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Current problems in the diagnosis and treatment of hospital-acquired methicillin-resistant *Staphylococcus aureus* pneumonia

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Abstract
Purpose. We aimed evaluate clinical problems in the diagnosis and treatment of hospital-associated pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA-HAP) at a single institute.
Methods. Forty-two patients, diagnosed with MRSA-HAP by a primary physician, who had received antimicrobial therapy during a period of 18 consecutive months at University Hospital, Kyoto Prefectural University of Medicine, were enrolled in the study. For comparison, 36 patients in whom MRSA was recovered from the respiratory tract during the same period, but who were not treated for pneumonia, were chosen as untreated controls. A clinical pulmonary infection score (CPIS) was calculated retrospectively by a chart review. The CPIS was calculated on day 1 and day 3. In the treated group, serum concentrations of each therapeutic drug used were also evaluated.
Results. The day-1 and day-3 CPIS showed a similar trend in the two at groups, at 2.5 ± 1.8 and 3.9 ± 1.9, respectively, in the treated group and 2.9 ± 1.9 and 3.8 ± 1.6 in the control group. Only two (5%) patients in the treated group showed a CPIS of more than 6 on day 1. Only five patients (12%) in the treated group were treated with antimicrobials at appropriate target therapeutic serum concentrations. The 30-day mortality in the treated group was significantly higher than that in the control group, even when we matched the baseline morbidity of patients using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.
Conclusion. This study revealed the clinical problems in our setting, in that MRSA colonization in the respiratory tract was frequently treated as pneumonia, and antimicrobial dosage was frequently insufficient. Prudent differential diagnosis of and treatment for HAP due to MRSA infection should be considered.

Key words Hospital-acquired pneumonia · Methicillin-resistant *Staphylococcus aureus* · Clinical pulmonary infection score · Therapeutic drug monitoring · Colonization

Introduction

Hospital-acquired pneumonia (HAP) is a frequent nosocomial infection, and is associated with high mortality and morbidity, specifically among critically ill patients [1,2]. Common microorganisms causative of HAP include aerobic gram-negative bacilli, such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*. Recent surveys, however, have indicated the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) as the second-most frequent pathogen in HAP [3,4].

Clinical strategies for treating HAP due to MRSA (MRSA-HAP) should include appropriate differential diagnosis of infection from colonization, especially in patients with artificial airways [5,6]. One should consider whether or not the organism recovered from the lower respiratory tract is a true pathogen of pneumonia. The diagnosis of HAP, however, is frequently difficult, as there has been no "gold-standard" for the differential diagnosis. Recently, Pugin et al. [7] suggested the use of a clinical pulmonary infection score (CPIS) as a diagnostic method for patients suspected to have pneumonia. This score can be applied without invasiveness and the results can be obtained immediately.

Another problem in treating MRSA-HAP is the determination of appropriate glycopeptides dosing. Recent studies have stressed the usefulness of utilizing therapeutic drug monitoring (TDM) in antimicrobial chemotherapy [8,9].

In this study, we aimed to reevaluate the appropriateness of the diagnosis and treatment of MRSA-HAP in our clinical practice. We applied a CPIS for patients in

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whom MRSA was recovered from microbiological samples from the respiratory tract, and we reevaluated the diagnosis of MRSA pneumonia made originally by primary health services. Moreover, we also analyzed the status of the antimicrobial chemotherapy used for MRSA-HAP.

Methods

Patients

This study was conducted at the University Hospital, Kyoto Prefectural University of Medicine. The obtaining of informed consent was waived by the institutional committee, as all the data were collected retrospectively by medical chart review.

From April 2003 to October 2004, 250 patients were prescribed antimicrobial agents effective against MRSA (anti-MRSA drugs), including two types of glycopeptides (vancomycin [VCM] or teicoplanin [TEIC]) or arbekacin (ABK). Among these patients, we found these who had been administered with these antimicrobials for a diagnosis of MRSA-HAP; these patients constituted our treated group. We also selected patients who had not received antimicrobial therapy despite the detection of MRSA in their lower respiratory tract samples during the same period; these patients were our untreated control group. We excluded patients who died within 2 days of the initiation of antimicrobial therapy.

CPIS

A modified CPIS, proposed by Singh et al. [10] (Table 1), was applied for the diagnosis of MRSA-HAP. The day-1 CPIS in the treated group was calculated on the first day the antimicrobial therapy was started, using the first five variables listed in Table 1. In the untreated control group, the day-1 CPIS was set when the microbiological sample was submitted to a microbiological laboratory. Two days after the calculation of the day-1 CPIS, the day-3 CPIS was calculated, using all seven variables listed in Table 1. For the calculations of the score, the worst values recorded on the day were used. All the variables were obtained by retrospective chart review.

TDM

In the treated group, the dose, treatment duration, and/or serum concentration of anti-MRSA agents were recorded for each agent. For glycopeptides, the initial trough levels were measured at around 3 days after the initiation of therapy, and peak levels for ABK were measured immediately after the first dosing. At our institution, the following values were recommended as target levels; VCM, 10–15 $\mu g \cdot ml^{-1}$ (trough); TEIC, 15–20 $\mu g \cdot ml^{-1}$ (trough); ABK, 5–10 $\mu g \cdot ml^{-1}$ (peak).

Other data collection

Age, sex, and a simplified Acute Physiology and Chronic Health Evaluation II (APACHE II) score were evalu-

Table 1. Clinical pulmonary infection score (CPIS)

Parameter	Value	Points
1. Temperature (°C)	≧36.5 and ≦38.4	0
	≧38.5 and ≦38.9	1
	≧39.0 and ≦36.0	2
2. Blood leukocytes (/mm^3)	≧4000 and ≦11000	0
	<4000 or >11000	1
	+Band forms ≧50%	Add 1
3. Tracheal secretions	Absence of tracheal secretions	0
	Presence of nonpurulent tracheal secretions	1
	Presence of purulent tracheal secretions	2
4. Oxygenation (Pa_{O_2}/FI_{O_2})	>240 or presence of ARDS	0
	≦240 and absence of ARDS	2
5. Chest radiograph	No infiltrate	0
	Patchy or diffuse infiltrate	1
	Localized infiltrate	2
6. Progression of pulmonary infiltrate	No radiographic progression	0
	Radiographic progression	2
7. Culture of tracheal aspirate	Rare or light quantity or no growth	0
	Moderate or heavy quantity	1
	Same pathogenic bacteria seen on Gram stain	Add 1

CPIS on day 1 was calculated from five variables (nos. 1–5). CPIS on day 3 was calculated from all seven variables. A score of more than 6 was considered as pneumonia
ARDS, acute respiratory distress syndrome

Table 2. Baseline and clinical characteristics of patients

	Treated group (n = 42)	Control group (n = 36)	P value
Age (years mean ± SD)	63 ± 22	53 ± 30	NS
Sex, male/female	32/10	26/10	NS
Medical	28 (67)	22 (61)	NS
Surgical	14 (33)	14 (39)	NS
Chronic organ insufficiency[a]	19 (45)	15 (42)	NS
COPD or chronic lung disease	9 (21)	6 (17)	NS
Serum creatinine >1.5 mg /dl	4 (10)	1 (3)	NS
APACHE II score (mean ± SD)	17.1 ± 6.6	12.6 ± 5.0	0.004
Mechanical ventilation	12 (29)	4 (11)	0.09
Tracheostomy	16 (38)	11 (31)	NS
Tracheal tube	10 (24)	5 (14)	NS

COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology And Chronic Health Evaluation Score II
[a] Chronic organ insufficiency describes patients who have the following underlyng complications or conditions: liver cirrosis, portal hypertension, hepatic failure, NYHA class IV, COPD, chronic hypoxia or hypercapnia, severe exercise restriction, chronic renal failure, immunosuppressive therapy, chemotherapy, leukemia, or lymphoma

ated as background data. The existence of an artificial airway, such as a tracheal tube or tracheotomy tube, was recorded. In patients who had received mechanical ventilation, this was also recorded. The 30-day mortality and the causes of death were evaluated. Minimal inhibitory concentrations of each drug for the target MRSA were also recorded.

Statistical analysis

Numerical data are expressed as means ±SD and categorical data are expressed as numbers with percentages in parentheses. Continuous variables, such as age and APACHE II score were compared using Student's *t*-test. Fisher's exact test was used to compare categorical data. For all tests, P values of less than 0.05 were considered significant.

Results

Baseline and clinical characteristics (Table 2)

Baseline characteristics were similar in the two groups, excluding the APACHE II score. The APACHE II score was significantly higher in the treated group compared with the untreated control group (17.1 ± 6.6 versus 12.6 ± 5.0; P = 0.004). The percentage of patients who had received mechanical ventilation tended to be greater in the treated group compared with the untreated control group (29% vs 11%; P = 0.09). Considerable numbers of patients in both groups had had an artificial respiratory tract (62% vs 45%; not significant [NS]). No patient had a diagnosis of HAP based on the findings of a quantitative culture of tracheal aspirate and/or bronchoalveolar lavage fluid (BALF) or protected specimen brush (PSB) samples.

Table 3. Antibiotic treatment

VCM	30 (71)
TEIC	8 (19)
ABK	4 (10)
Duration of treatment (days)[a]	9.8 ± 7.6
TDM performed	31 (74)
Target level reached	5 (16)

Values are n (%) if not specified
VCM, vancomycin; TEIC, teicoplanin; ABK, arbekacin; TDM, therapeutic drug monitoring
[a] mean ± SD

CPIS

The day-1 CPIS in the treated group was 2.5 ± 1.8, which showed no significant difference from that in the untreated control group (2.9 ± 1.9). Again, no difference was observed in the day-3 CPIS (3.9 ± 1.9 vs 3.8 ± 1.6). Only two patients in each group showed a CPIS of more than 6 on day 1, indicating 4.8% and 5.5% of the patients were diagnosed as HAP based on the CPIS score. In one of the two patients in the treated group, the CPIS decreased from 7 to 4 points after the initiation of the treatment, but the score was not reduced in the other patient, indicating that there was only a single patient with true pneumonia effectively treated with antimicrobial therapy.

Antimicrobial therapy and TDM in the treated group

In the treated group, 38 patients had received glycopeptides (30, VCM; 8, TEIC) and the remaining 4 patients had received ABK (Table 3). The daily doses administered of each drug were 1.00 ± 0.27 g for VCM, 0.34 ± 0.01 g for TEIC, and 0.2 ± 0.0 g for ABK. The duration of the therapy was 10.0 ± 7.6 days.

Table 4. Mortality

	Treated group	Control group	*P* value
Overall patients			
30-Day mortality, *n* (%)	12/42 (29)	2/36 (6)	0.0156
Adjusted subgroups (APACHE II score < 20)			
APACHE II score	14 ± 5 (*n* = 35)	12 ± 5 (*n* = 35)	NS
30-Day mortality, *n* (%)	11/35 (31)	2 /35 (6)	0.0118
Cause of death			
Pneumonia	1	0	
Other infectious cause	2	0	
Noninfectious cause	8	2	
Unknown	1	0	

TDM was performed in 31 (74%) patients. The number of these patients in whom the serum drug concentration successfully reached the aforementioned target levels was only 5 (16%). In the aforementioned single patient diagnosed with pneumonia who showed significant response to the treatment, the therapeutic antimicrobial was TEIC, and the initial trough level was 14.3 $\mu g \cdot ml^{-1}$.

The MIC 90 of the isolated MRSA was 2.0 $\mu g \cdot ml^{-1}$ for VCM and TEIC, and 0.5 or less for ABK.

Mortality

The 30-day mortality was significantly higher in the treated group compared with the control group (29% vs 6%; Odds ratio [OR], 6.80; 95% confidence interval [CI], 1.40–32.86, $P = 0.01$; Table 4). The leading cause of death in the treated group was exacerbation of primary malignant disease. Pneumonia was considered as the direct cause of death in only 1 patient in the treated group. In addition, 2 patients in the treated group had suffered from other extrapulmonary infection, followed by death. We evaluated differences in mortality by matching patients' severity of illness, excluding those patients who showed an APACHE II score of more than 20. After the matching, 35 patients in each group were compared. The APACHE II score showed no significant differences between these groups, at 14 ± 5 vs 12 ± 5, in the treated and control groups, respectively. The 30-day mortality, however, was again, significantly higher in the treated group compared with the untreated control group (31% vs 6%; OR, 7.56; 95% CI, 1.53–37.29; $P = 0.01$, Table 4).

Discussion

In this retrospective cohort study, we were able to extract several problems in the diagnosis and treatment of MRSA pneumonia in our clinical setting. First, the differential diagnosis of the infection versus colonization in the respiratory tract was still difficult in patients in whom MRSA was recovered from the respiratory tract. Only a small number of the treated patients (4.8%) could actually be diagnosed with pneumonia based on the day-1 CPIS criteria. No difference in the CPIS was observed between the treated group and untreated control group, indicating that the diagnosis depended on each physician's arbitrary, vague decision-making. Second, the antimicrobial treatment appeared to be insufficient from the standpoint of TDM. Only a small proportion (12%) of the treated patients was able to reach the target serum level for each therapeutic drug. Finally, it appeared that antimicrobial treatment in patients with MRSA colonization in the respiratory tract might be associated with a worse outcome.

Recently, HAP due to MRSA has been increasingly common in patients with several risk factors, including those with diabetes mellitus, head trauma, or hemodialysis, and those receiving intensive care [11]. Recent data suggest that up to 33% of HAP is caused by MRSA [12], which has become the second most frequent HAP causative microorganism. The difficulty, however, of differential diagnosis of infection versus colonization has been a great concern. Tracheal colonization is an important process in the development of HAP, but it can occur quite frequently in intubated patients, without signs of pneumonia [5,6], and antimicrobial therapy should not be indicated for the colonization [13,14]. The diagnosis of HAP, however, is frequently difficult, as there has been no "gold-standard" for the differential diagnosis. The CPIS was originally proposed by Pugin et al. [7], in order to improve the specificity of the clinical diagnosis of pneumonia. Our study suggests that a considerable number of patients with colonization were treated unnecessarily for HAP, based on the CPIS findings. The use of a CPIS in the clinical diagnosis of MRSA-HAP may help to reduce unnecessary treatments and their associated costs. Patients with a CPIS of 6 or less could have discontinued the antibiotic treatment safely [10].

We found that patients diagnosed with and treated for pneumonia showed no decreases in CPIS subsequent to the treatment. A previous study has suggested that patients with appropriate treatment have signs of improvement in clinical symptoms by day 3 [15], and that a sustained higher CPIS level suggests treatment failure. It is known that glycopeptides and aminoglycosides have poor penetration into lung tissue [16]. This indicates that inadequate dosing and/or an insufficient serum concentration could be strongly associated with treatment failure. Given that in the treated group in our study only 5 (12%) patients reached the therapeutic range, the establishment of protocols to ensure adequate antimicrobial use should be considered. Recent investigations have suggested that the trough levels of VCM and TEIC should reach 20 $\mu g \cdot ml^{-1}$ to achieve a sufficient therapeutic effect for MRSA pneumonia [17].

In our study it was surprising that greater mortality was observed in the treated group than in the untreated controls. This finding probably suggests that clinicians tend to make a diagnosis of "pneumonia" in patients having greater severity of illness. It should be noted, however, that significantly greater mortality was observed in the treated group even when we performed an additional analysis by adjusting the baseline severity of illness, based on the APACHE II score. Inappropriate diagnosis and unnecessary treatment of pneumonia may have contributed to the worse outcome, as suggested in a previous study [10]. Moreover, one should consider the risk that a misleading diagnosis of pneumonia and unnecessary treatment might obscure other critical infections.

This study has some limitations. Firstly, the retrospective nature of data collection should be considered. Secondly, the diagnosis of "pneumonia" depended on each attending physician, without any intervention by infectious disease specialists, or the use of invasive strategies (BAL or PSB) and quantitative cultures [18]. Thirdly, the appropriateness of using the CPIS for the differential diagnosis of lower respiratory tract infection versus colonization is still unclear. In other words, a CPIS cannot detect tracheitis and/or tracheobronchitis, which are less severe than pneumonia but still clinically important nosocomial infections requiring antimicrobial treatment [19]. No significant difference in CPIS, however, was observed on day 3 between the treated and untreated groups in our study. This finding, at least, can exclude the possibility of lower respiratory tract infection having progressed to pneumonia.

In conclusion, this study has revealed a significant diagnostic and treatment failure in patients with colonized MRSA in the respiratory tract. Prudent diagnosis of pneumonia, with an appropriate diagnostic approach, including the use of a CPIS and the establishment of therapeutic protocol to ensure that the antimicrobial target level is reached should be considered. Prospective studies to validate the usefulness of a CPIS and TDM in MRSA-HAP are warranted in the future.

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