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Safety of antimicrobial de-escalation for culture-negative severe pneumonia

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ABSTRACT

Purpose: This study investigated the outcomes of antimicrobial de-escalation (ADE) based on mortality and the incidence of multi-drug resistant (MDR) pathogen occurrence in patients with culture-negative pneumonia presenting with sepsis and septic shock.
Materials and Methods: We retrospectively analyzed patients diagnosed with severe pneumonia requiring intensive care unit (ICU) admission and possessing negative microbiological culture results at a tertiary referral hospital in South Korea from March 2008 to July 2018.
Results: We identified 107 patients with culture-negative pneumonia. The Acute Physiologic and Chronic Health Evaluation (APACHE) II and Sepsis-related Organ Failure Assessment (SOFA) mean scores were 20.3 ± 8.6 and 9.6 ± 3.3, respectively. Among the patients, 40 (37.4%) underwent ADE. The APACHE II, SOFA, and follow-up SOFA scores did not differ significantly between the groups, and no differences were found in ICU mortality and MDR pathogen occurrence (27.5% vs 41.8%, $P = .137$ and 15.0% vs 16.9% $P = .794$, respectively).
Conclusions: We observed similar ICU mortality and MDR pathogen occurrence in patients with culture-negative pneumonia presenting with sepsis/shock regardless of whether they received ADE. Additionally, ADE lowered the antimicrobial burden.

1. Introduction

Although the incidence and mortality of sepsis and septic shock vary across regions, the incidence of these conditions is showing an increasing trend and poses a major public health burden worldwide [1-5]. Pneumonia is the leading cause of sepsis in critically ill patients hospitalized in intensive care units (ICUs) [6]. The current guidelines for sepsis and septic shock management recommend empirical administration of broad-spectrum antibiotics at the initiation of therapy [7] and de-escalation to narrow-spectrum antibiotics if the patient responds [7,8]. Previous studies have attempted to show a relationship between antimicrobial de-escalation (ADE) and multidrug-resistant (MDR) pathogen occurrence but have been unable to demonstrate consistent results [9,10].

Although pneumonia or culture-negative pneumonia has not been the specific target of previous investigations, the appropriateness of empirical antimicrobial therapy has been consistently shown to be an independent factor related to ADE, and the mortality of patients who do not receive ADE has not been found to be inferior [10-14]. However, the effect of ADE in patients with sepsis or septic shock and undocumented etiologic pathogens is unclear. Despite improvements in diagnostic modalities, the rate of positive microbiological cultures is approximately 40–60% for patients with severe sepsis [15]. Moreover, mortality is not related to pathogen identification [16].

Therefore, we investigated the impact of ADE in patients with culture-negative pneumonia who presented with sepsis and septic shock requiring ICU admission. We focused on ICU and in-hospital mortality and the emergence of MDR pathogens.

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2. Materials and methods

2.1. Study patients

This was a retrospective study conducted in the medical ICU of Asan Medical Center, which is a 2700-bed referral hospital in Seoul, Korea. Since 2008, a rapid response team (RRT) whose goal is the early recognition and treatment of sepsis has operated in the hospital. This team has resulted in the establishment of an RRT registry of septic patients. We retrospectively reviewed this registry from March 2008 to July 2018. Among the 2614 patients who met the registry criteria, we screened those who were diagnosed with sepsis or septic shock due to pneumonia requiring ICU admission regardless of the clinical setting (i.e., community-acquired or hospital-acquired). Subsequently, only patients with culture-negative pneumonia were included. Patients were excluded based on the following criteria: (i) cases in which the etiologic agents were identified between admission and ICU day 5; (ii) patients who died within 2 days of ICU admission; (iii) cases in which the patients were immunocompromised, such as those with hematologic malignancies, organ transplantation recipients, or receiving immune suppressants to treat connective tissue disease; (iv) patients with non-infectious causes, such as asthma, chronic obstructive pulmonary disease, or interstitial lung disease; and (v) or patients younger than 18 years. Only the first admission for each patient was included. The details were evaluated using the STROBE checklist [17].

The study protocol was approved by the institutional review board of Asan Medical Center (IRB No.: 2018-0685), which waived the requirement for informed consent due to the retrospective nature of the analysis.

2.2. Definitions

In the current study, we defined septic patients according to the 2016 definition of sepsis [18]. According to the guidelines, the Sequential Organ Failure Assessment (SOFA) score was calculated, and patient eligibility was evaluated. Pivotal antibiotics consisted of carbapenems, anti-pseudomonal antibiotics (β-lactam/β-lactamase inhibitor and 4th generation cephalosporin or ceftazidime), 3rd generation cephalosporins (excluding ceftazidime), glycopeptides, and aminopenicillins. Companion antibiotics consisted of fluoroquinolones, macrolides, and tetracyclines. We defined ADE as the discontinuation of pivotal or companion antibiotics or switching of pivotal antibiotics up to ICU day 5 as follows: carbapenems were replaced with another class of pivotal antibiotics, and anti-pseudomonal antibiotics were changed to those without an anti-pseudomonal effect [19-21]. We defined the antibiotic burden for the first 5 days as the product of the treatment duration and number of antibiotics. For patients who died or were transferred to the general ward within 5 days, the burden of antibiotics was calculated up to the day of death or transfer. ICU mortality was defined as death during treatment in the ICU or within one day after being transferred to a general ward for terminal care. In-hospital mortality was defined as death during the hospital stay. We categorized the cause of death as either pneumonia-related or pneumonia-unrelated.

2.3. Data collection

The primary outcome was ICU mortality. The secondary outcomes were in-hospital mortality and the occurrence rate of MDR pathogens. The Acute Physiologic and Chronic Health Evaluation (APACHE) II and SOFA scores were evaluated on the date of ICU admission. The SOFA score was reassessed on the day of antimicrobial de-escalation in the ADE group or on ICU day 5 in the non-ADE group. We also calculated the Δ-SOFA score (initial SOFA score – follow-up SOFA score) [22]. In addition, we evaluated underlying medical conditions (i.e., diabetes mellitus, chronic liver or kidney disease, and congestive heart failure) and the duration of antimicrobial treatment prior to ICU admission. To evaluate the occurrence of MDR pathogens, samples for stool cultures and toxin assays were collected for *Clostridium difficile*, and samples for microbiological cultures were collected to test for methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).

2.4. Microbiological evaluation

Positive cultures were established when etiologic agents were identified from the blood, sputum, endotracheal aspiration, or bronchoalveolar lavage fluid. We also considered positive tests to be culture-positive, such as reverse-transcription polymerase chain reaction (RT-PCR) for respiratory viruses, PCR for *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, or a urinary antigen test for *Pneumococcus* (Binax Inc., Portland, ME, USA) or *Legionella* serogroup 1 (Binax Inc.). The RT-PCR assay detects influenza viruses A and B, adenovirus, bocavirus, coronavirus 229E/NL63, coronavirus OC43/HKU1, enterovirus, human metapneumovirus, and parainfluenza viruses 1 to 4 (Seegene Inc., Seoul, Republic of Korea). We considered a case to be culture-negative when the above tests were negative from the day of ICU admission to ICU day 5. For surveillance of MRSA and carbapenem-resistant pathogens, all patients admitted to the ICU underwent nasal swab cultures for MRSA and sputum or endotracheal aspirate cultures at the time of ICU admission and every week thereafter until the day of ICU discharge.

2.5. Statistical analysis

All analyses were performed using the SPSS Statistics software (version 20.0; IBM Corp., Armonk, NY, USA). Student's *t*-test or the Mann-Whitney *U* test was used for continuous variables, and the χ^2 or Fisher's exact test was used for categorical variables. All tests of significance were two-sided; *P* values <.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Eligibility screening identified 107 patients admitted to the ICU with a diagnosis of sepsis or septic shock due to pneumonia whose microbiological culture tests were negative (Fig. 1). Of the 107 patients with pneumonia, 10 (9.3%) patients were diagnosed with community-acquired pneumonia, and the remaining 97 (90.7%) patients were diagnosed with hospital-acquired pneumonia. The average age was 68.5 ± 11.3 years, with a preponderance of male patients (72.2%). Approximately 91% of the patients required mechanical ventilation at the time of RRT activation. The mean APACHE II and SOFA scores were 20.3 ± 8.6 and 9.6 ± 3.3, respectively. The median duration of antibiotic treatment before ICU admission was 3 days (interquartile range [IQR] 1.0–8.0), and the median length of general ward stay was 4 days (IQR 1.0–14.0). Among the 107 patients, ADE was performed in 40 patients (37.4%). The baseline characteristics are shown in Table 1.

3.2. De-escalation of antimicrobial therapy

A total of 98 patients (91.6%) received two or more antibiotics at ICU admission. The most common antibiotic combination was carbapenem, glycopeptide, and fluoroquinolone. No difference was found in the types of antibiotics administered between the two groups. In the ADE group, glycopeptide (60.0%) was the most common de-escalated antimicrobial agent, followed by carbapenem (32.5%) (Table 2). The median time between the day of admission and the day of de-escalation in the ADE group was three days (IQR 2.0–4.0).

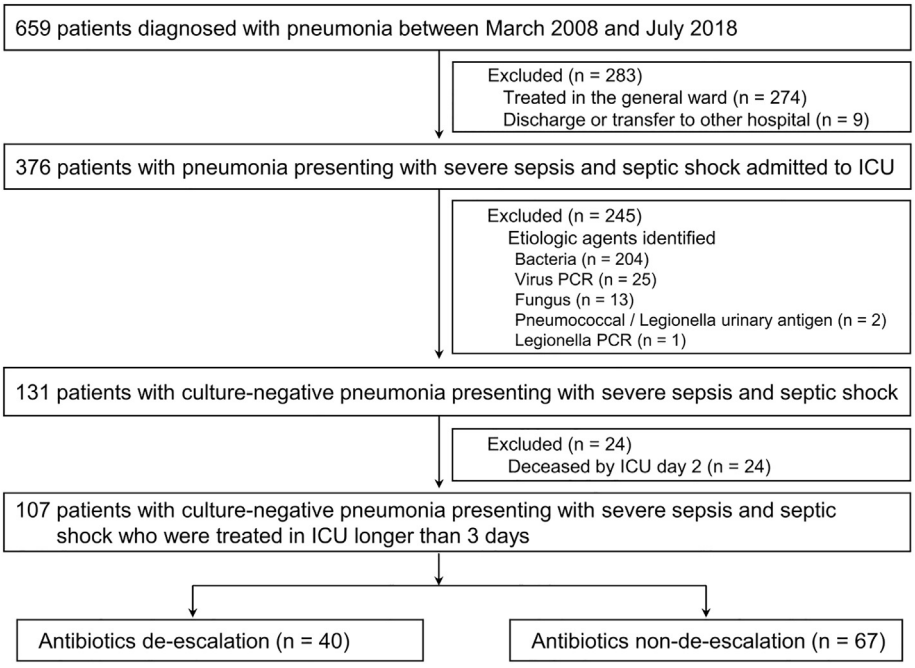

Fig. 1. Study flow chart. ICU, intensive care unit; PCR, polymerase chain reaction.

Table 1
Clinical characteristics of 107 patients with culture-negative pneumonia who presented with sepsis or septic shock and required ICU admission according to whether or not antimicrobials were de-escalated.

Characteristics	Total (n = 107)	De-escalation (n = 40)	Non-de-escalation (n = 67)	P-value
Age, years	68.5 ± 11.3	68.7 ± 10.4	68.4 ± 12.0	0.902
Sex				0.202
Male	78 (72.2%)	32 (80.0%)	46 (68.7%)	
Female	29 (27.1%)	8 (20.0%)	21 (31.3%)	
Underlying condition				
Diabetes mellitus	30 (28.0%)	11 (27.5%)	19 (28.4%)	0.924
Lung disease	21 (19.6%)	9 (22.5%)	12 (17.9%)	0.563
Renal disease	7 (6.5%)	4 (10.0%)	3 (4.5%)	0.421
Malignancy	56 (51.9%)	22 (55.0%)	34 (50.7%)	0.670
Hepatobiliary disease	10 (9.3%)	3 (7.5%)	7 (10.4%)	0.740
Congestive heart failure	24 (23.8%)	7 (19.4%)	17 (26.2%)	0.448
Cerebrovascular disease	17 (15.9%)	7 (17.5%)	10 (14.9%)	0.724
Pre-ICU antibiotic duration, days	3 (1–8.0)	2 (1–5.5)	3.5 (1–11.0)	0.200
Prior length of ward stay, days	4 (1–14.0)	3.5 (1–13.0)	6 (1–15.0)	0.372
ICU admission				
APACHE II score	20.3 ± 8.6	20.7 ± 8.9	20.1 ± 8.4	0.755
SOFA score	9.6 ± 3.3	9.4 ± 3.5	9.8 ± 3.2	0.516
Use of mechanical ventilation	97 (90.7%)	34 (85.0%)	63 (94.0%)	0.121
Renal replacement therapy	25 (24.0%)	9 (23.7%)	16 (24.2%)	0.949

ICU, intensive care unit; APACHE, Acute Physiologic And Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment.
Categorical variables are expressed as n (%).
Continuous variables are expressed as mean ± standard deviation or median (interquartile range).

3.3. Clinical outcomes

The average follow-up SOFA score was 9.0 ± 4.2 in the ADE group and 8.8 ± 3.6 in the non-ADE group. No significant differences were found in the follow-up SOFA and Δ-SOFA scores between the two groups. ICU mortality was 27.5% in the ADE group and 41.8% in the non-ADE group (P = .137, Table 3). The mean ICU length of stay was similar between the ADE (11.5 days, IQR 5–18.8) and non-ADE groups (10 days, IQR 6.0–21.0) (P = .592). In the multivariate analysis, ADE

Table 2
Antibiotic regimen, number of antibiotics, and de-escalation of antibiotics in 107 patients with culture-negative pneumonia who presented with sepsis or septic shock and required ICU admission according to whether or not antimicrobials were de-escalated.

	Total (n = 107)	De-escalation (n = 40)	Non-de-escalation (n = 67)	P-value
Initial antibiotics				
Carbapenem	56 (52.3%)	18 (45.0%)	38 (56.7%)	0.240
ß-lactam/ß-lactamase inhibitor	42 (39.3%)	17 (42.5%)	25 (37.3%)	0.595
Fluoroquinolone	75 (70.1%)	28 (70.0%)	47 (70.1%)	0.987
Glycopeptide	67 (62.6%)	27 (67.5%)	40 (59.7%)	0.420
Cephalosporin	9 (8.4%)	2 (5.0%)	7 (10.4%)	0.479
Macrolide	1 (0.9%)	0 (0.0%)	1 (1.5%)	1.000
Tetracycline	3 (2.8%)	1 (2.5%)	2 (3.0%)	1.000
Number of antibiotics				0.256
1	9 (8.4%)	4 (10.0%)	5 (7.5%)	
2	47 (43.9%)	19 (47.5%)	28 (41.8%)	
3	41 (38.3%)	15 (37.5%)	26 (38.8%)	
4	10 (9.3%)	2 (5.0%)	8 (11.9%)	
De-escalated antibiotics				
Glycopeptide[a]		24 (60.0%)		
Carbapenem[b]		13 (32.5%)		
Fluoroquinolones[c]		12 (30.0%)		
ß-lactam/ß-lactamase inhibitor[d]		5 (12.5%)		

Categorical variables are expressed as n (%).
[a] total of 24 patients received ADE; 24 (100%, discontinuation).
[b] A total of 13 patients received ADE; 5 (38.5%, piperacillin/tazobactam), 3 (23.1%, 3rd-generation cephalosporin), 2 (15.4%, ampicillin/sulbactam), 1 (7.7%, aztreonam), and 2 (15.4%, discontinuation).
[c] A total of 12 patients received ADE; 12 (100% discontinuation).
[d] A total of 5 patients received ADE; 5 (100%, 3rd-generation cephalosporin).

Table 3
Survival outcomes of 107 patients with culture-negative pneumonia who presented with sepsis and septic shock.

	Total (n = 107)	De-escalation (n = 40)	Non-de-escalation (n = 67)	P-value
ICU mortality	39 (36.8%)	11 (27.5%)	28 (41.8%)	0.137
In-hospital mortality	52 (48.6%)	15 (37.5%)	37 (55.2%)	0.076
ICU length of stay, days	11 (6.0–19.0)	11.5 (5–18.8)	10 (6.0–21.0)	0.592
Duration of MV, days	10 (4.3–16.8)	10.5 (4.8–15.3)	9 (4.0–18.3)	0.782
Duration of antibiotic administration	22 (14.8–40.3)	21 (13.0–41.3)	24 (15.0–39.0)	0.737
Burden of antibiotics[a]	12.0 ± 4.6	11.0 ± 3.6	12.6 ± 5.0	0.050
Follow-up SOFA score	8.9 ± 3.8	9.0 ± 4.2	8.8 ± 3.6	0.805
Δ-SOFA score[b]	0.8 ± 3.7	0.4 ± 3.7	1.0 ± 3.8	0.392

ICU, intensive care unit; MV, mechanical ventilation; SOFA, Sepsis-related Organ Failure Assessment.
Categorical variables are expressed as n (%).
Continuous variables are expressed as mean ± standard deviation or median ± interquartile range.
[a] Antibiotics burden is defined as the product of the treatment duration and number of antibiotics.
[b] Δ-SOFA score is defined as the difference between the initial and follow-up SOFA scores.

was not significantly associated with reduced mortality (hazard ratio 0.739 [95% confidence interval 0.317–1.723], P = .483, Table 4).

Of the 68 patients transferred to the general ward, 4 patients in the ADE and 9 patients in the non-ADE groups died. Hospital mortality was similar between the ADE (37.5%) and non-ADE groups (55.2%) (P = .076, Table 3). No difference was noted in the clinical characteristics or cause of death between the two groups (data not shown). The antibiotic burden was significantly lower in the ADE group than in the non-ADE group (P = .050). The antibiotics duration was 22 (14.8–40.3) days for all of the patients. At day 28 of the ICU stay, all three patients with >20 antibiotic-free days were alive, whereas 34 of the 104 patients with ≤20 antibiotic-free days had died.

3.4. Multi-drug resistant pathogens

Microbial cultures for 18 patients identified multi-drug resistant pathogens during ICU hospitalization. CRAB or CRPA was identified in 12 (10.8%) patients, and MRSA was identified in 7 (6.3%) patients. In one patient, CRAB and MRSA superinfection was documented. *Clostridium difficile* infection (CDI) was identified in 8 (7.5%) cases. No difference was observed between the ADE and non-ADE groups (P = 1.000, Table 5).

Table 4
Risk factors for ICU mortality in 107 patients with culture-negative pneumonia who presented with sepsis and septic shock.

Risk factors	Univariate analysis		Univariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	0.968 (0.941–0.996)	0.027	0.964 (0.938–0.991)	0.009
Sex		0.067		0.564
Male	1		1	
Female	1.903 (0.957–3.785)		1.246 (0.590–2.632)	
Underlying condition				
Lung disease	1.964 (0.973–3.963)	0.060	1.332 (0.635–2.794)	0.449
Severity score				
Follow-up SOFA score	1.227 (1.097–1.373)	<0.001	1.262 (1.109–1.435)	< 0.001
Antimicrobial de-escalation	0.831 (0.394–1.752)	0.627	0.739 (0.317–1.723)	0.483

HR, hazard ratio; CI, confidence interval; APACHE, Acute Physiologic and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment.

Table 5
Incidence of multi-drug resistant pathogens in 107 patients with culture-negative pneumonia who presented with sepsis and septic shock.

	Total (n = 107)	De-escalation (n = 40)	Non-de-escalation (n = 67)	P-value
Clostridium difficile infection	8 (7.5%)	3 (7.5%)	5 (7.5%)	1.000
MDR pathogen	18 (16.2%)	6 (15.0%)	12 (16.9%)	0.794
CRAB/CRPA	12 (10.8%)	3 (7.5%)	9 (12.7%)	0.532
MRSA	7 (6.3%)	3 (7.5%)	4 (5.6%)	0.701

MDR, multi-drug resistance; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*.
Categorical variables are expressed as n (%).

4. Discussion

Some evidence suggests that appropriate antimicrobial choices may reduce the mortality and likelihood of MDR pathogen occurrence in critically ill patients with sepsis and septic shock [23,24]. The current guidelines recommend that empirical antibiotics be changed to a narrower spectrum when etiologic agents are documented [7,8]. However, research on the effectiveness of de-escalation stewardship in cases of culture-negative sepsis has been limited. To the best of our knowledge, this study was the first to evaluate a relatively large number of patients with severe pneumonia whose microbiological identification tests, including multiplex-PCR and urinary antigen tests, could not positively identify a specific pathogen. We found no differences in ICU mortality or MDR pathogen emergence between the ADE and non-ADE patients. However, in-hospital mortality tended to be better in the ADE group. These findings suggest that ADE should be considered when the microbiological identification test is negative in ICU patients with pneumonia.

Previous observational studies that described the effect of ADE on mortality had limitations in drawing the conclusion that ADE could be safely performed in culture-negative sepsis and septic shock patients with pneumonia; these limitations included a small number of culture-negative patients with pneumonia or ADE [23,25,26], inclusion of patients admitted to the ICU for reasons other than pneumonia, or admission to the surgical ICU, which is a risk factor for a polymicrobial infection [11,12]. Recently, the first randomized controlled trial on ADE revealed that the mortality rate did not differ between ADE and antimicrobial continuation groups of septic patients, including those with other causes, such as urinary tract or intra-abdominal infections. The primary outcome measurement was based on the patients. In that study's subgroup analysis of 56 patients with pneumonia, the ICU stays and superinfection episodes did not differ between the ADE and non-ADE groups [20]. Given that antibiotic streamlining should be determined by a combination of the microbiological culture results, infection source, patient's clinical course, and effective source control, we chose to focus on patients with culture-negative sepsis or septic shock due to pneumonia. In our study, we excluded patients with positive tests for viral pneumonia, since the mortality of viral pneumonia is not significantly different from that of bacterial pneumonia [27].

The decision to pursue de-escalation may mean that clinical symptoms have improved [28], and serial SOFA scores or other severity measurement assessments have been used to determine whether ADE can be performed safely [21,25]. However, we found that the initial APACHE II and SOFA scores were similar between the two groups and that the Δ-SOFA scores of the ADE group tended to be less improved, although not significantly so, than those of the non-ADE group. This finding suggests that ADE can be safely performed when the clinical parameters have not deteriorated up to ICU day 5. Indeed, the follow-up SOFA score was the independent risk factor for ICU mortality in the multivariate analysis (P < .001). Nonetheless, an unmeasured clinical

factor not detected by the APACHE or SOFA score may determine whether or not ADE is performed.

The relationship between prolonged antimicrobial treatment and the emergence of MDR pathogens remains unclear [28]. The incidence of MDR pathogens in our study was 16.2%, which was comparable to that of other published studies [13,20,24]. The most common de-escalated antibiotics were glycopeptides, followed by carbapenems, which reflected the concern about the emergence of pathogens resistant to these classes of antibiotics. Notably, in a subgroup analysis, we found no correlation between carbapenem discontinuation and the emergence of CRAB or CRPA (Table S1 in the online supplement file). Carlier and colleagues reported that the probability of reaching the targeted pharmacokinetics (PK) and pharmacodynamics (PD) of narrow-spectrum antibiotics was less than that of broad-spectrum agents [29]. Although a longer duration of therapy would contribute to an increased risk of MDR pathogen emergence, not reaching the PK or PD target could indicate that insufficient drug was administered to obtain a therapeutic response. In this light, patients who receive ADE may be more likely to have a longer duration of antimicrobial therapy and thus an increased incidence of MDR pathogens [20]. Although we did not evaluate the PK and PD of the antimicrobial agents, the duration of antibiotics did not differ between the ADE and non-ADE groups. Further studies with a large number of patients are warranted to evaluate the relationship between ADE and MDR pathogen emergence.

The current study had several limitations. First, this study was conducted at a single center and was designed retrospectively. Thus, the findings of the current study may not be applicable to all patients with culture-negative pneumonia. Additionally, although we conducted meticulous surveillance cultures and other diagnostic tests, patients with clinical deterioration due to non-infectious causes may have been included. Second, there is no consensus on the definition of ADE, which makes comparisons between studies using different or conflicting definitions difficult. Third, serial procalcitonin was checked in only 40.2% (43/107) of the patients. Thus, procalcitonin-guided antimicrobial stewardship could not be evaluated in our study. However, among the patients who had follow-up procalcitonin data, no association was found between procalcitonin and antimicrobial de-escalation (Table S2 in the online supplement file). Fourth, the information in the RRT registry consisted of patients with suspected sepsis who were already receiving antibiotic therapy. Fifth, since the study duration was 10 years, a time effect on the result might have occurred. However, when we performed the analysis in two groups according to the time periods, no significant difference was observed in the effect of ADE on ICU mortality (Tables S3–12 in the online supplement file). Lastly, the most important limitation of the current study was that no antimicrobial stewardship protocols existed during this timeframe. Absence of an antimicrobial protocol led to an excessive treatment duration in our subjects that strongly deviated from the current guidelines. In addition, no difference in mortality was found between those with ≤8 days and > 8 days of antibiotic use. Thus, although our study showed the safety of ADE for patients with culture-negative pneumonia, it also indicated the importance of early discontinuation of antibiotics in these patients.

5. Conclusions

In conclusion, we found that ICU mortality and the occurrence of MDR superinfection were not higher in patients who received ADE than in those who continued to receive broad-spectrum therapy. In addition, patients who underwent ADE showed a lower burden of antimicrobial agents. These findings suggest that ADE should still be considered for patients with culture-negative pneumonia presenting with sepsis or septic shock who continue to be negative at ICU day 5.

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Declaration of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.026.

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