Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial

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Abstract

Introduction: Although early use of broad-spectrum antimicrobials in critically ill patients may increase antimicrobial adequacy, uncontrolled use of these agents may select for more-resistant organisms. This study investigated the effects of early use of broad-spectrum antimicrobials in critically ill patients with hospital-acquired pneumonia.

Methods: We compared the early use of broad-spectrum antimicrobials plus subsequent de-escalation (DE) with conventional antimicrobial treatment (non-de-escalation, NDE) in critically ill patients with hospital-acquired pneumonia (HAP). This open-label, randomized clinical trial was performed in patients in a tertiary-care center medical intensive care unit (MICU) in Korea. Patients (n = 54) randomized to the DE group received initial imipenem/cilastatin plus vancomycin with subsequent de-escalation according to culture results, whereas patients randomized to the NDE group (n = 55) received noncarbapenem, nonvancomycin empiric antimicrobials.

Results: Between November 2004 and October 2006, 109 MICU patients with HAP were enrolled. Initial antimicrobial adequacy was significantly higher in the DE than in the NDE group for Gram-positive organisms (100% versus 14.3%; P < 0.001), but not for Gram-negative organisms (64.3% versus 85.7%; P = 0.190). Mean intensive care unit (ICU) stay, and 14-day, 28-day, and overall mortality rates did not differ in the two groups. Among culture-positive patients, mortality from methicillin-resistant Staphylococcus aureus (MRSA) pneumonia was higher in the DE group, even after early administration of vancomycin. Multidrug-resistant organisms, especially MRSA, were more likely to emerge in the DE group (adjusted hazard ratio for emergence of MRSA, 3.84; 95% confidence interval, 1.06 to 13.91).

Conclusions: The therapeutic advantage of early administration of broad-spectrum antimicrobials, especially with vancomycin, was not evident in this study.
Introduction
Early use of broad-spectrum antimicrobials and subsequent de-escalation (DE) after microbiologic culture results may minimize the emergence of drug-resistant organisms [1-3] and costs [1] during the treatment of patients with hospital-acquired pneumonia (HAP). This strategy may reduce the overall duration of antimicrobial treatment [4] and mortality rates [5,6]. These studies, however, were observational, with successful DE indicating less-resistant pathogens and/or less severity of infection.

The combination of carbapenem and vancomycin is frequently prescribed for the treatment of HAP, in which the prevalence of infection by multidrug-resistant (MDR) organisms is high. Although inadequate initial therapy may increase mortality rates [7], the frequent use of carbapenem plus vancomycin predisposes to the emergence of MDR organisms. Vancomycin may select for resistant pathogens once colonization takes place [8], and vancomycin use has been associated with increases in vancomycin-resistant enterococci (VRE) [9] and vancomycin-intermediate and -resistant S. aureus [10]. Treatment with carbapenems has also been reported to increase the overall risk for emergence of MDR organisms [11-13]. Moreover, the efficacy of vancomycin as empiric therapy for HAP in hospitals with a high prevalence of methicillin-resistant Staphylococcus aureus (MRSA) has not been completely addressed. Vancomycin is a relatively large molecule, with poor penetration into the alveolar lining and alveolar macrophages [14,15]. In addition, the cure rate for vancomycin in patients with MRSA pneumonia has been disappointing [16,17]. A study of febrile neutropenic patients with MRSA infection showed that these patients did not experience worse outcomes when vancomycin therapy was delayed until definitive diagnosis [18]. The use of carbapenem, which has the broadest spectrum of activity against Gram-negative organisms, must also be controlled to limit the selection and spread of MDR pathogens.

To examine these concerns, we conducted a randomized clinical trial in a large tertiary care center in Korea, where the methicillin resistance rate of S. aureus isolated from blood has been reported to be 72% [19]. In this trial, we compared the effects of early treatment with broad-spectrum antimicrobials followed by subsequent DE, with conventional antimicrobial regimens.

Materials and methods
Study design
This prospective, open-label, randomized clinical trial was performed in the 28-bed medical ICU of a 2,200-bed tertiary care hospital in Seoul, Korea (Asan Medical Center). Written informed consent was obtained from each patient or his or her legal guardian. This study was approved by the institutional review board at Asan Medical Center and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. From November 2004 to October 2006, patients were randomly assigned to receive either initial treatment with imipenem/cilastatin plus vancomycin, with de-escalation starting 3 to 5 days later, based on initial culture results (de-escalation group, DE), or conventional empiric noncarbapenem antimicrobial therapy (non-de-escalation group, NDE). The collected data are described in Additional file 1.

Inclusion and exclusion criteria
Patients were eligible for inclusion if they were older than 18 years, had been hospitalized > 48 hours, and had been admitted to the ICU for treatment of established HAP. Patients were excluded if their pathogen(s) had been previously identified, if their antimicrobial regimen for HAP had been changed > 48 hours before ICU admission, if they were pregnant or lactating, or if they had HAP within 1 month before enrollment.

Randomization
After eligibility had been confirmed and consent was given, patients were randomized 1:1 to the DE or NDE group, by using an allocation sequence based on a block size of four, generated by a computer random-number generator.

Primary and secondary end points
The primary end point was initial antimicrobial adequacy. The secondary end points were mortality, emergence of MDR organisms, duration of antimicrobial treatment, and ICU stay. To compare the emergence of MDR organisms in the NDE and DE groups, patients with initially present MDR organisms were excluded.

Sample size and statistical analysis
Based on a previous study [20], it was expected that the antimicrobial adequacy would be 48% for NDE and 94.2% for DE. To detect this difference, we calculated that inclusion of 60 patients per group was required (two-tailed $\alpha = 0.05; 80\%$ power), allowing for 10% dropout. Recruitment period of 2 years was planned. We analyzed a modified intention-to-treat population. Categoric variables were compared by using the $\chi^2$ test or the Fisher Exact test, and continuous variables were compared by using the Student t test. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the emergence of MDR organisms with and without de-escalation.
To determine whether the proportional hazards assumptions held, we performed tests based on Schoenfeld residuals. All tests of significance were two-tailed, with P < 0.05 regarded as significant. Data were analyzed by using Stata version 11.1 (StataCorp, College Station, TX).

**Antimicrobial therapy and de-escalation policy**

DE patients were treated with imipenem/cilastatin (0.5 g every 6 hours) and vancomycin (15 mg/kg every 12 hours), with dosages adjusted in patients with renal or hepatic functional impairment. After 3 to 5 days, imipenem/cilastatin and/or vancomycin were de-escalated individually, based on culture results and clinical status (Figure 1). If the organism(s) could not be identified (culture negative), the treatment was adjusted according to the day 3 to 5 clinical pulmonary infection score (CPIS) results. In culture-negative patients with a CPIS > 6 on day 3 of antimicrobial treatment, the initial antimicrobial treatment was not de-escalated, and the patient was re-evaluated for possible etiologic organisms. In culture-negative patients with CPIS of 6 or less, the initial antimicrobial treatment was either discontinued (vancomycin) or de-escalated (imipenem/cilastatin) [21].

NDE patients received initial antimicrobials empirically according to the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia [22], except that none received carbapenem antimicrobials or vancomycin, and no de-escalation was used. The initial choice of antimicrobials and all subsequent changes of regimens, due to antimicrobial inadequacy or treatment failure, were determined by the attending physician.

Discontinuation of antimicrobial treatment in both groups was recommended in the absence of purulent sputum, if WBC was < 10,000/mm³ or decreased > 25% from its peak value, if body temperature was < 38.3°C, if improvement or lack of progression appeared on the chest radiograph, and if the PaO₂/FiO₂ ratio was > 250 mm Hg [4]. The usual durations of antimicrobial treatment were 7 days for non-MDR organisms, such as *S. aureus* and *H. influenzae*, and 8 to 14 days for MDR organisms such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and MRSA. If clinical improvement was not evident, the attending physician decided when to stop antimicrobial treatment [23].

**Definitions**

HAP was diagnosed according to the American College of Chest Physicians criteria [22,24], defined as the...
occurrence of a new and persistent radiographic infiltrate occurring 48 hours or more after admission, in conjunction with two of the following: (a) fever (38.5°C or higher) or hypothermia (< 36.5°C); (b) leukocytosis (white blood cells > 10,000/mm³ or < 4,000/mm³); or (c) purulent tracheal aspirate or sputum. Adequate antimicrobial treatment was defined as the administration of one or more antimicrobial agents with in vitro activity against the bacterial species associated with HAP [20]. Patients from whom pathogenic microorganisms could not be isolated from respiratory cultures were continued on their initial antimicrobial regimen [20]. These patients were considered not evaluable when determining antimicrobial adequacy and were excluded from the analysis. MDR organisms included MRSA; vancomycin-resistant enterococci; and certain Gram-negative bacilli, including those producing extended spectrum β-lactamase ESBLs; imipenem-resistant *Pseudomonas aeruginosa*; and organisms such as *Acinetobacter baumannii, Stenotrophomonas maltophilia*, and *Burkholderia cepacia*, which are intrinsically resistant to the broadest-spectrum antimicrobial agents [8]. Emergence of MDR organisms was defined as newly isolated MDR organisms during therapy, after excluding patients with MDR organisms isolated from initial cultures.

**Results**

**Patients**

During the 2-year study period, 217 patients were newly treated for HAP in our ICU. Of these, 108 patients were excluded because of previously identified pneumonia pathogens in 49, alterations in the antimicrobial regimen 48 hours or more before ICU admission in 36, refusal to participate in 18, and for other reasons in five. The remaining 109 patients were consecutively enrolled, with 108 included in our modified intention-to-treat analysis (Figure 1).

Table 1 shows a summary of baseline characteristics of the DE and NDE groups. Of the 109 patients, 88 were male (80.7%), and 21 were female (19.3%) patients. Their mean acute physiology and chronic health evaluation (APACHE) II score was 23.1 (standard deviation [SD], 5.6; range, 11 to 35). Other parameters did not differ significantly in these two groups. Adverse events that occurred during the study period are listed in Additional file 2.

**Organisms identified at the initiation of the study**

Initially isolated organisms in both study groups are shown in Additional file 3. Overall, 54 (50%) patients were culture positive. Culture methods included bronchoalveolar lavage in 37 patients, endotracheal aspirate in 62, expectorated sputum in 11, and blood culture in 20. No significant between-group differences were found in isolation rates of Gram-positive (*P* = 0.173) and Gram-negative (*P* = 0.920) organisms. Gram-positive organisms were more frequently isolated than were Gram-negative organisms (33.3% versus 26.9%), with MRSA being the single most frequent organism isolated from patients with HAP (*n* = 31; 28.7%).

**Initial antimicrobial agents and adequacy**

The initial antimicrobial adequacy was significantly higher in the DE than in the NDE group (75.9% versus NDE, 48%; *P* = 0.035, Table 2). This was mostly due to the activity of vancomycin against Gram-positive organisms (*P* < 0.001 for Gram-positive and *P* = 0.190 for Gram-negative organisms). The most frequently prescribed antimicrobial combination in the NDE group was piperacillin/tazobactam plus ciprofloxacin (63.6%), followed by piperacillin/tazobactam plus aminoglycoside (20%), and ceftazidime plus either ciprofloxacin or aminoglycoside (9.1%).

**Rate of de-escalation in the DE group, and regimen change or escalation in the NDE group**

We identified 36 patients in the DE group eligible for DE of vancomycin, and 33 eligible for DE of imipenem/cilastatin. Vancomycin was discontinued in 30 of these 36 patients (83.3%), whereas imipenem/cilastatin was de-escalated in 28 (84.8%) of 33, including DEs to piperacillin/tazobactam, with or without ciprofloxacin, in 17 patients, to ceftiraxone in five, to ceftazidime in three, to ampicillin/subbactam in three, and to cefazolin in two. Of the patients in the NDE group, 18 underwent change of escalation of their antimicrobial regimen, either to carbapenem alone (*n* = 10) or to carbapenem plus vancomycin (*n* = 8).

**Treatment outcomes**

The mean (SD) total duration of antimicrobial agents did not differ significantly in the DE and NDE groups (12.5 [5.8] days versus 14.1 [7.3] days; *P* = 0.222). In addition, no significant between-group differences were found in overall hospital mortality (44.2% versus 34.6%; *P* = 0.316), day-14 mortality (24.5% versus 13%; *P* = 0.314), and day-28 mortality (44.2% versus 25.9%; *P* = 0.131) rates (Table 3). The mean duration of ICU stay among survivors was longer in the DE than in the NDE group (21.1 versus 14.1 days), but the difference was not significant (*P* = 0.464). Hospital mortality rates did not differ significantly among patients with different types of pneumonia, being 40/99 (40.4%) for patients with HAP and three of nine (33.3%) in patients with ventilator-associated pneumonia (*P* > 0.999, data not shown). Overall, the mortality rates associated with Gram-positive organisms were higher than those associated with Gram-negative organisms (Table 4).

**Emergence of MDR organisms**

In 18 (25.7%) patients, new MDR organisms appeared within 1 month of antimicrobial treatment, at a mean of
21 days (range, 9 to 30 days). The overall rate of emergence of MDR organisms was significantly higher in the DE than in the NDE group (37.9% versus 16.7%; \( P = 0.043 \); Table 3), due primarily to the emergence of MRSA (27.6% versus 9.5%; \( P = 0.059 \)).

To examine further the association between antimicrobial DE and the emergence of MDR organisms, we performed a multivariable analysis adjusting for potential confounders (Additional file 4). Multivariable-adjusted hazard ratio (HR) for emergence of MRSA was significantly higher with DE than NDE (HR, 3.84; 95% confidence interval (CI), 1.06 to 13.91; \( P = 0.041 \)). The adjusted HR for emergence of MDR Gram-negative rods with DE was lower than NDE (HR, 0.60; 95% CI, 0.17 to 2.07; \( P = 0.418 \)).

**Discussion**

This prospective, randomized clinical trial showed that the adequacy of initial antimicrobial therapy is significantly higher with early use of broad-spectrum antimicrobials followed by subsequent DE than with it is conventional therapy. The higher antimicrobial adequacy observed in the DE group was mainly due to MRSA coverage by early administration of vancomycin.
Table 2 Number of patients who received adequate initial empiric antimicrobials in the DE and NDE groups

| Organism                          | DE            | NDE           | Total          | P   |
|----------------------------------|---------------|---------------|----------------|-----|
|                                   | n/m (%)       | n/m (%)       | n/m (%)        |     |
| All patients                     | 22/29 (75.9)  | 12/25 (48)    | 34/54 (63)     | 0.035 |
| Gram-positive organisms          | 21/21 (100)   | 2/14 (14.3)   | 22/35 (65.7)   | < 0.001 |
| Gram-negative organisms          | 9/14 (64.3)   | 12/14 (85.7)  | 21/28 (75)     | 0.190 |

Values given as number (percentage) of patients. DE, de-escalation group; m, number of patients with isolated organisms; n, number of patients with adequate initial antimicrobial treatment; NDE, non-de-escalation group. *Only culture-positive patients were included. **With χ² or the Fisher Exact test.

However, no significant between-group differences were noted in overall duration of antimicrobial therapy and mortality rates, with the DE group showing a higher rate of MRSA acquisition. Although vancomycin was administered early, the mortality associated with MRSA infections was higher among DE patients. Thus, early administration of vancomycin failed to show therapeutic benefits in our study, and early MRSA coverage before microbiologic documentation seems to be unnecessary.

Early use of broad-spectrum antimicrobials with subsequent de-escalation is considered a promising strategy for optimizing the responsible use of antimicrobials [1]. An observational study of 398 ICU patients with suspected VAP reported that the mortality rate was significantly (P = 0.001) lower in patients with DE (17%) than in those with no change in therapy (23.7%) or escalation (42.6%) [5]. That study, however, was observational, with no randomization, and other factors, such as baseline disease severity, may have influenced treatment outcomes, rather than the DE itself.

Previous studies, however, have reported that DE was associated with higher antimicrobial adequacy and more favorable outcomes [6, 25-27]. The difference between these results and ours may be attributable to various factors. First, our strategy may have improved antimicrobial adequacy for Gram-positive organisms, most of which were MRSA. Despite increased antimicrobial adequacy of vancomycin against Gram-positive organisms in the DE group, vancomycin had only limited overall efficacy in the treatment of HAP, with no difference in treatment outcomes. Moreover, the mortality rate was higher in our DE than in our NDE group. Vancomycin has been the only antimicrobial available for the treatment of MRSA pneumonia for years [14], but its cure rate has been disappointing [16, 17]. Also, despite the broad antimicrobial spectrum of imipenem, its adequacy for Gram-negative organisms was similar in our DE and NDE groups (64.3% versus 85.7%; P = 0.19). In a previous study, the adequacy of treatment for Gram-negative organisms was found to be higher in patients treated with a DE regimen, in which the major comparison was between cefotaxime and imipenem, which were used in 39% and 100% of NDE and DE patients, respectively [6]. In contrast, piperacillin/tazobactam (87.3%) and ciprofloxacin (61.8%) were the most frequently used initial antimicrobials in our NDE group. Previous studies have suggested that piperacillin/

Table 3 Treatment outcomes of patients with HAP in the DE and NDE groups

| Outcome                              | DE (n = 53) | NDE (n = 55) | Overall (n = 108) | P   |
|--------------------------------------|-------------|--------------|-------------------|-----|
| Time to adequate antimicrobials, days (SD) | 1.9 (0.5)   | 2.8 (0.6)    | 2.4 (0.4)         | 0.280 |
| Mortality                            |             |              |                   |     |
| Day 14                               | 13 (24.5%)  | 9 (16.7%)    | 22 (20.6%)        | 0.314 |
| Day 28                               | 21 (39.6%)  | 14 (25.9%)   | 35 (32.7%)        | 0.131 |
| Hospital mortality                   | 23 (44.2%)  | 18 (34.6%)   | 41 (39.4%)        | 0.516 |
| ICU stay, days, mean (IQR)           | 21.1 (6-35) | 14.1 (6-19)  | 17.2 (6-19)       | 0.464 |
| Emergence of MDR organisms           | 11 (37.9%)  | 7 (16.7%)    | 18 (25.4%)        | 0.043 |
| Time to development, days, mean (IQR)| 19.4 (11-30) | 22.7 (9-30) | 21 (11-30)        | 0.108 |
| Methicillin-resistant S. aureus       | 8 (27.6%)   | 4 (9.5%)     | 12 (16.9%)        | 0.059 |
| Gram-negative non-Enterobacteriaceae | 4 (13.8%)   | 5 (11.9%)    | 9 (12.9%)         | > 0.999 |
| S. maltophilia                       | 3 (10.7%)   | 2 (4.8%)     | 5 (7.1%)          | 0.383 |
| Imipenem-resistant A. baumannii      | 0           | 2 (4.8%)     | 2 (2.9%)          | 0.513 |
| Imipenem-resistant P. aeruginosa     | 0           | 1 (2.4%)     | 1 (1.4%)          | > 0.999 |
| ESBL-producing K. pneumonia          | 1 (3.6%)    | 0            | 1 (2.9%)          | 0.400 |

Values given as number (%) of patients, unless otherwise stated. DE, de-escalation group; ESBL, extended spectrum β-lactamase; IQR, inter-quartile range; MDR, multidrug-resistant; NDE, non-de-escalation group; SD, standard deviation. *Time from initial diagnosis of pneumonia to administration of adequate antimicrobial agent among initially culture-positive patients. †Excluding patients who died. ‡With the Kruskal-Wallis rank test. §MDR organisms isolated within 1 month of study enrollment. Patients with initial MDR organisms were excluded (24 patients in the DE and 13 in the NDE group). MDR organisms include methicillin-resistant S. aureus, imipenem-resistant P. aeruginosa, imipenem-resistant A. baumannii, S. maltophilia, and extended-spectrum β-lactamase-producing organisms.
vancomycin and 84.8% for imipenem/cilastatin). Another
Nevertheless, the DE rates were relatively high (83.3% for
attending physicians showed a tendency not to de-escalate.
Moreover, this study was not double-blinded. Indeed, the
quent analyses for emergence of MDR organisms.
DE than in the NDE group, which may have influenced
baseline prevalence of MDR organisms was higher in the
findings.
Adequacy No. of deaths/episodes (%) P
Overall (n = 54) 6/20 (30%) 0.304
Inadequate 15/34 (44.1%)
Adequate Gram-positive organism (n = 35)
Inadequate 4/12 (33.3%) 0.476
Adequate 12/23 (52.2%)
Gram-negative bacilli (n = 28)
Inadequate 1/7 (14.3%) 0.639
Adequate 6/21 (28.6%)
Excluding culture-negative patients.
tazobactam and imipenem/cilastatin have similar efficacy
and safety profiles [28-30]. Only one patient had ESBL-
producing Enterobacteriaceae, and broad-spectrum antimicrobials may have different sensitivity patterns at other centers. In addition, the definition of “de-escalation” dif-
fered among studies, in that most defined DE with regard
to Gram-negative organisms. For example, the activity
spectrum of antimicrobials was ranked against Gram-
negative bacteria, with DE defined as a switch to or dis-
continuation of a drug class with a less-broad spectrum
of coverage [5]. Others have defined de-escalation simi-
larly, by ranking the antimicrobial spectra of these agents
[6,31]. In contrast, imipenem/cilastatin and vancomycin
were de-escalated individually, with the former de-esca-
lated only in patients with Gram-negative organisms.
Categorizing all these definitions by using the single term
“de-escalation” is confusing and may result in divergent
findings.
The strengths of our study include its prospective
design, high initial prevalence of MDR organisms, and
relatively high severity of infection. To our knowledge, this
is the first randomized clinical trial comparing the DE of
imipenem plus vancomycin with that of non-carbapenem,
non-vancomycin in a medical ICU. This study, however,
had several limitations. First, it was performed in a single
center MICU, which may have biased patient selection.
The proportion of patients with VAP was relatively small,
and carbapenems other than imipenem, such as doripe-
nem, may yield different results. Therefore, the generaliz-
ability of this study may be limited. Furthermore, the
baseline prevalence of MDR organisms was higher in the
DE than in the NDE group, which may have influenced
treatment outcomes [32,33]. However, we sought to mini-
mize this effect by excluding these patients from subse-
quent analyses for emergence of MDR organisms.
Moreover, this study was not double-blinded. Indeed, the
attending physicians showed a tendency not to de-escalate.
Nevertheless, the DE rates were relatively high (83.3% for
vancomycin and 84.8% for imipenem/cilastatin). Another
limitation was our inability to identify pathogens in 50% of
our study patients. The percentage of patients who under-
went bronchoalveolar lavage at the time of enrollment was
relatively low; thus, our rate of obtaining adequate speci-
mens was not high. A possibility of cross-contamination
exists as a source of MDR organisms. We also used the
Clinical and Laboratory Standards Institute (CLSI) stan-
dards, rather than the European Committee on Antimicro-
bial Susceptibility Testing (EUCAST) standards to define
antimicrobial susceptibility, which may have resulted in a
small difference in the incidence of MDR organisms. In
addition, our secondary end points, including mortality
rates and emergence of MDR organisms, may not have
been sufficiently powered to detect significant differences.
Also, rectal swabs to identify carriers were not routinely
checked. Finally, the dosage of imipenem (2 g/day) may
have been insufficient for patients with Pseudomonas
pneumonia.
Conclusions
Although early use of broad-spectrum antimicrobials
significantly increased initial antimicrobial adequacy,
treatment outcomes were not improved. The therapeutic
advantage with early use of broad-spectrum antimicro-
bials, especially vancomycin, was not evident in this
study. Our results should be considered as hypothesis
generating, as discussed earlier, and additional clinical
research to verify our observations is needed.
Key messages
♦ Although early use of broad-spectrum antimicro-
bial agents significantly increased the initial ade-
quacy against multidrug-resistant pathogens among
critically ill patients with hospital-acquired pneumo-
nia, it failed to improve survival.
♦ Our data suggest that efficacy of early vancomycin
administration is limited, considering that emergence
of MRSA in the de-escalation group was even higher
than that in the non-de-escalation group.

Additional material

Additional file 1: Additional data collection. Additionally collected
data including severity scores and culture specimens.
Additional file 2: Adverse events during the study period. Adverse
events during study period in de-escalation and in non-de-escalation
groups.
Additional file 3: Initially identified organisms associated with
hospital-acquired pneumonia. Differences in initially identified
organisms in de-escalation and in non-de-escalation groups.
Additional file 4: Unadjusted and multivariable-adjusted analysis for
emergence of MDR organisms by using Cox proportional hazards
models. Multivariable Cox proportional hazards models showing
emergence of multidrug-resistant organisms in de-escalation and in non-
de-escalation groups.
Abbreviations

APACHE II score: acute physiology and chronic health evaluation score II; ATS/IDSA: American Thoracic Society/Infectious Diseases Society of America; CLSI: Clinical and Laboratory Standards Institute; CPS: clinical pulmonary infection score; DE: de-escalation; EUCAST: European Committee on Antimicrobial Susceptibility Testing; HAP: hospital-acquired pneumonia; HR: hazard ratio; ICU: intensive care unit; MDR: multidrug resistant; MRSA: methicillin-resistant Staphylococcus aureus; NDE: non-de-escalation; PaO₂: partial pressure of oxygen; PaO₂/FiO₂ ratio of the partial pressure of oxygen to the fraction of inspired oxygen; VAP: ventilator-associated pneumonia; VRE: vancomycin-resistant enterococci; WBC: white blood cell.

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Authors’ contributions

This study was designed by YSK, JC, SBH, and CML. Acquisition of the data was performed by JC, HJJ, SBH, CML, and YK. Analysis and interpretation of data was done by JWK, JC, SHC, and YSK. The manuscript was drafted by JWK, JC, and SHC. Critical revision of the manuscript for important intellectual content was done by SHC and YSK. The statistical analysis was done by JWK and SHC. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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