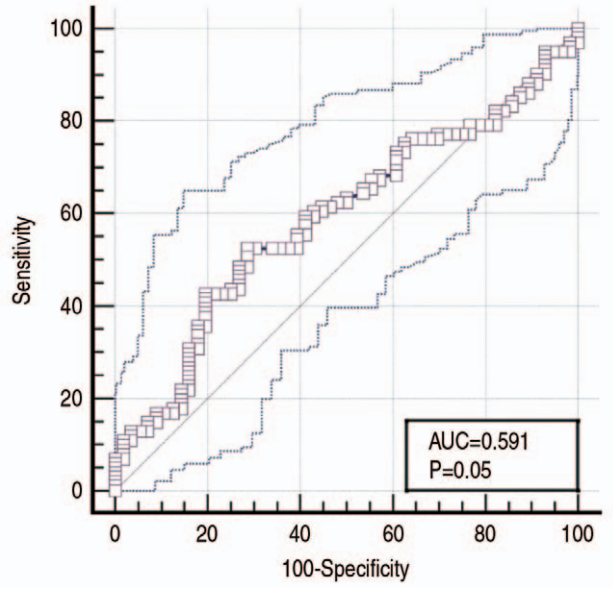

Fig 2. The receiver operating characteristic curves of heart rate and PaO_2/FiO_2

Table 3. Risk factors for pathogen positive culture results.

Variable	Adjusted OR	95% CI	p-value
PaO_2/FiO_2	1.005	1.002-1.008	0.005

OR: odds ratio, CI: confidence interval, PaO_2/FiO_2: partial pressure of arterial oxygen to the fraction of inspired oxygen
The odds ratio were adjusted with sex, age, time from ingestion to culture, heart rate, and PaO_2/FiO_2

aspiration pneumonia is helpful in differentiation from aspiration pneumonitis. In addition, the presence of more than one oropharyngeal colonization risk factors such as old age, malnutrition, smoking, poor oral hygiene or prior antibiotic use increases the probability of aspiration pneumonia.

Antimicrobial therapy should be initiated if aspiration pneumonia is suspected. In antibiotic selection, local susceptibility patterns for the most likely pathogens is one of the factors to be considered. The organisms mostly found in older studies employing transtracheal aspiration as a method for obtaining specimens from the lower airways were anaerobic bacteria. Whereas aerobic bacteria are predominant organisms in more recent studies. In addition, it has been shown that the predominant pathogenic organisms in community acquired aspiration pneumonia (*Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Staphylococcus aureus*) are different from those most commonly found in nosocomial infection (gram negative [*Escherichia coli*, *Klebsiella pneumoniae*, *Serratia* spp., *Proteus* spp.])[13]. In our study, all poisoning events occurred in outpatient settings, such as residences, car, and workplace. In addition, all sputum specimens were collected within 48 hours of admission to hospital. Nevertheless, in our study, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterobacter* species were main isolated pathogens, which are commonly isolated pathogens in hospitalized patients with severe aspiration pneumonia. This discrepancy is presumed to the severity of culture positive patients: about all patients admitted to intensive care unit and 91% had received mechanical ventilation therapy at time of obtaining respiratory tract specimens. Given these results, antibiotics covering GNPs would be considered in early antibiotic treatment although the aspiration occurs in outpatient situations.

This study had several limitations. First, this study was a single-center observational study, and the results may not be applicable to other institutions. Second, there is a possibility of undetected microorganisms in respiratory tract culture, such as *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, or *Legionella pneumophilia*. In addition, anaerobic bacteria cannot be cultured in specimens because of inevitable contamination by the normal flora of the mouth. Therefore, a prevalence of anaerobic bacteria was not evaluated. Third, culture results may be affected by the process of obtaining specimen, depending on the expertise, which can affect the quality or volume of specimens. Thus, it seems reasonable that negative culture results do not necessarily mean the absence of bacterial infection, that is, aspiration pneumonitis.

CONCLUSION

This study aimed to identify factors predicting pathogen positive culture results in acute poisoning patients with suspected aspiration. We found that pathogen positive and negative patients had similar characteristics excepting for time from ingestion to culture, HR and PaO_2/FiO_2. However, these variables were not suitable for positive culture results due to prediction ability and insignificant statistical results. In addition, microbiology of pathogen positive culture results showed that gram-negative bacteria were the prevailing etiological agents. Therefore, antibiotics against gram-negative bacteria could be considered in the antibiotic regimen at the time of suspected aspiration.

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