Prognostic Impact of Early Appropriate Antimicrobial Therapy in Critically Ill Patients With Nosocomial Pneumonia Due to Gram-Negative Pathogens: A Multicenter Cohort Study

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OBJECTIVES: To evaluate whether early appropriate antimicrobial therapy (EAAT) is associated with improved outcomes in critically ill patients with hospital-acquired pneumonia (HAP), ventilated HAP (vHAP), or ventilator-associated pneumonia (VAP) involving Gram-negative bacteria (GNB).

DESIGN: Retrospective cohort study based on prospectively collected data.

SETTING: Thirty-two French ICUs (OutcomeRéa network).

PATIENTS: All patients with a first HAP, vHAP, or VAP due to GNB during their ICU stay.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The relationship between EAAT and day 28 all-cause mortality (primary endpoint) was explored through Cox proportional-hazard models, with subgroup analyses according to pneumonia types, causative GNB, features of EAAT, and the occurrence of septic shock at pneumonia diagnosis. The course of Sequential Organ Failure Assessment (SOFA) score values, the clinical cure rate at day 14, and the time to mechanical ventilation (MV) weaning and ICU discharge after pneumonia diagnosis were investigated as secondary endpoints. Among the 804 included patients, 495 (61.6%) received EAAT (single-drug, 25.4%; combination, 36.2%). Day 28 mortality was 32.6%. EAAT was not independently associated with this outcome (adjusted hazard ratio, 0.87; 95% CI, 0.67–1.12). This result was confirmed in subgroup analyses as in a second model considering all episodes of pneumonia occurring during the ICU stay. EAAT was not associated with a faster decrease in SOFA score values ($p = 0.11$), a higher day 14 clinical cure rate (overall, 43.7%), or a shorter MV duration (cause-specific hazard ratio [HR] for extubation, 0.84; 95% CI, 0.69–1.01) or ICU stay (cause-specific HR for discharge alive, 0.85; 95% CI, 0.72–1.00).

CONCLUSIONS: In this study, EAAT was not associated with a reduced day 28 mortality, a faster resolution of organ failure, a higher day 14 clinical cure rate, or a shorter time to MV weaning or ICU discharge in critically ill patients with HAP, vHAP, or VAP due to GNB. However, a prognostic benefit from EAAT cannot be ruled out due to lack of statistical power.

KEYWORDS: antimicrobial therapy; Enterobacterales; hospital-acquired pneumonia; outcome; *Pseudomonas aeruginosa*; ventilated hospital-acquired pneumonia; ventilator-associated pneumonia

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are the most common healthcare-associated infections managed in the ICU (1, 2). Both conditions have been repeatedly linked with several negative patient-centered outcomes, including extended

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KEY POINTS

Question: To investigate whether early appropriate antimicrobial therapy (EAAT) is associated with improved survival in critically ill patients with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) involving Gram-negative bacteria.

Findings: Among the 804 included patients, 495 (61.6%) received EAAT. All-cause day 28 mortality was 32.6%. After adjustment on potential confounders, EAAT was not independently associated with this outcome (hazard ratio, 0.87; 95% CI, 0.67–1.12). This result was confirmed in subgroup analyses as in a second model considering all episodes of pneumonia occurring during the ICU stay.

Meaning: EAAT is not associated with improved survival in critically ill patients with HAP or VAP due to Gram-negative bacteria.

lengths of hospital stay and a substantial increase in short-term fatality rates (3, 4). This latter association appears especially pronounced in patients with severe HAP requiring invasive mechanical ventilation (MV)—that is, ventilated HAP (vHAP) (5–7).

Prompt initiation of empirical antimicrobial agents is advocated in critically ill patients with suspected HAP or VAP, whatever the severity of clinical presentation, with subsequent tailoring according to the culture results of lower respiratory tract samples and clinical reevaluation (8–10). Short-term survival in individuals with HAP or VAP appears mostly conditioned by non-modifiable factors such as age (11), chronic diseases (especially immune deficit) (12, 13), severity indexes at ICU admission (3, 14), and the extent of organ failures at pneumonia onset (14). Whether the early administration of appropriate antimicrobial therapy may positively impact this outcome remains unsettled due to conflicting evidence from relatively small-sized cohorts of patients (15–19).

The primary objective of this multicenter retrospective cohort study based on prospectively collected data was to investigate the association between early appropriate antimicrobial therapy and all-cause mortality at day 28 in critically ill patients with HAP, vHAP, or VAP due to Gram-negative bacteria. Secondary objectives were to investigate whether early appropriate antimicrobial therapy is associated with a higher rate of clinical cure at day 14 and a faster resolution of organ failures, an accelerated weaning from MV or a shorter length of the ICU stay after pneumonia diagnosis.

PATIENTS AND METHODS

Study Design and Data Source

This observational study was conducted using the OutcomeRéa prospective database fueled since 1996 by a total of 32 ICUs in France, including 18 ICUs located in university hospitals. The methodology implemented for data collection and quality control has been extensively described elsewhere (20). The protocol of the OutcomeRéa database was submitted to the Institutional Review Board (IRB) of the Clermont-Ferrand University Hospital (Clermont-Ferrand, France) who waived the need for informed consent (approval in 1996, IRB No. 5891), and abides by the Helsinki Declaration of 1975. The OutcomeRéa database has been approved by the French Advisory Committee for Data Processing in Health Research and registered by the French National Informatics and Liberty Commission (registration n°8999262), in compliance with French law on electronic data sources. The methods and results of this study are exposed according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (www.strobe.org).

Study Population and Definitions

All patients admitted between January 1, 2008, and September 1, 2019, and presenting a first HAP, vHAP, or VAP exclusively due to Gram-negative bacteria were included in the study. Only pneumonia episodes managed or acquired in the ICU were considered.

Day 0 was defined as the date of pneumonia diagnosis—that is, the date of sampling of the first lower respiratory tract specimen with positive culture above the significance threshold (**Electronic Supplementary Material**, http://links.lww.com/CCM/H684). HAP and VAP were classified according to usual definitions (8, 9). vHAP were defined as HAP requiring invasive MV (arbitrarily, tracheal intubation between day –1 and day 2), in agreement with available studies in

this field (7, 21, 22). All episodes were prospectively entered in the database by the attending ICU physicians provided that standardized clinical, biological, radiological, and microbiological diagnostic criteria were met (Electronic Supplementary Material, http://links.lww.com/CCM/H684). Pneumonia involving both Gram-negative and Gram-positive bacteria was discarded. Ventilator-associated tracheobronchitis was not considered.

Early appropriate antimicrobial therapy was defined as the administration of one (single-drug) or two (combination) agents with in vitro activity against the causative Gram-negative bacteria at day 0 and/or day 1. For combination regimen, the companion drug was defined as the first discontinued antimicrobial (de-escalation), while the drug class pursued as definite therapy was defined as pivotal (23). Regarding patients with pneumonia involving more than one Gram-negative bacterium (polymicrobial pneumonia), those treated with two antimicrobials active against all isolated pathogens were classified as receiving appropriate combination therapy, while those with one pathogen susceptible to one drug and the other one susceptible to both drugs were classified as receiving appropriate single-drug therapy.

Multidrug-resistant bacteria (MDR) were defined according to the United States and European Centers for Disease Control and Prevention classification (24). Immune deficiency was defined as any form of immunosuppression excepting HIV infection without acquired immune deficiency syndrome (Electronic Supplementary Material, http://links.lww.com/CCM/H684). Sepsis and septic shock were defined according to the Sepsis-3 criteria (25). The acute respiratory distress syndrome was defined according to the Berlin definition (26). The Sequential Organ Failure Assessment (SOFA) score was calculated using the daily clinical and biological variables entered in the database—missing biological values were imputed as normal. The definition used for clinical cure at day 14 is detailed in the Electronic Supplementary Material (http://links.lww.com/CCM/H684).

The primary study endpoint was all-cause mortality at day 28 (27). Secondary endpoints were: 1) the course of daily SOFA score values from day 0 to day 28, 2) the clinical cure rate at day 14, 3) MV duration after day 0, and 4) the length of stay (LOS) in the ICU after day 0.

Statistical Analyses

Data are expressed as number (percentage) for categorical variables and median (interquartile range) for continuous variables, unless otherwise indicated. Categorical and continuous variables were compared using the Fisher exact test or the chi-square test and the Kruskal-Wallis test or the *t* test, respectively. The observed cumulative incidence of all-cause death at day 28 was compared between patients with and without early appropriate antimicrobial therapy using Kaplan-Meier curves and the log-rank test.

The potential association between the administration of early appropriate antimicrobial therapy and the study endpoint was explored in the framework of Cox proportional-hazard models adjusted on inclusion subperiods, Simplified Acute Physiology Score-2 (SAPS-2) values at ICU admission, chronic diseases other than immune deficiency, immune deficiency, pneumonia types, SOFA score values at pneumonia diagnosis, and prior ICU LOS. In the main model, receiving or not early appropriate antimicrobial therapy for the first pneumonia was handled as the explanatory variable, without considering further episodes, if any. To assess whether this association was modified in patients with more than one pneumonia due to Gram-negative bacteria during the ICU stay, a confirmatory model was built handling all episodes—treated appropriately or not—as time-dependent and cumulative variables (counting process). Subgroups analyses were performed using the main model in patients with a first HAP/vHAP, a first VAP, a first pneumonia (either HAP/vHAP or VAP) due to MDR Gram-negative bacteria, a first pneumonia due to *Pseudomonas aeruginosa*, those receiving an aminoglycoside or a fluoroquinolone as companion drug, those receiving appropriate initial combination therapy for less than or equal to 2 or greater than 2 days, and those presenting with septic shock at pneumonia diagnosis. Adjusted hazard ratios (aHRs) are provided with their 95% CIs. Multicollinearity was assessed using the variance inflation factor (VIF).

The course of SOFA score values from day 0 to day 28 (i.e., the value at day 0 minus the value measured for each subsequent day until day 28) was compared between patients who received early appropriate antimicrobial therapy and those who did not using a mixed-effect linear model. The impact of early appropriate

antimicrobial therapy on MV duration and ICU LOS after day 0 was investigated through cause-specific hazard models handling extubation or ICU discharge alive, respectively, as the outcome of interest. Potential difference in MV duration and LOS for patients who received early appropriate therapy, compared to those who did not, was calculated using the following formula: median MV duration or ICU LOS after day 0 in patients not receiving early appropriate therapy (in days) × (1–cause-specific hazard ratio).

A *p* value of less than 0.05 was considered significant. Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Study Population and Characteristics of Pneumonia Episodes

A total of 804 patients were enrolled in the study cohort (**Table 1**; and **Fig. S1**, http://links.lww.com/CCM/H684), including 170 (21.1%) who were immunocompromised. SAPS-2 and SOFA score values at ICU admission were 50 (38–65) and 8 (5–11). Most of patients (78.0%) experienced a single episode of pneumonia during the ICU stay (Table 1).

Among the 804 first episodes of pneumonia, 556 (69.2%), 131 (16.3%), and 117 (14.6%) were VAP, HAP, and vHAP, respectively (**Table 2**). The characteristics of patients transferred to the ICU for the management of HAP acquired in wards (n = 149) and those with ICU-acquired HAP (n = 99) are exposed in **Table S1** (http://links.lww.com/CCM/H684). Enterobacterales accounted for 394 episodes (49.0%) while *P. aeruginosa* was involved in 312 cases (38.8%). MDR pathogens were isolated in 215 episodes (23.5%). The median SOFA score value at pneumonia diagnosis was 6 (4–9). Criteria for sepsis and septic shock were met in 615 (76.5%) and 180 (22.4%) patients, respectively. Only nine patients (1.2%) were neutropenic at the time of pneumonia.

Characteristics of subsequent episodes of pneumonia are exposed in Table 2 and **Table S2** (http://links.lww.com/CCM/H684)

Appropriateness of Antimicrobial Therapy for First Pneumonia Episodes

Early appropriate single-drug and combination therapies were administered in 204 (35.4%) and 291 (36.2%) patients, respectively (Table 2). The appropriate pivotal drug was a β-lactam for 486 patients (60.4%)—most often an antipseudomonal penicillin (with or without β-lactamase inhibitor) or an antipseudomonal carbapenem. The appropriate companion drug was an aminoglycoside in 218 patients (27.2%) and a fluoroquinolone in 65 patients (8.1%). The remaining 309 patients (38.4%) did not receive appropriate antimicrobial agents at day 0 and/or day 1; among them, 135 (16.8%), 50 (6.2%), and 45 (5.6%) were appropriately treated from day 2, day 3, and day 4 or later, respectively—79 patients died (9.8%) without having received appropriate antimicrobials.

Patients who received early appropriate therapy, compared to those who did not, presented more frequently with septic shock at pneumonia diagnosis, and were less often infected with MDR Gram-negative bacteria (Table 1).

Primary Study Endpoint

Two hundred sixty-two patients (32.6%) had died at day 28 (Table 1). The cumulative incidence of all-cause death at day 28 did not differ between patients with and without early appropriate antimicrobial therapy (32.9% vs. 32.0%, respectively; $p = 0.30$ by the log-rank test; **Fig. 1**). In the main Cox proportional-hazard model not considering subsequent episodes (if any), the SAPS-2 value at ICU admission (aHR, 1.01 per 1-point increase; 95% CI, 1.00–1.02; $p = 0.003$) and the SOFA score value at pneumonia diagnosis (aHR, 1.13 per 1-point increase; 95% CI, 1.09–1.12; $p < 0.001$) were the sole independent predictors of death at day 28 (**Table 3**). The early administration of appropriate antimicrobial therapy was not associated with this outcome (aHR, 0.87; 95% CI, 0.67–1.12), including when analyzing early appropriate single-drug therapy (aHR, 0.83; 95% CI, 0.60–1.14) and early appropriate combination therapy (aHR, 0.910; 95% CI, 0.697–1.19) separately. No significant multicollinearity was observed between the SAPS-2 value at ICU admission and the SOFA score value at pneumonia diagnosis (VIF, 1.13) (**Table S3**, http://links.lww.com/CCM/H684). The confirmatory model handling all episodes as cumulative time-dependent variables provided similar results, without impact of early appropriate therapy (for all episodes if > 1) on day 28 mortality (aHR, 0.94; 95% CI, 0.68–1.31) (Table 3).

TABLE 1.
Characteristics of the Study Population According to the Appropriateness of Early Antimicrobial Therapy for the First Pneumonia Episode

Characteristics	All Patients (*n* = 804)	Patients With Early Appropriate Therapy (*n* = 495)	Patients Without Early Appropriate Therapy (*n* = 309)	*p*
Admission period				
2008–2011	359 (44.7)	209 (42.2)	150 (48.5)	0.19
2012–2015	325 (40.4)	211 (42.6)	114 (36.9)	
2016–2019	120 (14.9)	75 (15.2)	45 (14.6)	
Male sex	561 (69.8)	352 (71.1)	209 (67.6)	0.30
Age, yr	65 (54–75)	65 (54–74)	64 (53–76)	0.83
Chronic diseases				
Any, except immune deficiency[a]	330 (41.0)	211 (42.6)	119 (38.5)	0.25
Immune deficiency	170 (21.1)	111 (22.4)	59 (19.1)	0.26
Simplified Acute Physiology Score 2 at ICU admission	50 (38–65)	50 (36–63)	51 (40–65)	0.07
SOFA score at ICU admission	8 (5–11)	8 (5–11)	8 (6–11)	0.72
Organ support at ICU admission[b]				
Invasive MV	602 (74.9)	365 (73.7)	237 (76.7)	0.35
Vasopressors	489 (60.8)	291 (58.8)	198 (64.1)	0.14
Extracorporeal membrane oxygenation	35 (4.4)	27 (5.5)	8 (2.6)	0.05
Renal replacement therapy	145 (18)	87 (17.6)	58 (18.8)	0.67
Sepsis at ICU admission	509 (63.3)	310 (62.6)	199 (64.4)	0.61
Septic shock at ICU admission	248 (30.8)	147 (29.7)	101 (32.7)	0.37
ICU LOS before pneumonia, d[c]	6 (3–12)	6 (2–12)	8 (4–13)	< 0.0001
Classification of pneumonia[c]				< 0.0001
Ventilator-associated pneumonia	556 (69.2)	313 (63.2)	243 (78.6)	
HAP	131 (16.3)	87 (17.6)	44 (14.2)	
Ventilated HAP	117 (14.6)	95 (19.2)	22 (7.1)	
Features at pneumonia diagnosis[c]				
SOFA score	6 (4–9)	7 (4–10)	6 (3–9)	0.009
Sepsis	615 (76.5)	388 (78.4)	227 (73.5)	0.11
Septic shock	180 (22.4)	123 (24.8)	57 (18.4)	0.03
Acute respiratory distress syndrome	535 (66.5)	346 (69.9)	189 (61.2)	0.01
Neutropenia[d]	9 (1.2)	6 (1.3)	3 (1.1)	1.00
Pneumonia due to multidrug-resistant Gram-negative bacteria[c]	199 (24.8)	102 (20.6)	97 (31.4)	0.0006
Treatment limitation decision[c]	211 (26.2)	131 (26.5)	80 (25.9)	0.86

(*Continued*)

TABLE 1. (*Continued*)
Characteristics of the Study Population According to the Appropriateness of Early Antimicrobial Therapy for the First Pneumonia Episode

Characteristics	All Patients (*n* = 804)	Patients With Early Appropriate Therapy (*n* = 495)	Patients Without Early Appropriate Therapy (*n* = 309)	*p*
Outcomes				
Clinical cure at day 14	351 (43.7)	204 (41.2)	147 (47.6)	0.08
MV days after pneumonia	9 (4–16)	9 (4–17)	8 (3–15)	0.04
ICU LOS after pneumonia, d	14 (8–24)	14 (7–25)	14 (8–23)	0.54
In-ICU death	279 (34.7)	173 (34.9)	106 (34.3)	0.85
In-hospital death	338 (42.0)	213 (43.0)	125 (40.5)	0.47
Death at day 28	262 (32.6)	163 (32.9)	99 (32.0)	0.79

HAP = hospital-acquired pneumonia, LOS = length of stay, MV = invasive mechanical ventilation, SOFA = Sequential Organ Failure Assessment.
[a]First 48 hr of the ICU stay.
[b]Overall prevalence of chronic diseases: respiratory, *n* = 155 (19.3%); cardiovascular, *n* = 147 (18.3%); renal, *n* = 55 (638%); and hepatic, *n* = 50 (6.2%). No significant difference was observed regarding the prevalence of chronic diseases between patients with and without early appropriate antimicrobial therapy.
[c]First episode of HAP of ventilator-associated pneumonia due to Gram-negative bacteria during the ICU stay.
[d]Blood neutrophil count < 500/mm^3 (missing values, *n* = 77).
Data are exposed as *n* (%) or median (interquartile range).

No association between the administration of early appropriate therapy and day 28 mortality was observed in subgroup analyses, whatever the pneumonia type, the causative pathogen, or the characteristics of antimicrobial regimen (**Table 4**; and additional subgroup analyses exposed in **Tables S4** and **S5**, http://links.lww.com/CCM/H684). We were not able to demonstrate that receiving early appropriate antimicrobial therapy was independently linked to this endpoint in patients with septic shock at pneumonia diagnosis (aHR, 0.85; 95% CI, 0.52–1.39) (Table 4; and Table S5, http://links.lww.com/CCM/H684).

Secondary Study Endpoints

No significant difference was observed between patients with and without early appropriate antimicrobial therapy regarding the rate of clinical cure at day 14 (41.2% vs. 47.6%, respectively; p = 0.08) (Table 1) and the course of daily SOFA score values from day 0 to day 28 (p = 0.11) (**Fig. 2**). MV duration from day 0 was 9 days (4–17 d) and 8 days (3–15 d) in patient with and without early appropriate therapy, respectively (p = 0.04) (Table 1). The cause-specific hazard ratio (HR) for extubation was 0.84 (95% CI, 0.69–1.01) in patients who received early appropriate therapy, corresponding to a difference of median MV duration of 1.3 days when compared to those who did not. The ICU LOS from day 0 was 14 days (7–25 d) and 14 days (8–23 d) in patient with and without early appropriate therapy, respectively (p = 0.54) (Table 1). The cause-specific HR for ICU discharge alive was 0.85 (95% CI, 0.72–1.00) in patients who received early appropriate therapy, corresponding to a median LOS difference of 2.1 days when compared to those who did not.

DISCUSSION

In this multicenter cohort study including 880 critically ill patients with HAP or VAP due to Gram-negative bacteria, the administration of early appropriate antimicrobial therapy was not independently linked with a reduced likelihood of all-cause death at day 28. Clinical cure rates at day 14 and the time to organ failure resolution, MV weaning or ICU discharge did not significantly differ between patients who received early appropriate therapy and those who did not.

The delayed initiation of appropriate antimicrobial therapy in critically ill patients with HAP or VAP has been shown to correlate with an amplified hazard of

TABLE 2.
Features of Nosocomial Pneumonia Episodes

Characteristics	First Episode of Pneumonia (*n* = 804)	Subsequent Episodes of Pneumonia (*n* = 252)
Pneumonia classification		
Ventilator-associated pneumonia	556 (69.2)	223 (88.5)
HAP	131 (16.3)	29 (11.5)
Ventilated HAP	117 (14.6)	0
Early appropriate antimicrobial therapy		
None	309 (38.4)	158 (62.7)
Single drug	204 (25.4)	25 (9.9)
Combination	291 (36.2)	70 (27.8)
Early appropriate pivotal drug (missing = 7)		
β-lactams and β-lactam-like drugs		
Nonantipseudomonal penicillins/cephalosporins	82 (10.2)	3 (1.2)
Antipseudomonal penicillins ± β-lactamase inhibitor	177 (22.0)	28 (11.3)
Antipseudomonal cephalosporins	98 (12.2)	23 (9.3)
Antipseudomonal carbapenems	129 (16.0)	33 (13.4)
Fluoroquinolones	11 (1.4)	1 (0.4)
Aminoglycosides	4 (0.5)	0 (0)
Colistin	3 (0.4)	1 (0.4)
Others	4 (0.5)	0 (0)
Early appropriate companion drugs (missing = 9)		
Aminoglycosides	218 (27.2)	45 (18.4)
Fluoroquinolones	65 (8.1)	20 (8.2)
Cotrimoxazole	10 (1.2)	1 (0.4)
Colistin	3 (0.4)	1 (0.4)
Gram-negative bacteria responsible for pneumonia		
Enterobacterales		
Escherichia coli	126 (13.4)	30 (9.6)
Klebsiella species	96 (10.2)	36 (11.5)
Enterobacter species	98 (10.4)	28 (8.9)
Others	128 (15.9)	31 (12.3)
Nonfermenting Gram-negative bacteria		
Pseudomonas aeruginosa	324 (40.3)	147 (58.3)
Stenotrophomonas maltophilia	61 (6.5)	25 (8.0)
Acinetobacter baumannii	24 (2.6)	9 (2.9)
Others	6 (0.6)	3 (1.0)
Haemophilus species	76 (8.1)	4 (1.3)
Multidrug-resistant isolates (missing = 58)	215 (23.5)	94 (31.1)
Pneumonia involving multiple Gram-negative bacteria	117 (14.5)	55 (21.8)

HAP = hospital-acquired pneumonia.
Data are exposed as *n* (%).

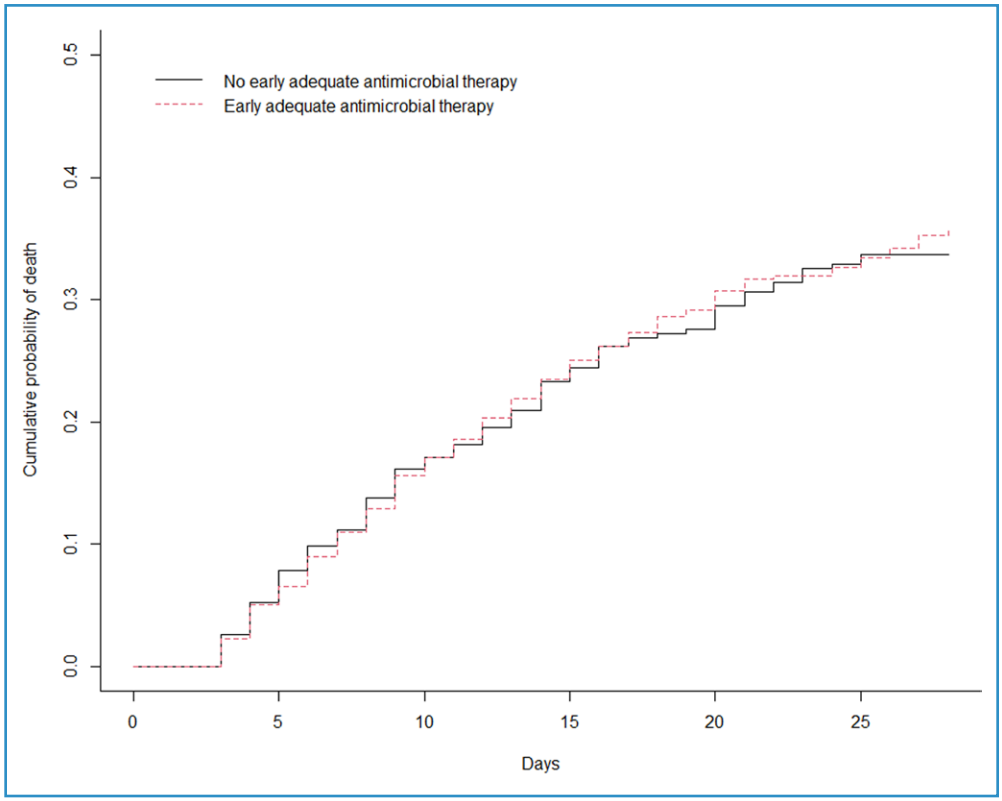

Figure 1. Cumulative probability of all-cause death after pneumonia diagnosis in patients with and without early appropriate antimicrobial therapy. $p = 0.30$ for the comparison between patients with and without early appropriate antimicrobial therapy (log-rank test).

in-hospital death in several single-center cohort studies, most often through unadjusted analyses on relatively small patient populations (17, 18, 28–30). Many surrogate severity markers such as prolonged ICU stay, exposure to invasive procedures or previous need for broad-spectrum antimicrobials also stand as risk factors for pneumonia due to MDR pathogens, a condition at-risk for inappropriate empirical coverage (8, 9). Hence, a degree of collinearity might be considered when interpreting these data. In our study, the largest to date focused on this issue, receiving early appropriate therapy was not associated with day 28 mortality after careful adjustment on plausible confounders, including severity indexes at ICU admission and at pneumonia diagnosis, chronic diseases, immune status, and prior LOS. This lack of association was consistently observed in clinically relevant subgroups as in a confirmatory model considering all episodes in patients with more than one pneumonia due to Gram-negative bacteria during the ICU stay.

This unexpected result has potential explanations. First, included patients were severely ill, with high SAPS-2 and SOFA score values at ICU admission, and most had VAP. The attributable mortality of VAP has been evaluated as close to zero in the general population of medical ICU patients, especially in those with high severity indexes at admission (3, 31). Although the attributable mortality of HAP and vHAP remains to be specifically investigated, these conditions could exert only a marginal effect on survival—whatever the appropriateness of initial antimicrobial therapy—in patients at high baseline risk for death. Next, most of patients met the Sepsis-3 criteria for sepsis at the time of pneumonia diagnosis. Evidence regarding the relationship between early appropriate therapy and survival in patients with sepsis is conflicting (32–35), putatively due to incertitude regarding the exact timing of sepsis start and, therefore, the actual delay before active antimicrobials are initiated. Along this line, SOFA score values at pneumonia diagnosis were high in our cohort, with comparable subsequent course in the two groups, suggesting that the prognostic impact of early appropriate therapy dwindles once sepsis-induced organ failures are established. This assumption is corroborated by the findings of a previous multicenter study that reported a survival benefit of early appropriate therapy in patients with limited VAP-related organ dysfunctions (as reflected by a logistic organ dysfunction score ≤ 4), but not in those with more severe presentations (15). Of note, the link between early appropriate therapy and survival in sepsis has been mainly studied in patients with community-acquired infections and remains under-investigated in those with hospital-acquired infections, the latter appearing intrinsically at higher probability of unfavorable outcomes (36, 37). Last, patients receiving early appropriate therapy were

TABLE 3.

Impact of Early Appropriate Antimicrobial Therapy on Day 28 All-Cause Mortality: Full Results of Final Multivariate Models

	Main Model[a]		Main Model[b]		Confirmatory Model[c]	
Variables	**aHR (95% CI)**	***p***	**aHR (95% CI)**	***p***	**aHR (95% CI)**	***p***
Inclusion subperiods						
2008–2011	1	0.33	1	0.32	1	0.31
2012–2015	1.17 (0.89–1.53)		1.17 (0.89–1.52)		1.17 (0.90–1.53)	
2016–2019	1.28 (0.89–1.83)		1.29 (0.90–1.86)		1.29 (0.90–1.85)	
Chronic diseases, except immune deficiency	0.97 (0.76–1.24)	0.79	0.97 (0.75–1.24)	0.78	0.97 (0.76–1.24)	0.79
Immune deficiency	1.15 (0.87–1.53)	0.33	1.15 (0.87–1.53)	0.33	1.16 (0.87–1.54)	0.31
Simplified Acute Physiology Score 2 at ICU admission, per 1-point increase	1.01 (1.00–1.02)	0.003	1.01 (1.00–1.02)	0.003	1.01 (1.00–1.02)	0.003
ICU length of stay before first episode, per day	1.01 (0.99–1.02)	0.33	1.01 (0.99–1.02)	0.35	1.01 (0.99–1.02)	0.33
Pneumonia classification[d]						
Ventilated HAP	1	0.24	1	0.25	1	0.25
HAP	1.15 (0.71–1.85)		1.16 (0.72–1.87)		1.15 (0.71–1.86)	
Ventilator-associated pneumonia	0.85 (0.59–1.24)		0.86 (0.59–1.25)		0.85 (0.59–1.24)	
Sequential Organ Failure Assessment at pneumonia diagnosis, per 1-point increase[d]	1.13 (1.09–1.12)	< 0.0001	1.13 (1.09–1.17)	< 0.0001	1.13 (1.09–1.17)	< 0.0001
Early appropriate antimicrobial therapy[d]						
None	1	0.28	1	0.50	–	–
Any (single drug or combination)	0.87 (0.67–1.12)		–			
Single drug	–		0.83 (0.60–1.14)			
Combination	–		0.90 (0.67–1.19)			
Episodes without early appropriate antimicrobial therapy (cumulative time-dependent variable)	–	–	–	–	1.06 (0.80–1.40)	0.68
Episodes with early appropriate antimicrobial therapy (cumulative time-dependent variable)	–	–	–	–	0.94 (0.68–1.31)	0.73

aHR = adjusted hazard ratio, HAP = hospital-acquired pneumonia.

[a]Administration of any early appropriate antimicrobial therapy (either single-drug or combination therapy).

[b]Same model than [a] with distinction between early appropriate single-drug therapy and early appropriate combination therapy.

[c]All episodes of HAP or ventilator-associated pneumonia (VAP) due to Gram-negative bacteria during the ICU stay (first pneumonia, plus subsequent episode if any) handled as cumulative time-dependent variables (counting process).

[d]First episode of HAP or VAP due to Gram-negative bacteria during the ICU stay.

See the *Methods* section for model descriptions. Dashes indicate data is not appropriate.

TABLE 4.
Impact of Early Appropriate Antimicrobial therapy on Day 28 All-Cause Mortality: Results of Subgroup Analyses

Subgroups	Adjusted Hazard Ratio (95% CI)	*p*
Early appropriate therapy for first HAP/vHAP ($n = 261$)	1.01 (0.60–1.71)	0.96
Early appropriate therapy for first VAP ($n = 602$)	0.85 (0.64–1.13)	0.27
Early appropriate therapy for first HAP or VAP due to non-MDR GNB ($n = 626$)	0.77 (0.57–1.04)	0.09
Early appropriate therapy for first HAP or VAP due to MDR GNB ($n = 238$)	1.34 (0.88–2.04)	0.17
Early appropriate therapy for first VAP due to non-MDR GNB ($n = 459$)	0.72 (0.52–1.01)	0.06
Early appropriate therapy for first VAP due to MDR GNB ($n = 187$)	1.37 (0.84–2.22)	0.21
Early appropriate therapy for first HAP or VAP due to *Pseudomonas aeruginosa* ($n = 343$)	0.93 (0.64–1.36)	0.72
Early appropriate therapy for first VAP due to *P. aeruginosa* ($n = 278$)	0.99 (0.65–1.51)	0.96
Early appropriate combination therapy for first HAP or VAP–drug ($n = 324$)		
Aminoglycoside as companion drug	1	0.11
Fluoroquinolone as companion drug	0.67 (0.40–1.10)	
Early appropriate combination therapy for first HAP or VAP–duration ($n = 341$)		
Combination therapy for ≤ 2 d	1	0.83
Combination therapy for > 2 d	1.04 (0.72–1.52)	
Septic shock at HAP or VAP diagnosis ($n = 202$)	0.85 (0.52–1.39)	0.51

GNB = Gram-negative bacteria, HAP = hospital-acquired pneumonia, MDR = multidrug-resistant, VAP = ventilator-associated pneumonia, vHAP = ventilated hospital-acquired pneumonia.
Numbers within brackets correspond to the headcount in each subgroup. Not receiving early appropriate antimicrobial therapy is handled as reference (hazard ratio = 1) for all subgroups. See the *Methods* section for model description. Note that early appropriate single-drug and combination antimicrobial therapies were pooled for these analyses—see Table S5 (http://links.lww.com/CCM/H684) in the Electronic Supplementary Material for distinction between single-drug and combination therapies.
First pneumonia: first HAP/vHAP or VAP (whichever occurred first). Day 0 corresponds to the date of the first episode in each given subpopulation.

mostly treated with broad-spectrum β-lactams, often in combination with an aminoglycoside or a fluoroquinolone. Although this was not investigated in our work, the lack of survival impact of early appropriate therapy might partly ensue from a counterbalance between a benefit in terms of clinical response and an increased incidence of antimicrobial-related ecological or nonecological adverse events (38). Overall, our results suggest that the prognosis of critically ill patients with HAP or VAP is primarily conditioned by baseline severity and the extent of organ failure at pneumonia onset, in accordance with previous studies (11–14), with little or even no impact of early appropriate antimicrobial therapy. Interestingly, similar observations have recently been made in an international cohort of ICU patients with severe hospital-acquired bloodstream infection (39). Of note, the early administration of appropriate therapy was not associated with a shorter time to MV weaning or ICU discharge. Conversely, MV duration and ICU LOS trended to be higher in patients appropriately treated upon day 0 and/or day 1, which likely correlates with a more severe presentation of pneumonia when compared to patients without early appropriate therapy, as reflected by higher SOFA score values and prevalence of septic shock at diagnosis.

The administration of early appropriate antimicrobial therapy was not independently associated with improved survival in patients with septic shock at pneumonia diagnosis. This result must be interpreted with caution given the low statistical power for this subgroup analysis and the lack of data regarding the exact time in hours from shock onset to antimicrobial initiation. Although the quality of evidence is weak, prompt

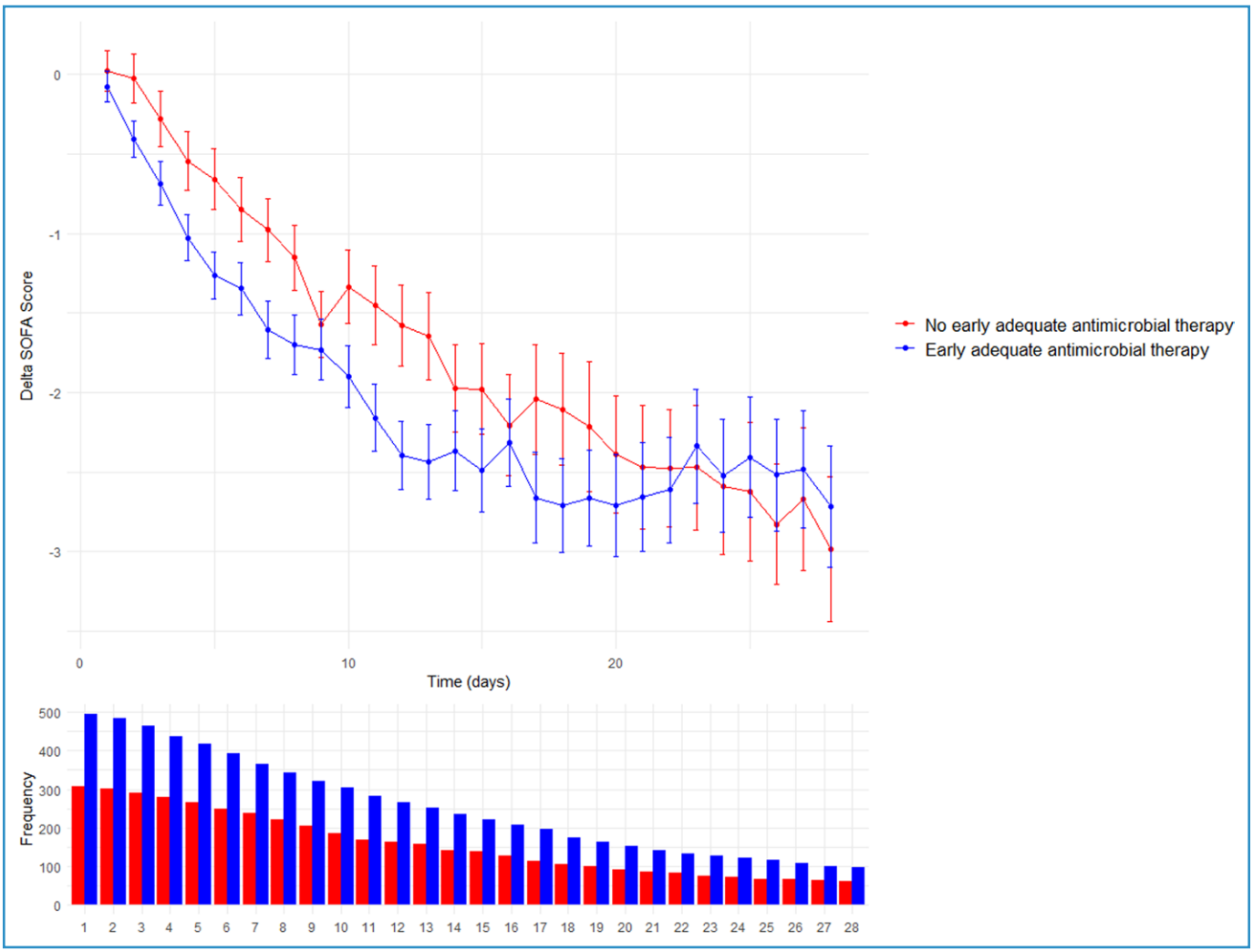

Figure 2. Evolution of daily Sequential Organ Failure Assessment (SOFA) score values after pneumonia diagnosis. *Bars* indicate SEM. The number of patients alive in the ICU at each time point is indicated at the *bottom* of the figure. $p = 0.11$ for the comparison between patients with and without early appropriate antimicrobial therapy (mixed-effect linear model).

initiation of antimicrobials remains pivotal in patients with suspected septic shock (35). Nevertheless, our findings could have relevant implications for the management of critically ill patients with suspected HAP or VAP and not presenting with circulatory failure. Yet, as clinical and radiological criteria for HAP and VAP suspicion dramatically lack specificity (40), a liberal approach for initiating broad-spectrum agents may drive unnecessary exposure to antimicrobial-related adverse events, which exert their own deleterious effects on patient prognosis (38, 41), and contribute unnecessarily to the dissemination of antimicrobial resistance. Restrictive strategies encouraging antimicrobial initiation for microbiologically confirmed rather than clinically suspected ICU-acquired infection in hemodynamically stable patients have shown no negative impact on survival in a few observational studies (42, 43). Likewise, our results suggest that initiating antimicrobial therapy after microbiological confirmation rather than upon clinical suspicion might not affect the outcomes of critically ill patients with HAP or VAP. Recently completed studies are expected to shed further light on this issue (NCT04438187, NCT05205525).

This observational study has limitations. First, despite the use of prospectively collected data and carefully adjusted analyses, residual confounding factors on the primary outcome measure cannot be ruled out. Notably, the time elapsed between the first signs of pneumonia and its diagnosis was not evaluable as chest roentgenograms or CT scans were not entered in the database. Second, our sample size could have

been insufficient to demonstrate a benefit of early appropriate therapy on outcomes. Third, many aspects of intensive care have changed over the 11-year inclusion period; however, the subperiods of inclusion were not independently associated with the primary study endpoint. Fourth, early appropriate therapy was defined as the administration of one or more active agents at day 0 and/or day 1; that the prognostic impact of initiating appropriate antimicrobials may vary over this 48-hour timeframe cannot be excluded, especially in patients with sepsis or septic shock at pneumonia diagnosis. Fifth, dosing schemes and results of therapeutic drug monitoring (when performed) were not routinely available in the database. Thus, initial antimicrobials might have been under-dosed in certain patients classified as receiving early appropriate therapy, thereby contributing to the lack of association with day 28 mortality. However, all ICUs contributing to the OutcomeRéa network follow current standards and guidelines for optimized antimicrobial pharmacokinetic in critically ill individuals. Sixth, single-drug therapies with an aminoglycoside or colistin were considered as appropriate when fully active in vitro though the pulmonary diffusion of these agents may be suboptimal. This scenario applied for a very low number of patients, making unlikely any significant impact on our results. Seventh, as the inclusion period ended in September 2019, we did not include mechanically ventilated COVID-19 patients, a population at high risk for VAP (44). Last, we did not address the impact of early appropriate therapy in patients with HAP or VAP involving pathogens other than Gram-negative bacteria (e.g., *Staphylococcus aureus*).

CONCLUSIONS

In this study, early appropriate antimicrobial therapy was not associated with a reduced likelihood of death at day 28, a faster resolution of organ failure, a higher rate of clinical cure at day 14, or a shorter time to MV weaning or ICU discharge in critically ill patients with HAP or VAP due to Gram-negative bacteria. However, a prognostic benefit from early appropriate antimicrobial therapy cannot be firmly ruled out due to potential residual confounding and lack of statistical power.

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Members of the OutcomeRéa Study Group are listed in the ***Supplemental Data*** *(http://links.lww.com/CCM/H699).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Barbier and Timsit designed the study. Mr. Ruckly and Dr. Timsit performed statistical analyses. Drs. Barbier, Dupuis, Buetti, Zahar, and Timsit interpreted the results. Drs. Barbier and Timsit have written the article. All other authors contributed to data collection and critical revision of the article.

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