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Antibacterial therapy of aspiration pneumonia in patients with methicillin-resistant *Staphylococcus aureus*-positive sputum: identification of risk factors

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Inappropriate antimicrobial treatment could adversely affect the recovery of patients with aspiration pneumonia. We attempted to identify inappropriate antibacterial treatment and to determine the standard use of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs in aspiration pneumonia patients with MRSA-positive in sputum. Aspiration pneumonia patients with MRSA-positive sputum treated between January 2013 and May 2013 were included in this study to determine the risk factors for death during hospitalization. The relationship between anti-MRSA medicine use and death during hospitalization was also investigated. More than 10^7 MRSA colony-forming units in sputum culture, creatinine clearance of less than 30 mL/min, and quinolone use were found to be risk factors for death during hospitalization. The death rate during hospitalization was significantly lower in cases a Geckler classification of 4 or 5 when anti-MRSA treatment was initiated soon after the culture was obtained. Therefore, we concluded that the use of quinolones as antibacterial treatment in aspiration pneumonia patients with MRSA-positive sputum should be avoided and that anti-MRSA treatment should be started in cases with good quality sputum cultures.

1. Introduction

Aspiration pneumonia is a common but unfavorable disease with a high mortality rate. Antibiotics are used as the primary method of treatment for aspiration pneumonia. However, choosing the correct antibacterial drug can be difficult owing to difficulties in the detection of pathogenic bacterium. Sputum culture is a common method used to detect pathogenic bacteria in patients with aspiration pneumonia, but the bacteria cultured are not always the pathogenic bacteria responsible for causing pneumonia. The standard empirical antibiotic therapy often involves treatment with a beta-lactamase inhibitor in combination with penicillin or quinolone, but the best antibiotic drug choice is controversial (Mandell et al. 2007; Daoud and Guzman 2010; Paul et al. 2001). In addition, methicillin-resistant *Staphylococcus aureus* (MRSA) is detected at a high rate in patients diagnosed with aspiration pneumonia. However, to the best of our knowledge, there are no reports in the literature demonstrating whether targeted anti-MRSA antibiotic therapy leads to improvement in patients with aspiration pneumonia in whom sputum culture detected the presence of MRSA.

In this study, we investigated the risk factors leading to death during hospitalization in a patient diagnosed with aspiration pneumonia where sputum culture detected the presence of MRSA. We also examine the effectiveness of targeted anti-MRSA treatments in a patient with MRSA-positive aspiration pneumonia.

2. Investigations and results

2.1. Patient background

The study population consisted of patients at the Ogaki Municipal Hospital who were diagnosed with aspiration pneumonia and whose sputum cultures tested positive for MRSA from January 2013 to May 2013. Aspiration pneumonia was defined as pneumonia with a clearly defined episode of aspiration via a cough reflex or other event, or the presence of underlying diseases such as cerebrovascular or neurodegenerative diseases that put the patient at higher risk of aspiration. A patient who aspirated a large volume of fluid and another patient with ventilator related-pneumonia were both excluded from the study. Cases that satisfied the definition above were identified in a patient's electronic medical record and were included in the target population. The population was classified into two groups: a survival group (n = 56) and a death group (n = 45). Patients classified into the death group died during hospitalization. Additional information including age, sex, sputum culture results, medical history, asparagine aminotransferase, alanine aminotransferase, serum creatinine, and C reactive protein levels, as well as white blood cell counts and the antibacterial drug prescribed were collected from the target patients' electronic medical record.

2.2. The risk factors for death during hospitalization

As identified by a univariate analysis, a history of stroke (P = 0.044) and treatment with quinolone antibiotics (P = 0.025)

Table 1: Patient characteristics and univariate analysis between both groups

		Survival Deal (n = 56)	Death (n = 45)	p value
	MRSA colony-forming units in sputum culture > 10^7	25	33	0.081
	Performance status > 3	50	39	0.762
	Male	48	41	0.540
	Age > 80 years	40	33	0.812
	Creatinine clearance < 30 mL/min	21	25	0.107
	Serum albumin < 2.8 g/dL	25	27	0.180
	Blood urea nitrogen > 40 mg/dL	26	27	0.247
	C-reactive protein > 10 mg/dL	8	7	0.855
	White blood cell count > 8000	24	21	0.856
Medical history	Chronic obstructive pulmonary disease	8	8	0.785
	Stroke	20	26	0.044
	Alzheimer's disease	22	12	0.262
	Parkinson's disease	8	5	0.839
	Diabetes	10	14	0.187
Detection of bacteria	Detection of non-MRSA bacteria	36	30	0.968
	Gram negative bacteria	35	21	0.158
	Gram positive bacteria	6	4	1.000
Antibiotic drug before cultivation	Yes	12	16	0.176
	Levofloxacin/Tosufloxacin	6/3	11/0	
	Amoxicillin clavulanate	3	4	
	Cefditoren pivoxil	0	1	
Antibiotic drug after cultivation	Cephalosporin	7	4	0.750
	Ceftri axone/Cefozopran	7/0	2/2	
	Penicillin	33	24	0.718
	Ampicillin sulbactam/Piperacillin tazobactam	24/9	21/3	
	Quinolone	1	8	0.010
	Levofloxacin/Garenoxacin	1/0	5/3	
	Anti-MRSA medicine	8	3	0.337
	Vancomycin/Teicoplanin/Arbekacin	3/3/2	0/1/2	
	Meropenem	7	7	0.908
	Clindamycin	4	2	0.690
	Flomoxef	1	0	1.000
	Combination therapy	5	3	0.729
Antibiotic drug after changing	Changed the antibacterial drug during follow up	9	13	0.191
	Anti-MRSA medicine	6	4	
	Meropenem	0	2	
	Piperacillin tazobactam	1	0	
	Ampicillin sulbactam	3	3	
	Others	2	4	
	Quinolone use	10	18	0.025
	Anti-MRSA medicine use	14	7	0.360

Table 2: Result of multivariate logistic regression analyses of risk factor for mortality

Variable	odds rate	95% confidence interba	p value
MRSA colony-forming units in sputum culture > 10^7	1.30-10.70	0.015	
Creatinine clearance $\leq$ 30mL/min	3.68	1.31−10.30	0.013
Serum albumin < 2.8g/mL	2.56	0.96−6.83	0.060
Stroke	2.53	0.98−6.55	0.056
Diabetes	0.85	0.25−2.88	0.800
Detection of gram negative bacteria	3.2	1.00−10.30	0.051
Antibiotic drug use before cultivation	0.38	0.09−1.66	0.200
Quinolone use	9.88	1.93−50.50	0.006

were significant differences between the two groups (Table 1). There was no significant difference in the risk of death in patients that received antibiotic treatment prior to sputum culture (survival group n = 12; death group n = 16). Quinolone was the most common antibacterial drug used in treatment before sputum culture (survival group n = 7; death group n = 11), followed by administration of amoxicillin/clavulanic acid (survival group n = 3; death group n = 4). Penicillin was the most common antibacterial drug administered after sputum culture results (survival group n = 33; death group n = 24). There was no significant difference in the risk of death in patients for whom the type of antibacterial drug administered was changed as a result of sputum culture results (survival group n = 9; death group n = 13). There were 14 cases in the survival group and 7 cases in the

Table 3: Geckler classification of sputum culture in both group. BSE, buccal squamous epithelial

Geckler classification	Survival (n = 56)	Death (n = 45)	Counts of Leukocytes*	Counts of BSE*
1	4	0	< 10	> 25
2	3	7	10-25	> 25
3	31	18	> 25	> 25
4	1	9	> 25	10-25
5	17	9	> 25	< 10
6	0	2	< 25	< 25

* 100 × magnification.

death group where targeted therapy using anti-MRSA drugs was administered, and no significant difference in the risk of death was found between the two groups.

Univariate analysis of the following variables indicated no significant differences between the survival and death groups ($P < 0.2$): detection of more than 10^7 MRSA colony-forming units in sputum culture; creatinine clearance less than 30 mL/min; serum albumin less than 2.8 g/dL; history of stroke or diabetes mellitus; detection of a gram-negative strain in sputum culture; antibiotic treatment prior to sputum culture; and quinolone treatment. Since the univariate analysis demonstrated no significant differences, multivariate logistic regression analyses were also used to evaluate the variables listed above. Presence of more than 10^7 MRSA colony-forming units in sputum culture ($P = 0.015$), creatinine clearance of less than 30 mL/min ($P = 0.013$), and quinolone use ($P = 0.006$) were all associated with increased risk of death during hospitalization.

2.3. Effect of targeted antibiotic treatment for MRSA in patients with positive sputum cultures

The Geckler classification system is shown in Table 3 (Geckler et al. 1977). The majority of the cases in this study were classified as Grade 3, with 55% of the survival group (n = 31) and 40% of the death group (n = 18) falling into this category. Of the remaining study population, 32% of the survival group (n = 18) and 40% of the death group (n = 18) produced good sputum samples with a Geckler classification of 4 or 5. The relative risk of death during hospitalization was evaluated in patients treated with targeted anti-MRSA medication who were able to produce sputum samples with a Grade of 4 or 5. In addition, cases where sputum samples were not graded as 4 or 5 were compared (Table 4). In cases where sputum samples were graded as a 4 or 5 in both groups, the patients receiving targeted antibiotic treatment for MRSA were 6 cases (33%) in the survival group and 2 cases (11%) in the death group, and there was no significant difference between the groups ($P = 0.228$). The effect of the timing of administration of targeted antibiotic treatment for MRSA was also considered between the two groups. In the survival group, 28% of the patients who were started on targeted antibiotic therapy immediately after MRSA-positive sputum culture obtained (n = 5), whereas none of the patients in the death group had been administered targeted antibiotic therapy immediately after sputum culture. This difference was statistically significant ($P = 0.046$).

Table 4: The relation of Geckler classification of sputum culture and anti-MRSA medicine use

Grade 4 or 5	Survival (n = 18)	Death (n = 18)	p value
anti-MRSA medicine use	6	2	0.228
Immediately use of anti-MRSA medicine	5	0	0.046
Not Grade 4 or 5	**Survival (n = 38)**	**Death (n = 27)**	**p value**
anti-MRSA medicine use	8	5	1
Immediately use of anti-MRSA medicine	3	3	1

There was no significant difference between the survival and death groups in cases where good sputum samples were not produced (*i.e.,* not Grade 4 or 5) regardless of whether or not targeted antibiotic treatment for MRSA was started immediately after sputum culture.

3. Discussion

The results of this study suggest that use of quinolones as the primary antibiotic treatment regimen for patients with aspiration pneumonia with MRSA-positive sputum cultures is a risk factor for mortality during hospitalization. Levofloxacin is also commonly used clinically, but it is not effective in treating infections caused by anaerobic bacteria. Recent studies have reported that the use of improper antibacterial therapy can extend the convalescence period in patients with pneumonia (Micek et al. 2007; Shindo et al. 2009). Therefore, levofloxacin may an inappropriate treatment for aspiration pneumonia. In addition, arrhythmia and unstable blood sugar levels are known adverse effects of treatment with quinolones as compared to treatment with beta-lactam antibiotics (Chou et al. 2013; Owens and Nolin 2006). Quinolone use has also been associated with an increased risk of cardiovascular events, including an increased risk of mortality (Chou et al. 2015). During improper antibiotic therapy using quinolones, bacteria may develop tolerance to this drug, which could lead to a superinfection by drug-resistant bacteria in these patients. Therefore, the use of quinolone is not recommended for treatment of patients with aspiration pneumonia with MRSA-positive sputum cultures. Other classes of antibiotics such as penicillin with beta-lactamase inhibitor are recommended.

The Geckler classification is used for evaluation of the quality of sputum samples (Geckler et al. 1977). In this study, the Geckler classification for sputum samples was used, and samples classified as Grade 4 and 5 were identified as good sputum samples. Sputum samples classified as either Grade 4 or 5 were cultured and pathogenic bacterial were identified. Previous studies have detected MRSA with a high frequency in patients with aspiration pneumonia (Micek et al. 2007). This study evaluated the efficacy of targeted antibiotic therapy for MRSA infection in patients where sputum samples of Grade 4 or 5 were available to be cultured. In this study, we demonstrated that initiating targeted antibiotic therapy for MRSA immediately after detection of MRSA in sputum cultures reduced the risk of death. The increased likelihood that MRSA is the pathogenic bacteria in patients who can produce sputum classified as Grade 4 and Grade 5 should be considered. In this study, we observed a significantly lower death rate in cases where targeted antibiotic therapy for MRSA was administered immediately after a MRSA-positive sputum culture. Therefore, we can consider to using targeted antibiotic therapy for MRSA after considering the nosocomial MRSA detection rate, and quality of sputum. When administering targeted antibiotic therapy for MRSA in elderly patients, it is critical to monitor renal function and limit drug interactions. Therefore, we conclude that the use of quinolone as the first choice for antibacterial treatment in patients with

aspiration pneumonia with MRSA-positive sputum should be avoided, and that targeted antibiotic therapy for MRSA should be started immediately in patients with good quality MRSA-positive sputum cultures.

4. Experimental

4.1. Statistical analysis

For statistical analysis, we used EZR version1.26 (Kanda, 2013). 2×2 data analysis was performed using the Chi-square test, and for data with less than 5 cases Fischer's exact test was used. Multiple logistic regression analysis was performed using a forced entry method, and odds risk ratios and 95% confidence intervals were calculated. A p value of < 0.05 was considered to be statistically significant.

4.2. Ethical considerations

This study complied with the ethical guidelines for clinical research and was approved by the medical research ethical review board at Ogaki Municipal Hospital. To protect the privacy of patients, personal information was anonymized in a linkable fashion for the data analysis. Patients' personal information could not be identified, and there was no disadvantage to patients participating in this study.

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

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