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(Citation)
International Journal of Clinical Pharmacy,41(6):1611-1617

(Issue Date)
2019-12

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90007068

Antibiotic de-escalation therapy in patients with community-acquired nonbacteremic pneumococcal pneumonia

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Abstract

Background De-escalation therapy is recommended as an effective antibiotic treatment strategy for several infectious diseases. While there is limited evidence supporting its clinical and cost-effective outcomes in patients with community-acquired bacteremic pneumonia, there is no evidence in patients with nonbacteremic pneumonia. *Objective* This study aimed to evaluate the antibiotic costs in patients who did and did not receive de-escalation therapy, based on the 2017 Japanese guidelines for the management of community-acquired nonbacteremic pneumococcal pneumonia of the Japanese Respiratory Society (JRS). *Setting* This study was conducted at a university hospital in Japan. *Methods* A retrospective case series review using the medical records was conducted from April 2008 to May 2019 at a university hospital in Japan. *Main outcome measure* Impact of antibiotic de-escalation therapy on the antibiotic costs. *Results* Among 55 patients who were eligible, the treating physicians de-escalated antibiotics in 28 (51%). The differences in the median length of hospital stay and the incidence of adverse drug reactions between the two groups were not statistically significant (p = 0.67 and 1.0, respectively). However, the median total antibiotic cost per infected patient in the de-escalated group was significantly lower than that in the non-de-escalated group [$269.8 ($195–$389) vs. $420.5 ($221–$799), p = 0.048]. *Conclusion* Antibiotic de-escalation based on the 2017 JRS guidelines leads to a reduction in total antibiotic costs for the management of community-acquired nonbacteremic pneumococcal pneumonia.

Keywords: antibiotic de-escalation therapy; community-acquired pneumococcal pneumonia; The JRS Guidelines for the Management of Pneumonia in adults; total antibiotic cost

Impacts of practice

・De-escalation therapy based on the 2017 JRS guidelines helps in reducing the total antibiotic costs without compromising clinical outcomes.

・Consultation with infectious disease physicians can lead to more appropriate antibiotic treatment practices.

Introduction

Antibiotic de-escalation therapy has been proposed as a strategy to replace the empirical broad-spectrum antibiotic regimen with a culture-directed single agent with a narrower spectrum, given intravenously or orally [1, 2]. The Infectious Diseases Society of America (IDSA) guidelines, which are the common guidelines on the management of community-acquired pneumonia in adults, recommend the initial use of broad-spectrum antibiotics with subsequent de-escalation based on culture results [3]. In Japan, the evidence-based guidelines of the Japanese Respiratory Society (JRS) are the major guidelines for the management of respiratory infections, and were updated in 2017 [4]. The 2017 JRS guidelines are prepared in accordance with Medical Information Network Distribution Service [5] and in consideration of high quality evidence, patient preferences, costs, risks, and benefits. The 2017 JRS guidelines weakly recommend de-escalation therapy based on low-quality evidence [4].

Pneumonia is a common cause of death worldwide and was the third leading cause of deaths in Japan in 2011 [6]. Because it is one of the most common diseases, community-acquired pneumonia is associated with a large economic burden [7]. According to a meta-analysis of research in Japan, the most common cause of community-acquired pneumonia is *Streptococcus pneumoniae* (*S. pneumoniae*) (18.8%) [4]. Because most broad-spectrum antibiotics are listed as being more expensive than narrow-spectrum ones [8], de-escalation therapy is expected to reduce costs. A previous report [9] showed limited evidence for the antibiotic cost reduction of de-escalation therapy for bacteremic pneumonia, but there are no studies investigating nonbacteremic pneumonia. Therefore, our study aims to evaluate the antibiotic cost of de-escalation therapy based on the 2017 JRS guidelines for community-acquired nonbacteremic pneumonia in Japan, particularly that caused by *S. pneumoniae* alone.

Aim of the study

We aimed to evaluate the antibiotic cost of de-escalation therapy according to the 2017 JRS guidelines for community-acquired nonbacteremic pneumonia, particularly those infections caused by *S. pneumoniae* alone.

Methods

We conducted a retrospective observational study at the Kobe University Hospital from April 1, 2008, to May 31, 2019, and reviewed the medical records of all patients who were > 18 years old. Patients were characterized based on the identification of *S. pneumoniae* alone in sputum cultures performed at the time of

hospital admission, and the appearance of a sudden pulmonary infiltrative shadow on a chest X-ray. Patients empirically treated with broad-spectrum antibiotics or a multiple antibiotics regimen were considered for de-escalation. Broad-spectrum antibiotics included antipseudomonal antibiotics, aminopenicillin/β-lactamase inhibitors (sulbactam/ampicillin), or anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents (vancomycin or daptomycin). Patients with severe immunosuppression associated with a relevant risk of opportunistic infection were excluded from the study [10].

In our study, antibiotic de-escalation was defined as switching from an empirical broad-spectrum antibiotic regimen to a culture-directed single narrower spectrum agent, listed as first- and second-line antibiotics in the 2017 JRS guidelines [4]. The 2017 JRS guidelines recommend amoxicillin, benzylpenicillin, and ampicillin as first-line antibiotics and oral respiratory fluoroquinolones and third-generation cephalosporin (ceftriaxone) as second-line antibiotics [4].

Organisms that developed resistance to empirical antibiotic agents for pneumococcal diseases, such as MRSA, extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, non-fermenting gram-negative bacilli including *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter* species in sputum, blood, or urine cultures within 30 days after hospitalization, were considered resistant organisms. The 30-day mortality was defined as death due to any cause within up to 30 days of hospitalization. The total antibiotic cost per infected patient was calculated based on the agent(s) by multiplying unit prices per dose with the number of total doses delivered. All costs are expressed in US dollars ($), and the exchange rate was yen 108.3 to $ 1 in May 2019. Time to clinical stability was calculated as the number of days from the date of admission to the date when the patient met the following clinical stability criteria: improved clinical signs (cough and shortness of breath), lack of fever for > 8 h, improving leukocytosis (decreased by > 10% from the previous day), tolerating oral intake, and not requiring pulmonary (mechanical ventilation), renal (hemodialysis), or cardiac (pressure) support. The quick Sequential Organ Failure Assessment (qSOFA) score was calculated at the time of diagnosis of acutely emerged pneumonia. The charlson comorbidity index was calculated according to the scoring system established by Charlson et al. [11]. The severity of pneumonia was evaluated using the age, dehydration, respiratory failure, orientation disturbance, and blood pressure (A-DROP) score of the Japanese Respiratory Society [12].

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables are presented as percentages of the specified group. Comparison of the continuous variables was performed using the Mann–Whitney U test. The association of categorical variables with different endpoints of interest was assessed using a Chi-square test or the Fisher's exact test. *P* values of < 0.05 were considered to be statistically significant.

Results

During the study period, 58 patients were diagnosed with pneumococcal pneumonia with negative blood cultures, who also received an initial broad-spectrum intravenous antibiotic regimen. After excluding 3 patients who had severe immunosuppression, finally, 55 patients were eligible for de-escalation. The causative agent in all the eligible patients was *S. pneumoniae* alone.

Table 1 summarizes the clinical and demographic characteristics of the patients whose antibiotic therapies were (n = 28) and were not (n = 27) de-escalated. No significant differences were found between the two groups with respect to age, sex, comorbidities, clinical history, and the initially prescribed antibiotics. Also, there were no differences in the charlson comorbidity index, and the severity indicators. There were 2 patients with a resistant organism at admission.

The median total antibiotic cost per patient in the de-escalated group was significantly lower than that in the non-de-escalated group [$269.8 ($195–$389) vs. $420.5 ($221–$799), $p = 0.048$] (Table 2). Fourteen patients (12 in the de-escalated group and 2 in the non-de-escalated group) were switched to oral antibiotics. In the de-escalated group, 7 patients were switched to oral amoxicillin and 5 were switched to oral respiratory fluoroquinolones (Table 3). In the non-de-escalated group, 2 patients were switched to amoxicillin/clavulanate.

Resistant organisms were detected in both groups (Table 2). The drug-resistant species identified included MRSA (n = 2), *S. maltophilia* (n = 1), and *P. aeruginosa* (n = 2). All resistant organisms were detected in sputum cultures.

An infectious diseases (ID) consultation was requested in 24% of the cases. Compared to the non-de-escalated group, patients in the de-escalated group required significantly more ID consultations ($p = 0.001$) (Table 2).

The de-escalated and non-de-escalated groups demonstrated no significant differences in the rates of 30-day mortality, the total duration of antibiotic therapy, time to clinical stability, length of hospitalization,

and incidence of adverse drug reactions (antibiotic-associated diarrhea; acute renal failure) (Table 2).

Discussion

The aim of our study was to assess the antibiotic cost of de-escalation therapy based on the 2017 JRS guidelines for community-acquired nonbacteremic pneumococcal pneumonia. The empiric antibiotic therapy was de-escalated to the definitive one in approximately 51% of patients without worsening 30-day mortality, length of hospitalization or time to clinical stability. Our findings demonstrate that de-escalation therapy was cost-effective and saved approximately $150.7 per patient. Results of this study indicate that antibiotic de-escalation based on the 2017 JRS guidelines led to a reduction in total antibiotic costs for the management of community-acquired nonbacteremic pneumococcal pneumonia.

Some previous studies have reported that de-escalation therapy seems to be safe and effective in reducing the duration of hospital stay length and the antibiotic costs with bacteremic community acquired pneumonia [13, 14]; however there is no evidence on patients with nonbacteremic pneumonia. Therefore, we focused on community-acquired nonbacteremic pneumonia caused by *S. pneumoniae* alone. During the study period, only 55 patients were eligible for de-escalation after excluding severely immunosuppressed patients, those who detected sputum cultures including organisms other than *S. pneumoniae*, or bacteremic patients. As with a previous study [13], several patients were given anti-pseudomonal antibiotics or anti-MRSA agents empirically (Table 1). Patients who visit university hospitals may have more complex disease histories than those visiting community hospitals; in our study, many of the patients who developed pneumonia and were hospitalized also had neoplastic disease, diabetes mellitus, or chronic obstructive pulmonary disease (Table 1). In these cases, physicians tend to prescribe broad-spectrum antibiotics due to concerns regarding worsening symptoms [15]. This may explain the higher frequency of anti-pseudomonal antibiotics or anti-MRSA agents given empirically for community-acquired pneumonia, although serious immunodeficiency cases were excluded.

While the previous reports [13, 14] showed that the clinical presentation at admission was more severe in the non-de-escalated group, there were no remarkable differences in the patient characteristics between the two groups in our study (Table 1). The A-DROP score is viewed as a marker of disease severity on admission and is well validated for predicting 30-day mortality [16], while the charlson comorbidity index is reported to predict 1-year mortality [17]. The qSOFA score for pneumonia is associated with in-hospital mortality, intensive care unit admission, and length of hospitalization [18]. In our study, these severity indicators were

comparable between the two groups (Table 1). Though the previous reports [13, 14] have shown that de-escalation therapy in patients with bacteremic community-acquired pneumonia was not associated with an increased risk of 30-day mortality or clinical failure, there is no such evidence in patients with nonbacteremic pneumonia. Our results showed that there were no significant differences in the 30-day mortality, the total duration of antibiotic therapy, time to clinical stability, and length of hospitalization between the two groups (Table 2). Furthermore, adverse drug reactions, which occurred in 5 patients (9.1%), were not severe. These results demonstrate that de-escalation therapy does not adversely affect patient outcomes.

In agreement with a previous study from the United States [9], we found that the median total antibiotic cost in the de-escalated group was lower than in the non-de-escalated group (Table 2). Switching from intravenous to oral therapy more frequently occurred in our de-escalated group ($p = 0.004$), which may have resulted in the lower cost of antibiotics. Early switch from intravenous to oral antibiotics in patients with severe community-acquired pneumonia is reported to be safe, and leads to lower drug costs and shorter duration of hospital stay [19, 20]. Because there is a shortage of ID physicians in Japan as compared to the European countries or the United States [21, 22, 23], doctors other than infectious disease specialists should also consider de-escalation therapy.

Oral fluoroquinolones, third-generation cephalosporins and macrolides are listed as the recommended antibiotics in the IDSA guidelines [3]. The IDSA guidelines also report that fluoroquinolones have been associated with a higher risk for quinolone-resistant pneumococci [3], but the prevalence of quinolone-resistant *S. pneumoniae* has not increased in Japan [24]. In our study, 5 patients were de-escalated to oral respiratory fluoroquinolones, but not to oral third-generation cephalosporins and macrolides (Table 3). Oral third-generation cephalosporins and macrolides are used for the treatment of community acquired pneumonia [25, 26, 27], but not listed in the 2017 JRS guidelines [4]. The bioavailability of the oral third-generation cephalosporins is relatively low [28], and the prevalence of macrolide-resistant *S. pneumoniae* has been increasing rapidly worldwide including Japan [24, 29, 30]. Therefore, the oral third-generation cephalosporins and macrolides are considered to be inappropriate for pneumonia in Japan, which means it is reasonable to de-escalate according to 2017 JRS guidelines.

De-escalation is reported to be a potential way of reducing antimicrobial resistant pathogens [31]. In our study, it was examined whether the absence of de-escalation was associated with the development of resistant bacteria, but there are various causes of development of resistant organisms, such as past medical history, hospital environment, outbreaks and thorough infection prevention measures. We found no difference in the

isolation of resistant organisms between the two groups (Table 2). There were some limitations, such as the retrospective study design and survey subjects (urine, sputum or blood) being collected for a routine medical care. It is difficult to assess causality in retrospective studies when reviewing medical records.

Infectious disease specialist consultation is associated with improved patient management or reduced mortality in bacteremic patients [9, 32, 33]. Among the 55 patients, 13 (24%) received ID consultations, and 42 (76%) did not. There was no difference in the 30-day mortality between the groups that did [1/13 (7.7%)] and did not [2/42 (4.8%)] receive ID consultation in our study ($p = 0.56$). The ID physicians tended to select de-escalation therapy ($p = 0.001$) (Table 2). An infectious disease consultation was considered to be associated with more judicious use of antibiotics.

In our study, de-escalation was done on the third day, but the observed improvement (defined as time to clinical stability) was no different between the two groups (4-5 day) (Table 2). Our results likely suggest that de-escalation can be done before improvement to reduce costs.

This study has some limitations. This is a retrospective study conducted in a single institution and evaluated for a small number of patients. The data were derived from the information extracted from medical records.

Conclusions

Our results demonstrate that antibiotic de-escalation based on the 2017 JRS guidelines for community-acquired nonbacteremic pneumococcal pneumonia is effective in reducing the total antibiotic costs without compromising the clinical outcomes. We suggest that de-escalation strategies should be more widely implemented in the management of hospitalized adults with community-acquired nonbacteremic pneumococcal pneumonia.

Funding

This research did not receive any specific grant from any public, commercial, or not-for-profit funding agencies.

Compliance with ethical standards

Disclosure of potential conflicts of interest: All authors declare that there are no conflicts of interest.

Research involving human participants and/or animals: This study was approved by the Ethics Committee of the Kobe University Graduate School of Health Sciences (Number 472-3) and was performed in accordance with the ethical standards of the Institutional Research Committee and the 1964 Helsinki Declaration.

Informed consent: Since this study was merely a retrospective review of the routine service that was put in place and data were gathered from existing documents based on routine work. Therefore, a formal consent by an individual patient was not required.

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Table 1. Patient demographics and characteristics

	De-escalated (n=28)	Not De-escalated (n=27)	*p* value
Demographic data			
Age (years), median (IQR)	72 (64-78)	70 (61-82)	0.93
Male sex, n (%)	13 (46.4)	19 (70.4)	0.10
Comorbidities, n（%）			
Neoplastic disease	9 (32.1)	9 (33.3)	1.0
Diabetes mellitus	6 (21.4)	2 (7.4)	0.25
Chronic obstructive pulmonary disease	4 (14.3)	4 (14.8)	1.0
Cerebrovascular disease	2 (7.1)	5 (18.5)	0.25
Nursing home resident	0 (0.0)	2 (7.4)	0.24
Chronic heart failure	3 (10.7)	0 (0.0)	0.24
Charlson Comorbidity Index	2 (1-4)	2 (1-3)	0.41
Severity indicators			
qSOFA score II-III, n (%)	8 (28.6)	7 (25.9)	1.0
A-DROP score III-V, n (%)	9 (32.1)	6 (22.2)	0.55
ICU admission, n (%)	7 (25.0)	10 (37.0)	0.39
Vasopressor use, n (%)	6 (21.4)	8(29.6)	0.55
Clinical history (within 3 months)			
history of pneumonia	0 (0.0)	1 (3.7)	0.49
treatment with antibiotics	1 (3.6)	1 (3.7)	1.0
hospital stays	2 (7.1)	3 (11.1)	0.67
Resistant organism carrier			
ESBL-producing Enterobacteriaceae	0 (0.0)	1 (3.7)	0.49
P. aeruginosa	0 (0.0)	1 (3.7)	0.49
Initial prescribed antibiotics, n (%)			
aminopenicillin/β-lactamase inhibitor	8 (28.6)	8 (29.6)	1.0
antipseudomonal β-lactam	7 (25.0)	6 (22.2)	1.0
fluoroquinolones	2 (7.1)	4 (14.8)	0.42
anti-MRSA agent	1 (3.6)	1 (3.7)	1.0
aminopenicillin/β-lactamase inhibitor plus an anti-MRSA agent	2 (7.1)	1 (3.7)	1.0
aminopenicillin/β-lactamase inhibitor plus a macrolide	1 (3.6)	2 (7.4)	0.61
aminopenicillin/β-lactamase inhibitor plus a tetracycline	1 (3.6)	1 (3.7)	1.0
antipseudomonal β-lactam plus an anti-MRSA agent	1 (3.6)	2 (7.4)	0.61
antipseudomonal β-lactam plus a macrolide	2 (7.1)	1 (3.7)	1.0
antipseudomonal β-lactam plus a tetracycline	3 (10.7)	1 (3.7)	0.61

Data are presented as median (IQR) or no. (%)

IQR, interquartile ranges; qSOFA, quick Sequential Organ Failure Assessment; A-DROP, age, dehydration, respiratory failure, orientation disturbance, and blood pressure; ICU, intensive care unit; ESBL, Extended spectrum β-lactamase; MRSA, methicillin-resistant *S. aureus*

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Table 2. Comparison of clinical outcomes of de-escalated and non-de-escalated patients

	De-escalated (n=28)	Non-de-escalated (n=27)	*p* value
Time to antibiotic de-escalation (days), median (IQR)	3 (2-5)	—	—
30-day mortality, n (%)	1 (3.6)	2 (7.4)	0.60
Total duration of antibiotic therapy (days), median (IQR)	11 (8-15)	9 (7-13)	0.37
Time to clinical stability (days), median (IQR)	5 (1-9)	4 (1-7)	0.62
Length of hospitalization (days), median (IQR)	12 (8-24)	16 (10-21)	0.67
Isolation of resistant organisms within 30 days, n (%)	1 (3.6)	4 (15.4)	0.20
Adverse drug reactions, n (%)			
Antibiotic-associated diarrhea	2 (7.1)	1 (3.8)	1.0
Acute renal failure	1 (3.6)	1 (3.8)	1.0
Total antibiotic cost ($), median (IQR)	269.8 (195-389)	420.5 (221-799)	0.048
Switch to oral antibiotics, n (%)	12 (42.9)	2 (7.4)	0.004
Infectious disease consultation, n (%)	12 (42.9)	1 (3.7)	0.001

Data are presented as median (IQR) or no. (%)

IQR, interquartile ranges

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Table 3. De-escalated antibiotics (n=28)

Amoxicillin	7 (25)
Benzylpenicillin	2 (7.1)
Ampicillin	12 (42.9)
Oral respiratory fluoroquinolone	5 (17.9)
Ceftriaxone	2 (7.1)

Data are presented as n (%)

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