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Extended-spectrum antibiotics for community-acquired pneumonia with a low risk for drug-resistant pathogens

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ABSTRACT

Objectives: The potential hazards of extended-spectrum antibiotic therapy for patients with community-acquired pneumonia (CAP) with low risk for drug-resistant pathogens (DRPs) remain unclear; however, risk assessment for DRPs is essential to determine the initial antibiotics to be administered. The study objective was to assess the effect of unnecessary extended-spectrum therapy on the mortality of such patients.

Methods: A *post hoc* analysis was conducted after a prospective multicenter observational study for CAP. Multivariable logistic regression analysis was performed to assess the effect of extended-spectrum therapy on 30-day mortality. Three sensitivity analyses, including propensity score analysis to confirm the robustness of findings, were also performed.

Results: Among 750 patients with CAP, 416 with CAP with a low risk for DRPs were analyzed; of these, 257 underwent standard therapy and 159 underwent extended-spectrum therapy. The 30-day mortality was 3.9% and 13.8% in the standard and extended-spectrum therapy groups, respectively. Primary analysis revealed that extended-spectrum therapy was associated with increased 30-day mortality compared with standard therapy (adjusted odds ratio 2.82; 95% confidence interval 1.20-6.66). The results of the sensitivity analyses were consistent with those of the primary analysis.

Conclusion: Physicians should assess the risk for DRPs when determining the empirical antibiotic therapy and should refrain from administering unnecessary extended-spectrum antibiotics for patients with CAP with a low risk for DRPs.

Introduction

Pneumonia is one of the most common and life-threatening diseases worldwide (World Health Organization, 2020). Previous studies have demonstrated that the administration of inappropriate initial antibiotics can lead to adverse outcomes, including death (Kumar *et al.*, 2009; Shindo *et al.*, 2009; Tumbarello *et al.*, 2013).

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Nevertheless, physicians often suggest the administration of unnecessary extended-spectrum antibiotics, such as antipseudomonal and antimethicillin-resistant *Staphylococcus aureus* (MRSA) drugs, for patients with pneumonia to avoid any potential delays in appropriate antibiotics administration (Klompas, 2020). Some studies have revealed that the use of extended-spectrum antibiotics for patients with community-acquired pneumonia (CAP), including healthcare-associated pneumonia (HCAP), was associated with increased mortality (Attridge *et al.*, 2011; Jones *et al.*, 2020; Webb *et al.*, 2019).

To accomplish the appropriate initial antibiotic treatment for patients with pneumonia, risk assessment for drug-resistant pathogens (DRPs) is essential (Aliberti *et al.*, 2012; Aliberti *et al.*, 2021; Kobayashi *et al.*, 2018; Shindo *et al.*, 2013; Shorr *et al.*, 2012; Webb *et al.*, 2016). Recent international guidelines on CAP have highlighted the importance of evaluation for the selection of initial antibiotics (Metlay *et al.*, 2019). The 2019 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) CAP guidelines recommend the following strategy to determine the initial antibiotics to administer: an initial assessment of disease severity and evaluation of previous respiratory isolation of DRPs, including *Pseudomonas aeruginosa* and MRSA, followed by the assessment of the risk factors for DRPs in patients with severe CAP (Metlay *et al.*, 2019). In terms of DRP risk assessment, differences in regional prevalence should be taken into consideration (Metlay *et al.*, 2019; Shindo and Hasegawa, 2017). In the last decade, several research groups have proposed different prediction models for DRPs (Aliberti *et al.*, 2012; Prina *et al.*, 2015; Shindo *et al.*, 2013; Shorr *et al.*, 2012; Webb *et al.*, 2016). However, their prediction of patients at high risk for DRPs may not be sufficient, whereas their predictive performance to identify patients at low risk was high (Kobayashi *et al.*, 2018; Webb *et al.*, 2016). Although the guidelines suggest the previously mentioned treatment approach, the association between adherence to this strategy and patient outcomes is relatively unclear. Furthermore, to the best of our knowledge, evidence of the detrimental effects of the unnecessary use of extended-spectrum antibiotics in patients with CAP with a low risk for DRPs is scarce and requires further evaluation.

We hypothesized that the unnecessary use of extended-spectrum antibiotics for patients with CAP with a low risk for DRPs is associated with increased mortality. This study aimed to clarify the effect of extended-spectrum antibiotics use in patients with CAP with a low risk for DRPs according to the treatment strategies of the 2019 ATS/IDSA CAP guidelines.

Patients and methods

Study design and setting

This study was a *post hoc* analysis based on a prospective observational study that was performed at four medical institutions in Japan (one 1000-bed university hospital and three major community hospitals with more than 500 beds) from April 1, 2013 to March 31, 2014. This study was approved by the ethics review committee of Nagoya University School of Medicine (number, 2019-0312) and the respective institutional review boards of the participating institutions. The study was registered with the University Hospital Medical Information Network (registration number UMIN000009837). The protocol of this study was in accordance with the Declaration of Helsinki and the Japanese Ethics Guidelines for Epidemiological Studies. Although the need for the participants' written informed consent was waived, the opt-out method was adapted according to the ethics guidelines. Eligible patients were provided with information about the study through the internet, brochures, and bulletin boards at the participating institutions and were given the opportunity to withdraw from the study if they wished to.

Participants

The study methods used in this study were as previously described (Kobayashi *et al.*, 2018; Shindo *et al.*, 2013). Briefly, all adult patients who were hospitalized (aged ≥20 years) with newly developed CAP (including HCAP) were enrolled and followed up after 1 month. Patients with a low risk for DRPs according to the 2019 ATS/IDSA CAP guidelines were considered eligible for this study (Metlay *et al.*, 2019). The following patients were excluded: those with previous isolation for DRPs and those with severe CAP with a high risk for DRPs using locally validated prediction rules in Japan (Kobayashi *et al.*, 2018; Shindo *et al.*, 2013).

Definitions of severity, the prediction rules for DRPs, and classification of antibiotics

The 2007 IDSA/ATS criteria were followed to assess disease severity (Mandell *et al.*, 2007). The severe CAP was considered if a patient satisfied one of the two major criteria (requiring mechanical ventilation or experiencing septic shock with the need of vasopressors) or three or more of the minor criteria (respiratory rate >30 breaths/min, arterial oxygen partial pressure to fractional inspired oxygen ≤250, multilobar infiltrates, confusion, blood urea nitrogen level >20 mg/dl, leukopenia resulting from infection, thrombocytopenia, hypothermia, or hypotension requiring aggressive fluid resuscitation) (Mandell *et al.*, 2007).

Prediction rules for DRPs that were derived and validated in our previous studies were followed (Kobayashi *et al.*, 2018; Shindo *et al.*, 2013). In these studies, CAP-DRPs were defined as identified pathogens that are not susceptible to the antibiotics commonly administered for CAP, including nonantipseudomonal β-lactam (ceftriaxone or ampicillin-sulbactam), macrolides (azithromycin or clarithromycin), and fluoroquinolones (moxifloxacin, levofloxacin, or garenoxacin). The risk factors of CAP-DRPs included the use of antibiotics within the previous 90 days, hospitalization for ≥2 days during the preceding 90 days, immunosuppression, use of gastric acid–suppressive agents, tube feeding, and nonambulatory status. In addition, MRSA-specific risk factors included chronic dialysis during the preceding 30 days, congestive heart failure, and positive MRSA history within the previous 90 days. Patients were defined to be at low risk for DRPs when they presented with no or one risk factor of CAP-DRPs or when they presented with two risk factors of CAP-DRPs and no MRSA-specific risk factors (Kobayashi *et al.*, 2018; Webb *et al.*, 2016).

Antibiotics were classified into two categories: standard and extended-spectrum therapy. Standard therapy for patients with nonsevere CAP involved a nonantipseudomonal β-lactam plus a macrolide (or minocycline) or a respiratory fluoroquinolone, whereas that for those with severe CAP involved a nonantipseudomonal β-lactam plus a macrolide or a nonantipseudomonal β-lactam plus a respiratory fluoroquinolone. Extended-spectrum therapy was defined as any antibiotics with antipseudomonal activity, such as piperacillin-tazobactam, ceftazidime, cefepime, cefozopran, cefoperazone-sulbactam, meropenem, imipenem-cilastatin, doripenem, or aztreonam, or with anti-MRSA activity, including vancomycin, teicoplanin, or linezolid (Shindo *et al.*, 2013; Shindo *et al.*, 2015). Fluoroquinolones were excluded from extended-spectrum antibiotics because they were recommended as a therapeutic regimen for patients with CAP at low risk for DRPs.

End points

The primary study end point was the 30-day all-cause mortality, defined as death within 30 days of admission. Patients who were discharged or transferred to other hospitals within 30 days of admission with improvement in pneumonia were considered alive for this analysis (Fine *et al.*, 1997; Kobayashi *et al.*, 2018; Shindo *et al.*, 2013; Shindo *et al.*, 2015). The effect of the extended-spectrum therapy on 30-day mortality was also evaluated according to the severity of illness as a subgroup analysis.

Statistical analyses

Demographic and clinical characteristics were described. All categorical data were summarized as frequencies and presented as percentages. All tests were two-tailed and considered statistically significant if *P*-values were <0.05.

To assess the effect of the extended-spectrum therapy on 30-day mortality, a multivariable logistic regression analysis was performed. Five factors (nonambulatory status, respiratory rate $\geq$30/min, albumin $<$3.0 g/dl, pH $<$7.35, and blood urea nitrogen $\geq$20 mg/dl) were selected as covariables associated with 30-day mortality in patients with CAP undergoing appropriate initial antibiotic treatment (Shindo *et al.*, 2015). The odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated by setting standard therapy as the reference.

To confirm the robustness of the results, three sensitivity analyses using different analytical approaches to covariable adjustment were performed. Initially, a multivariable logistic regression analysis including other covariables as potential confounders (age $\geq$80 years, nonambulatory status, body temperature $<$36.0°C, respiratory rate $\geq$30/min, white blood cell count $\leq$4,000 cells/μl, hematocrit $<$30.0%, albumin $<$3.0 g/dl, and arterial carbon dioxide partial pressure $\geq$50 Torr) was conducted, which were associated with the 30-day mortality in patients with CAP with a low risk for DRPs (Okumura *et al.*, 2018). A propensity score was then developed for the extended-spectrum therapy using a logistic regression analysis with the following covariables associated with mortality, disease severity, or isolation of DRPs: age, sex, comorbidities, nonambulatory status, residence at a nursing home or long-term care facility, infusion therapy, wound care, tube feeding, gastric acid suppression, physical findings, laboratory findings, arterial blood gas data, radiological findings, and requiring vasopressors or requiring mechanical ventilation (including noninvasive positive-pressure ventilation) at the time of CAP diagnosis (España *et al.*, 2006; Fine *et al.*, 1997; Mandell *et al.*, 2007; Okumura *et al.*, 2018; Shindo and Hasegawa, 2017; Shindo *et al.*, 2015). The inverse probability of treatment weighting (IPTW) analysis was then performed to assess the effect of extended-spectrum therapy on the 30-day mortality (Cole and Hernán, 2008). The details of the IPTW analysis have been described in the Supplementary Material. Finally, a stratified analysis was conducted using the composite score on disease severity, and the pneumonia severity index (PSI) classes (class I-III, IV, and V) (Fine *et al.*, 1997). Patients with missing values were excluded. All statistical analyses were performed using the SPSS statistics software (version 28; IBM, Armonk, NY, USA) and R (ver.4.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants and baseline characteristics

A total of 750 patients with CAP were evaluated, and 721 patients were eligible to be included in the current study. Of the 627 patients with a low risk for DRPs, 257 underwent standard therapy, and 159 underwent extended-spectrum therapy (Figure 1). The baseline characteristics of the patients undergoing both therapies are presented in Table 1. Frequencies of patients with chronic lung diseases, central nervous system disorders, immunosuppression, nonambulatory status, abnormal vital signs, platelet count $<$100,000/cells/μl, albumin $<$3.0 g/dl, blood urea nitrogen $\geq$20 mg/dl, pH $<$7.35, the ratio of arterial oxygen partial pressure to fractional inspired oxygen $\leq$250, arterial carbon dioxide partial pressure $\geq$50 Torr, bilateral lung involvement, and severe pneumonia were higher in the extended-spectrum therapy group than in the standard therapy group.

Identified pathogens

The proportion of the identified pathogens was 51.4% (132/257) and 52.2% (83/159) in the standard therapy and extended-spectrum therapy groups, respectively. The distribution of identified pathogens is presented in Supplementary Table 1. Non-CAP-DRPs, such as *Streptococcus pneumoniae,* MRSA, *Haemophilus influenzae*, and antibiotic-sensitive enteric gram-negative bacilli, were identified in 46.7% (120/257) of the patients in the standard therapy group and 42.8% (68/159) of the extended-spectrum therapy group. CAP-DRPs were identified in 12 patients (4.7%) undergoing standard therapy and in 15 patients (9.4%) undergoing extended-spectrum therapy.

Administered initial antibiotics

The administered initial antibiotics are listed in Table 2. In the standard therapy group, most patients received a nonantipseudomonal β-lactam plus a macrolide, regardless of disease severity, and all patients in this group received azithromycin. The most commonly used antibiotic therapy for the patients in the extended-spectrum therapy group was piperacillin-tazobactam monotherapy, followed by piperacillin-tazobactam plus macrolides and carbapenems plus azithromycin therapy in patients with nonsevere CAP, whereas the most frequently administered antibiotic therapy was carbapenems plus azithromycin therapy, followed by carbapenems and piperacillin-tazobactam monotherapy in patients with severe CAP. In the extended-spectrum therapy group, combination therapy was administered to more than 60% of patients with nonsevere as well as severe CAP. The administered initial antibiotics in patients who were not classified into the standard therapy or the extended-spectrum therapy groups are also described in Supplementary Table 2.

Primary study end point

Figure 2 presents the 30-day mortality proportions of the standard therapy and extended-spectrum therapy groups. The 30-day mortality of the standard therapy group was 3.9% (10/257), whereas that of the extended-spectrum therapy group was 13.8% (22/159) (Figure 2a). On categorizing disease severity into two groups according to the 2007 IDSA/ATS criteria (Mandell *et al.*, 2007), the 30-day mortality of the standard therapy and extended-spectrum therapy groups in patients with nonsevere CAP was 2.8% (6/215) and 9.7% (9/93), respectively (Figure 2b), whereas in patients with severe CAP, it was 9.5% (4/42) and 19.7% (13/66), respectively (Figure 2c).

Table 3 presents the effect of extended-spectrum therapy on 30-day mortality. In the crude analysis, extended-spectrum therapy appeared to increase the 30-day mortality compared with standard therapy (OR 3.97; 95% CI 1.83-8.62; P $<$0.001). In the primary multivariable logistic regression analysis, the extended-spectrum therapy was significantly associated with higher 30-day mortality than standard therapy (adjusted OR [aOR] 2.82; 95% CI 1.20-6.65).

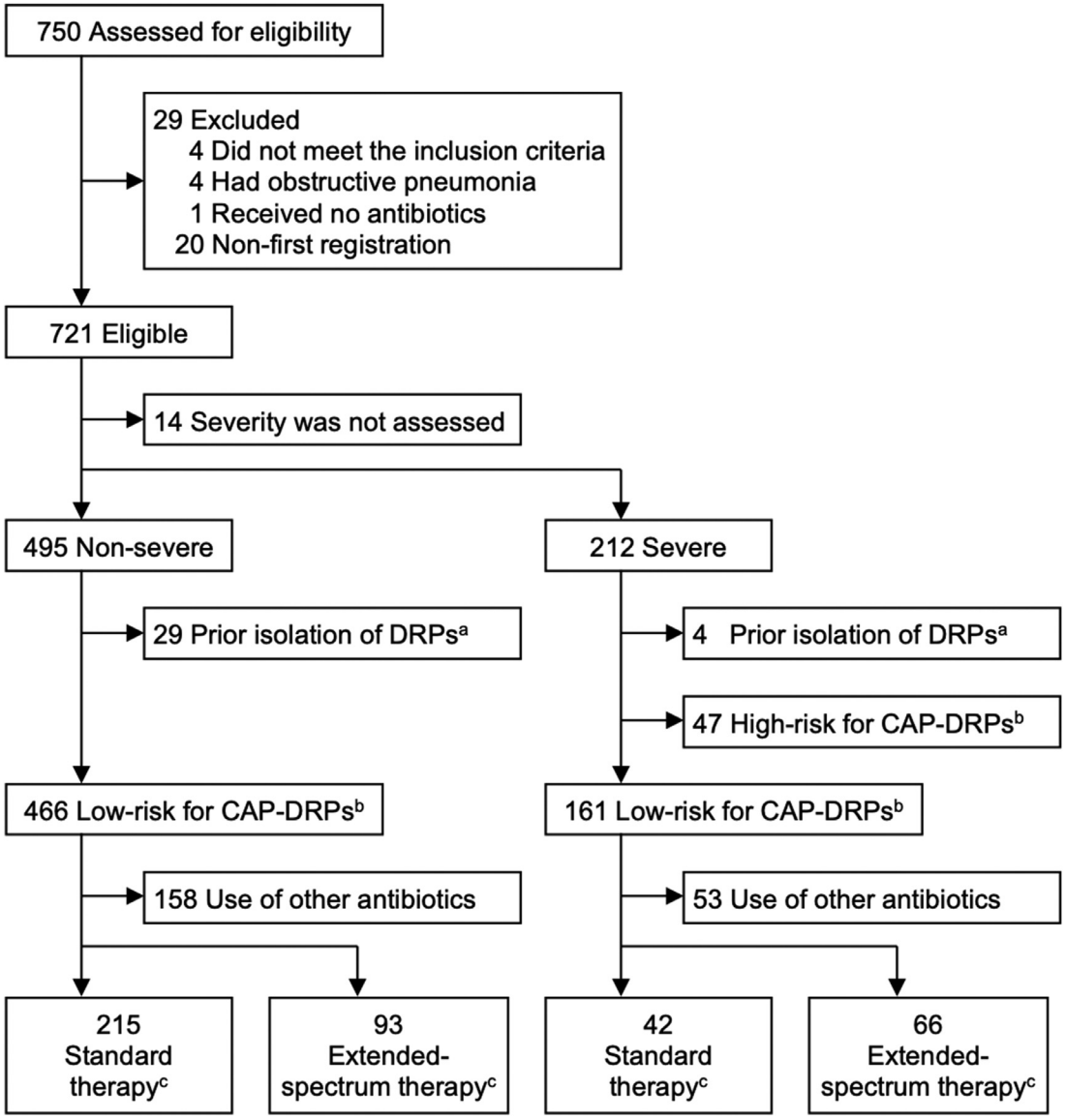

Figure 1. Patient flow.
Abbreviations: DRP, drug-resistant pathogen; CAP, community-acquired pneumonia.
CAP-DRPs were defined as pathogens not susceptible to antibiotics commonly administered in patients with CAP, including nonantipseudomonal β-lactam (ceftriaxone or ampicillin-sulbactam), macrolides (azithromycin or clarithromycin), and fluoroquinolones (moxifloxacin, levofloxacin or garenoxacin).
[a]Identified DRPs were as follows: 10, *Pseudomonas aeruginosa*; 18, methicillin-resistant *Staphylococcus aureus*; and 3, *Stenotrophomonas maltophilia* in patients with nonsevere CAP; 4, *P. aeruginosa* and 2, methicillin-resistant *S. aureus* in patients with severe CAP. *P. aeruginosa* and methicillin-resistant *S. aureus* were detected simultaneously in four patients, two nonsevere and two severe.
[b]Patients at low risk of CAP-DRPs were defined as those without prior isolation of DRPs and those with severe CAP and not at a high risk of CAP-DRPs using locally validated prediction rules in Japan.
[c]Standard therapy involved a nonantipseudomonal β-lactam plus a macrolide (or minocycline) or a respiratory fluoroquinolone for patients with nonsevere CAP and a nonantipseudomonal β-lactam plus a macrolide or a nonantipseudomonal β-lactam plus a respiratory fluoroquinolone for patients with severe CAP. Extended-spectrum therapy was defined as any antibiotics against *P. aeruginosa* or methicillin-resistant *S. aureus*.

Sensitivity analysis results are presented in Table 3. These trends are in accordance with the findings of the primary analysis. Multivariable logistic regression analysis including other covariables as potential confounders revealed that extended-spectrum therapy significantly increased the 30-day mortality compared with standard therapy (aOR 2.88; 95% CI 1.22-6.83). In the IPTW analysis, according to the propensity score, the extended-spectrum therapy also increased the 30-day mortality (aOR 2.82; 95% CI 1.11-7.16). Results associated with the validity of the IPTW propensity score analysis are provided in the Supplementary Material. The results of the stratified analysis of PSI classes also demonstrated the same trend (aOR 3.25; 95% CI 1.41-7.50) (Table 3). The 30-day mortality of the standard therapy and extended-spectrum therapy groups in each severity class (PSI class I-III [mild], IV [moderate], and V [severe]) is presented in Supplementary Table 3.

Subgroup analysis

Primary multivariable logistic regression analysis was also performed to assess the effect of extended-spectrum therapy on the 30-day mortality in each severity class as per the 2007 IDSA/ATS criteria (Supplementary Table 4). Although extended-spectrum therapy did not increase the 30-day mortality in patients with severe CAP (aOR 1.71; 95% CI 0.48-6.11), it was significantly

Table 1
Patient characteristics.

Variables	Standard therapy (n = 257)	Extended-spectrum therapy (n = 159)
Age ≥80 years	77 (30.0)	61 (38.4)
Sex, male	169 (65.8)	118 (74.2)
Comorbidities		
Neoplastic diseases	36 (14.0)	30 (18.9)
Chronic lung diseases	89 (34.6)	71 (44.7)
Congestive heart failure	33 (12.8)	27 (17.0)
Chronic renal diseases	24 (9.3)	12 (7.5)
Chronic dialysis	4 (1.6)	3 (1.9)
Chronic liver diseases	6 (2.3)	5 (3.1)
Central nervous system disorders	25 (9.7)	28 (17.6)
Diabetes mellitus	45 (17.5)	24 (15.1)
Immunosuppression[a]	11 (4.3)	19 (11.9)
Nonambulatory status[b]	20 (7.8)	30 (18.9)
Pneumonia type		
Community-acquired pneumonia	208 (80.9)	102 (64.2)
Healthcare-associated pneumonia	49 (19.1)	57 (35.8)
Physical findings		
Orientation disturbance, confusion	36 (14.0)	41 (25.8)
Systolic blood pressure <90 mmHg	7 (2.7)	15 (9.4)
Pulse rate ≥125 beats/min	20 (7.8)	26 (16.4)
Respiratory rate ≥30 breaths/min	41 (16.0)	47 (29.6)
Body temperature <36°C	1 (0.4)	5 (3.1)
Laboratory findings		
White blood cell count <4000 cells/μl	5 (1.9)	8 (5.0)
Hematocrit <30.0%	21 (8.2)	20 (12.6)
Platelet count <100,000 cells/μl	1 (0.4)	13 (8.2)
Albumin <3.0 g/dl	48 (18.7)	67 (42.1)
Total bilirubin ≥1.2 mg/dl[c]	40 (15.7)	29 (18.4)
Glucose <60 mg/dl or ≥250 mg/dl[d]	12 (4.7)	12 (7.6)
Blood urea nitrogen ≥20 mg/dl	98 (38.1)	83 (52.2)
Creatinine ≥1.2 mg/dl	52 (20.2)	37 (23.3)
Sodium concentration <130 mmol/l or ≥150 mmol/l	18 (7.0)	19 (11.9)
Potassium concentration <3.0 mmol/l or ≥6.0 mmol/l	8 (3.1)	7 (4.4)
C-reactive protein ≥20 mg/dl	66 (25.7)	48 (30.2)
pH <7.35[e]	14 (5.6)	24 (16.8)
PaO_2/F_IO_2 ratio ≤ 250[e]	61 (23.7)	69 (43.4)
$PaCO_2$ ≥50 Torr[e]	13 (5.2)	20 (14.0)
Radiological findings		
Bilateral lung involvement	106 (41.2)	96 (60.4)
Pleural effusion	40 (15.6)	35 (22.0)
Pneumonia severity index class[f]		
I-III (mild)	114 (45.2)	33 (22.9)
IV (moderate)	106 (42.1)	60 (41.7)
V (severe)	32 (12.7)	51 (35.4)

Abbreviation: PaO_2, partial pressure of oxygen; FIO_2, fraction of inspiration oxygen; $PaCO_2$, partial pressure of carbon dioxide.
Data are presented as no (%).
[a] Immunosuppression included any immunosuppressive disease, such as congenital or acquired immunodeficiency, hematologic diseases, and neutropenia (1000 cells/μl), treatment with immunosuppressive drugs within the previous 30 days, or corticosteroids at a daily dose of at least 10 mg/day of a prednisone equivalent for more than 2 weeks.
[b] Non-ambulatory status was defined as being bedridden or using a wheelchair due to difficulty in walking.
[c] The number of patients in which total bilirubin was assessed was 255 and 158 in the standard therapy and the extended-spectrum therapy groups, respectively.
[d] The number of patients in which glucose was assessed was 256 and 157 in the standard therapy and the extended-spectrum therapy groups, respectively.
[e] Arterial blood gas analysis was performed in 248 and 143 in the standard therapy and the extended-spectrum therapy groups, respectively. For patients in whom arterial blood gas analyses were not performed, PaO_2 was estimated from SpO_2.
[f] The pneumonia severity index was assessed in 252 receiving standard therapy and 144 receiving extended-spectrum therapy.

associated with increased 30-day mortality in patients with nonsevere CAP compared with standard therapy (aOR 4.47; 95% CI 1.30-15.36).

Discussion

To the best of our knowledge, this is the first *post hoc* analysis based on a multicenter prospective observational study to assess the effect of extended-spectrum antibiotic therapy on the 30-day mortality in patients with CAP with a low risk for DRPs undergoing treatment as per the 2019 ATS/IDSA CAP guidelines. The results of the primary analysis as well as those of three sensitivity analyses demonstrated that extended-spectrum therapy is constantly associated with increased 30-day mortality compared with standard therapy. In addition, subgroup analyses indicated that the increase in the 30-day mortality because of extended-spectrum therapy was distinct in patients with nonsevere CAP rather than in those with severe CAP. These results suggest that the administration of extended-spectrum antibiotics is harmful in patients with CAP with a low risk for DRPs.

The increased prevalence of DRPs is an escalating health problem worldwide (World Health Organization, 2021). The selection of appropriate target patients for the use of extended-spectrum antibiotics has been previously investigated in some studies (Gleason *et al.*, 1999; Menéndez *et al.*, 2005). Regarding patients with pneumonia, the HCAP concept was considered to resolve this issue and effectively identify patients at risk of DRPs (American Thoracic Society, 2005; Kollef *et al.*, 2008). However, several researchers

Table 2
Administered initial antibiotics.

Antibiotics	Standard therapy (n = 257)		Extended-spectrum therapy (n = 159)	
	Nonsevere (n = 215)	*Severe (n = 42)*	Nonsevere (n = 93)	Severe (n = 66)
Monotherapy				
Quinolones[a]	*16 (7.4)*	*0 (0)*	-	-
Piperacillin-tazobactam	-	-	23 (24.7)	11 (16.7)
Antipseudomonal cephalosporins[b]	-	-	9 (9.7)	1 (1.5)
Carbapenems[c]	-	-	4 (4.3)	12 (18.2)
Combination therapy				
Ampicillin-sulbactam + azithromycin	*87 (40.5)*	*22 (52.4)*	-	-
Ceftriaxone + azithromycin	*112 (52.1)*	*17 (40.5)*	-	-
Ampicillin-sulbactam + levofloxacin	*0 (0)*	*2 (4.8)*	-	-
Ceftriaxone + levofloxacin	*0 (0)*	*1 (2.4)*	-	-
Piperacillin-tazobactam + macrolides[d]	-	-	20 (21.5)	7 (10.6)
Piperacillin-tazobactam + levofloxacin	-	-	4 (4.3)	3 (4.5)
Antipseudomonal cephalosporins[b] + azithromycin	-	-	7 (7.5)	4 (6.1)
Carbapenems[c] + azithromycin	-	-	13 (14.0)	13 (19.7)
Carbapenems[c] + levofloxacin	-	-	10 (10.8)	8 (12.1)
Piperacillin-tazobactam + anti-MRSA antibiotics[e]	-	-	0 (0)	2 (3.0)
Piperacillin-tazobactam + azithromycin + anti-MRSA antibiotics[e]	-	-	1 (1.1)	1 (1.5)
Meropenem + anti-MRSA antibiotics[e]	-	-	1 (1.1)	1 (1.5)
Meropenem + azithromycin + vancomycin	-	-	0 (0)	1 (1.5)
Meropenem + levofloxacin + vancomycin	-	-	0 (0)	1 (1.5)
Ceftriaxone + teicoplanin	-	-	0 (0)	1 (1.5)
Levofloxacin + linezolid	-	-	1 (1.1)	0 (0)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus.*
Data are presented as no (%).
[a] Moxifloxacin, levofloxacin or garenoxacin were defined as quinolones.
[b] Ceftazidime, cefepime, cefozopran or cefoperazone-sulbactam were defined as antipseudomonal cephalosporins.
[c] Meropenem, imipenem-cilastatin or doripenem were defined as carbapenems.
[d] Azithromycin or clarithromycin was defined as macrolides.
[e] Vancomycin, teicoplanin or linezolid were defined as anti-MRSA antibiotics.

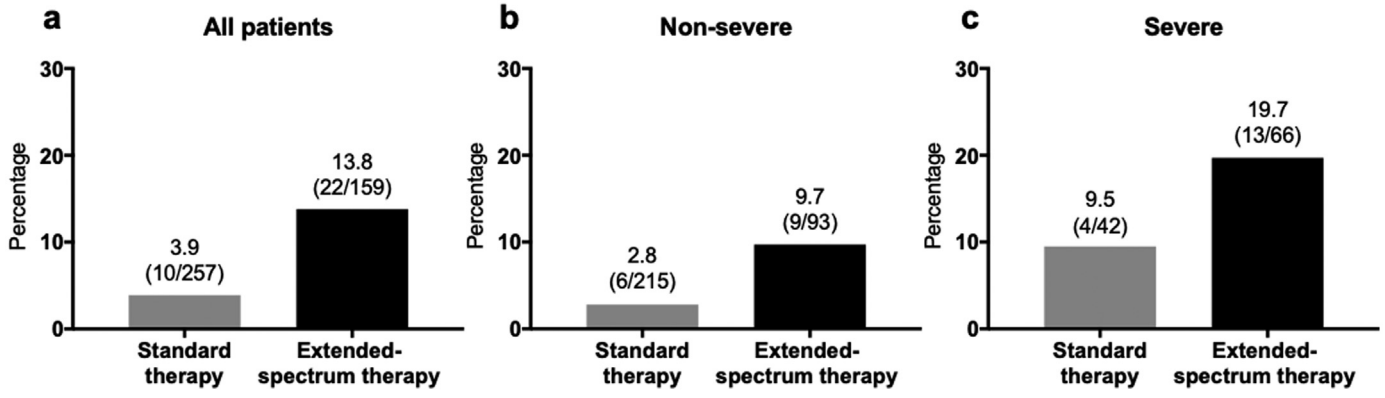

Figure 2. 30-day mortality in the treatment groups based on severity.
Abbreviation: CAP, community-acquired pneumonia.
Standard therapy involved a nonantipseudomonal β-lactam plus a macrolide (or minocycline) or a respiratory fluoroquinolone for patients with nonsevere CAP and a nonantipseudomonal β-lactam plus a macrolide or a nonantipseudomonal β-lactam plus a respiratory fluoroquinolone for patients with severe CAP. Extended-spectrum therapy was defined as any antibiotics against *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus.*
Proportions of 30-day mortality for the standard therapy and extended-spectrum therapy groups were compared for all patients (a), those with nonsevere CAP (b), and those with severe CAP (c).

have raised doubts on the HCAP concept, suggesting that it could increase the unnecessary use of extended-spectrum antibiotics (Aliberti *et al.*, 2021; Ewig *et al.*, 2019; Webb *et al.*, 2016). Indeed, several studies have revealed an association between the use of extended-spectrum antibiotics and increased mortality in patients with CAP, including HCAP (Attridge *et al.*, 2011; Jones *et al.*, 2020; Webb *et al.*, 2019). In the last decade, several research groups in different regions have reassessed the essential risk factors of DRPs to be considered when determining the initial antibiotics to be administered after pneumonia diagnosis (Aliberti *et al.*, 2012; Prina *et al.*, 2015; Shindo *et al.*, 2013; Shorr *et al.*, 2012; Webb *et al.*, 2016). The current international trend in determining the initial antibiotics to be administered for patients with CAP is to assess the history of DRP isolation and risk factors of DRPs (Metlay *et al.*, 2019; Pletz *et al.*, 2020). The use of extended-spectrum antibiotics, including those exhibiting antipseudomonal activity and anti-MRSA activity, is acceptable for patients with a history of DRP isolation or those at a high risk for DRPs. Therefore, the benefits and drawbacks of extended-spectrum antibiotics use should be carefully considered for patients without a history of DRP isolation and at a low risk for DRPs. The current study evaluated the effect of the extended-spectrum therapy in such patients.

The results of this study revealed that the extended-spectrum therapy was significantly associated with increased 30-day mor-

Table 3
Associations of antibiotics with 30-day mortalities in the crude, multivariable, propensity score and stratified analyses.

	30-day all-cause mortality
Analysis	
No. of events/ no. of patients at risk (%)[a]	
Standard therapy	10/257 (3.9%)
Extended-spectrum therapy	22/159 (13.8%)
Crude analysis-OR (95% CI)	3.97 (1.83-8.62)
Multivariable analysis-OR (95% CI)[b]	2.82 (1.20-6.65)
Sensitivity analyses	
Multivariable analysis-OR (95% CI)[c]	2.88 (1.22-6.83)
Propensity score analysis with inverse-probability of treatment weighting analysis[d]	2.82 (1.11-7.16)
Stratified analysis by pneumonia severity index[e]	3.25 (1.41-7.50)

Abbreviation: OR, odds ratio.

[a] Overall, 27 patients in the standard therapy group and 10 patients in the extended-spectrum therapy were lost to 30-day follow-up; however, they were all discharged from the hospital with improvement in pneumonia.

[b] OR from the multivariable logistic regression analysis. Covariables include nonambulatory status, respiratory rate ≥30/min, albumin <3.0 g/dl, pH <7.35, blood urea nitrogen ≥20 mg/dl. The analysis comprised 391 patients (248 who underwent standard therapy and 143 who underwent extended-spectrum therapy). 25 patients were excluded due to missing values.

[c] OR from the multivariable logistic regression analysis. Covariables include age ≥80 years, nonambulatory status, body temperature <36.0°C, respiratory rate ≥30/min, white blood cell count ≤4,000 cells/μl, hematocrit <30.0%, albumin <3.0 g/dl, arterial carbon dioxide partial pressure ≥50 Torr. The analysis comprised 391 patients (248 who underwent standard therapy and 143 who underwent extended-spectrum therapy). 25 patients were excluded due to missing values.

[d] OR from the inverse probability of treatment weighting analysis according to the propensity score for antibiotics. The analysis comprised 389 patients (247 who underwent standard therapy and 142 who underwent extended-spectrum therapy). 27 patients were excluded due to missing values.

[e] OR from the stratified analysis by pneumonia severity index classes. The analysis comprised 396 patients (252 who underwent standard therapy and 144 who underwent extended-spectrum therapy). 20 patients were excluded due to missing values.

tality in patients with a low risk for DRPs. This finding is consistent with those of previous studies.(Attridge *et al.*, 2011; Jones *et al.*, 2020; Webb *et al.*, 2019) The strategy for identifying patients with a low risk for DRPs in the current study complies with the 2019 ATS/IDSA CAP guidelines (Metlay *et al.*, 2019). The results suggest that the algorithm used for the selection of nonextended-spectrum antibiotics in CAP is appropriate and can improve patient outcomes. Furthermore, the current study revealed that adverse effects of the extended-spectrum therapy were more prominent in patients with nonsevere CAP than in those with severe CAP, indicating that physicians should refrain from administering extended-spectrum antibiotics to patients who are at a low risk for DRPs with nonsevere CAP. Moreover, no statistically different adverse effects were observed in patients with severe CAP undergoing extended-spectrum therapy compared with those with nonsevere CAP in the current study, implying that multidimensional management strategies, including appropriate respiratory care and adjunctive therapy, and the appropriate use of antibiotics are crucial for improving outcomes of patients with severe CAP (Aliberti *et al.*, 2021; Torres *et al.*, 2021; Wunderink and Waterer, 2017). Further prospective studies are warranted to validate the guidelines recommendations.

The possible explanation for the association of extended-spectrum antibiotics with increased mortality includes multiple mechanisms triggered by the antibiotics. The changes in the composition of microbiota after the administration of extended-spectrum antibiotics may be one of the key mechanisms (Thibeault *et al.*, 2021). A review of the microbiota associated with pneumonia revealed that extended-spectrum antibiotics compromise microbiota-dependent colonization resistance mechanisms. As a result, the use of extended-spectrum antibiotics may contribute to the increased risk for hospital-acquired and ventilator-associated pneumonia associated with increased mortality (Thibeault *et al.*, 2021). There may be other possible explanations, such as several extended-spectrum antibiotics can cause acute kidney injury; in particular, the combination of vancomycin with piperacillin-tazobactam, which is often prescribed for pneumonia, is associated with increased acute kidney injury (Bellos *et al.*, 2020; Lee *et al.*, 2021; Luther *et al.*, 2018). Moreover, *Clostridioides difficile* is the causative pathogen of antibiotic-associated colitis (McDonald *et al.*, 2018). A systematic review and meta-analysis revealed that carbapenems and cephalosporins induced *C. difficile* infection to a larger extent than penicillins or fluoroquinolones (Vardakas *et al.*, 2016). In addition, previous studies have demonstrated that extended-spectrum antibiotics predisposed patients to nosocomial lung infections (Metersky *et al.*, 2016; Shindo *et al.*, 2013; Thibeault *et al.*, 2021; Venier *et al.*, 2011). Furthermore, acute kidney injury and nosocomial infections, including *C. difficile* infection, are associated with increased mortality in pneumonia (Becerra *et al.*, 2015; Chawla *et al.*, 2017; Shindo *et al.*, 2013). Thus, multiple events induced by extended-spectrum antibiotics use may result in adverse outcomes in patients. Although acute kidney injury and *C. difficile* infection were not assessed in this study, we plan to evaluate them in an ongoing multicenter observational study.

This study has several limitations. There may be a potential bias because of the *post hoc* analysis based on a prospective observational study. Moreover, there might be unidentified confounding factors for the end point, and the number of events was relatively small. Accordingly, a primary multivariable logistic regression analysis and three sensitivity analyses were conducted. Moreover, the data used in this study were obtained before the COVID-19 pandemic. The results of this study may be applied to patients with CAP but not to those with COVID-19 pneumonia; we aim to investigate the effect of extended-spectrum therapy on mortality in patients with CAP, including COVID-19 pneumonia, in another multicenter observational study. Despite these limitations, the results of this study provided valuable information regarding the selection of appropriate initial antibiotics for patients with CAP with a low risk for DRPs.

Conclusion

The current study was focused on patients with CAP with a low risk for DRPs, and the results revealed that the use of extended-spectrum antibiotics is associated with increased mortality. Physicians should therefore acknowledge the significance of DRPs risk assessment when determining the empirical antibiotic therapy and should refrain from administering extended-spectrum antibiotics to patients with a low risk for DRPs.

Author contributions

All authors meet the International Committee of Medical Journal Editors authorship criteria. HK and YS designed this study. DK, YS, HK, TS, YM, TY, and HS participated in data acquisition. HK, YS, and SM created the statistical analysis plan, which was reviewed by all authors. HK, YS, TS, YM, MY, AM, KS, KM, RE, and SM contributed to data interpretation. HS and YH contributed to study supervision. HK and YS wrote the initial draft of the manuscript. TS, YM, MY, AM, TY, and SM contributed to the critical revision of the manuscript for important intellectual content. All authors approved the final draft.

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Declaration of Competing Interest

All of the following information provides relevant financial activities outside of the submitted work. YS reports personal fees (payment for lectures, including service on speaker bureaus) from KYORIN Pharmaceutical Co., Ltd.; AstraZeneca K.K.; Daiichi Sankyo Company, Limited; Nippon Boehringer Ingelheim Co., Ltd.; GlaxoSmithKline plc; and Gilead Sciences Inc. and participates as a member of the case adjudication committee of GlaxoSmithKline Biologicals SA. TY reports grants and personal fees (payment for lectures, including service on speakers bureaus) from Shionogi & Co., Ltd.; Dainippon Sumitomo Pharma Co., Ltd.; and MSD K.K. SM reports personal fees (payment for consultations in other studies) from Takeda Pharmaceutical Co., Ltd. YH reports grants and personal fees (payment for lectures, including service on speakers bureaus) from Chugai Pharmaceutical Co., Ltd.; MSD K.K.; GlaxoSmithKline plc; KYORIN Pharmaceutical Co., Ltd.; Pfizer Japan Inc.; Meiji Seika Pharma Co, Ltd.; Sanofi K.K.; and Daiichi Sankyo Inc. All other authors have no competing interests to declare.

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Supplementary materials

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