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Original article

Effect of positive microbiological testing on antibiotic de-escalation and outcomes in community-acquired pneumonia: a propensity score analysis

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ABSTRACT

Objectives: The usefulness of routine microbiological testing for rationalising antibiotic use in hospitalised patients with community-acquired pneumonia (CAP) continues to be a subject of debate. We aim to determine the effect of positive microbiological testing on antimicrobial de-escalation and clinical outcomes in CAP.

Methods: A retrospective analysis of a prospectively collected cohort of non-immunosuppressed adults hospitalised with CAP was performed. The primary study outcome was antimicrobial de-escalation. Secondary outcomes included 30-day case-fatality rate, adverse events, and CAP recurrence. Adjustment for confounders was performed by inverse probability weighting propensity score, logistic regression, and cause-specific Cox model.

Results: Of 3677 patients with CAP, 1924 (52.3%) had any positive microbiological test. Antimicrobial de-escalation was performed in 648/1924 (33.7%) of patients with positive microbiological testing and in 179/1753 (10.2%) of those with non-positive results. When propensity score was entered into the multivariate analysis, positive microbiological testing (adjusted OR (AOR)], 2.59; 1.96–3.41) and clinical stability at day 3 (AOR 1.87; 1.45–2.10) were two of the main factors independently associated with antimicrobial de-escalation. After applying an adjusted cause-specific Cox model, antimicrobial de-escalation was not associated with a higher 30-day case-fatality rate (adjusted hazard ratio (AHR), 0.44 (95% CI, 0.14–1.43)), higher frequency of adverse events (AHR, 0.77 (95% CI, 0.53–1.12)), or CAP recurrence (AHR, 0.65 (95% CI, 0.35–1.14)).

Discussion: Antimicrobial de-escalation was more often performed in hospitalised patients with CAP who had positive microbiological tests than in those with non-positive results, and it did not adversely affect relevant clinical outcomes. **Gabriela Abelenda-Alonso, Clin Microbiol Infect 2022;28:1602**

Introduction

Community-acquired pneumonia (CAP) is a major public health problem around the world. The prevalence of CAP is estimated to be between 1.5 and 14.0 cases per 1000 person-year [1], and it remains the fourth leading cause of death worldwide [2].

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Streptococcus pneumoniae is the leading causative agent of CAP in most countries [3]. However, in spite of the use of conventional microbiological techniques [4–6] (gram stain and sputum culture, blood cultures, *S. pneumoniae* and *Legionella pneumophila* urinary antigens), the aetiology of CAP remains unknown in 62% of cases [7]. The usefulness of routine microbiological testing to rationalise antibiotic use and improve CAP clinical outcomes is a subject of debate, and, in fact, the most recent clinical CAP guidelines identify the need for more sensitive methods for aetiological detection as a priority area for research [8,9].

The arguments in favour of determining the aetiology of CAP include the epidemiological surveillance of causative agents, the detection of specific microorganisms with significant public health implications, such as *L. pneumophila*, antibiotic susceptibility testing, and compliance with antimicrobial stewardship strategies. On the other hand, the main arguments against the regular use of microbiological studies in hospitalised patients with CAP are the limited yield of individual conventional tests [10,11] and the lack of clear evidence linking aetiological identification with improved antimicrobial stewardship, better clinical outcomes, or economic benefits [12,13].

CAP is one of the leading causes of antimicrobial prescription worldwide [14]. As stated above, the causative agent is often not identified, and patients are frequently overtreated with antibiotics. The excessive use of antibiotics is a matter of concern, since it is a key driver of antimicrobial resistance and is known to increase antibiotic-related adverse events. Therefore, applying efficient antimicrobial stewardship strategies is of paramount importance for rationalising antibiotic use. Antimicrobial stewardship should be based on the combination of interdisciplinary strategies in order to improve adherence to guidelines, ensure antimicrobial de-escalation, allow a timely switch to the oral route, and reduce duration of treatment [15]. Although there is some evidence supporting the feasibility and safety of antimicrobial de-escalation [16–19], there are a number of drawbacks that currently limit its implementation in hospitalised patients with CAP. Firstly, there are few clinical trials supporting systematic de-escalation [20]. Secondly, certain behavioural features among treating physicians preclude antimicrobial de-escalation, particularly among patients with severe infection of unknown aetiology [21,22]. Furthermore, there are few literature reports [12,23] of the effect of positive microbiological testing on antimicrobial de-escalation in CAP, particularly adjusting for confounding factors such as clinical stability.

The aim of this study was to assess the effect of positive microbiological testing on antimicrobial de-escalation and clinical outcomes, adjusting for clinical stability, in a large cohort of hospitalised patients with CAP.

Methods

Study design, setting, and patients

We performed a retrospective post hoc analysis of a prospectively collected cohort of hospitalised patients with CAP from January 1995 to February 2017 at Bellvitge University Hospital, a 700-bed public hospital in Barcelona, Spain. All immunocompetent patients over the age of 18, admitted to the hospital with radiologically proven CAP via the emergency department, were included. Patients who died within 72 hours of hospital admission, those with an already targeted antimicrobial treatment as described below, and cases lacking data on de-escalation were excluded. Patients with empyema or aspiration CAP were also excluded. This study is reported in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) recommendations (see Supplementary material, Appendix A).

Study outcomes

The primary outcome was antimicrobial de-escalation. The secondary outcomes were 30-day case-fatality rate, duration of antimicrobial intravenous (IV) therapy, total duration of antimicrobial therapy, adverse events, length of hospital stay, and CAP recurrence.

Clinical assessment

Patients were followed up during their hospital stay by one or more of the investigators, and data were recorded with the aid of a standardised computer-based protocol. Empirical antibiotic treatment was prescribed according to hospital guidelines, which recommend the administration of a β-lactam agent (ceftriaxone or amoxicillin/clavulanate) with or without a macrolide or a fluoroquinolone from 1998 onward. Combination treatment was recommended for patients with clinical suspicion of Legionella spp. or an atypical pathogen or, in the case of severe pneumonia, in the absence of a demonstrative sputum Gram stain. Levofloxacin monotherapy was allowed for patients with allergy to β-lactam antibiotics. During the influenza season and since year 2009, oseltamivir was recommended for cases with clinical suspicion of influenza pneumonia.

During the study period, because of the lack of a specific hospital policy, antimicrobial de-escalation was determined by the attending physicians in each case. The microbiological data and the antimicrobial de-escalation process in all study patients were assessed by at least two experienced clinical investigators who were blinded to the patient's outcomes. All patients were seen at the outpatient clinic at day 30 after hospital discharge.

Definitions

Positive microbiological testing was considered when any of the microbiological tests were positive and meet the aetiological diagnosis of CAP criteria (see Supplementary material, Appendix B). No positive microbiological testing was defined as the lack of positivity of any of the microbiological tests performed. Clinical stability was defined as described elsewhere [24]. Antimicrobial de-escalation was considered when the initial empirical antimicrobial therapy was narrowed to penicillin, amoxicillin, or amoxicillin/clavulanate; to a quinolone or macrolide in cases of Legionella pneumonia; and to oseltamivir in cases of influenza disease without proven bacterial co-infection.

Thirty-day case-fatality rate was defined as death due to any cause in the first 30 days of hospitalisation. Duration of antimicrobial IV therapy was considered from the day of the first IV antimicrobial dose to the last. Total duration of antimicrobial therapy was considered from the first day of antimicrobial treatment to the last, including all antimicrobial treatment received after hospital discharge. Adverse events were documented according to Medical Dictionary for Regulatory Activities (MedDRA) definitions. Length of hospital stay was measured from admission to emergency department until hospital discharge. CAP recurrence was defined as re-admission or consultation for persistence or clinical recurrence of the same clinical process of the first episode of CAP within 30 days of hospital discharge. Further definitions can be seen in the Supplementary material, Appendix B.

Microbiological studies

Microbiological workup at the admission commonly included two sets of blood cultures and sputum Gram stain and culture when available. Urinary antigen detection for *S. pneumoniae* and

L. pneumophila was performed if indicated by the attending physician. From 2009 onwards, several techniques to detect virus by PCR were used including influenza A; influenza B and human respiratory syncytial virus were also performed if requested by the attending physician. Information regarding these methods can be seen in the Supplementary material, Appendix C.

Ethics

The study was approved by the Ethics Committee of the coordinating centre in accordance with Spanish legislation, and the procedures followed complied with the ethical standards of the Helsinki Declaration (PR140/20). Because of the observational and anonymous nature of the study, informed consent was waived by the local Ethics Committee.

Statistical analysis

A descriptive analysis was performed to characterize clinical profile of subjects included. Means and standard deviations were used for continuous variables, and medians and interquartile ranges for those with a non-normal distribution. To address potential bias in patients with positive microbiological testing, we performed an inverse probability weighting propensity score (IPW-PS), including all the variables that reached statistical significance in the univariate analysis between positive and non-positive microbiological testing patients. Then, we performed a logistic regression model, including this IPW-PS, to estimate the probability that a patient would be de-escalated based on his/her probability to have a positive microbiological test.

Afterwards, to evaluate the effect of the antimicrobial de-escalation on the secondary outcomes, we performed a IPW-PS based on the variables that reached statistical significance in the univariate analysis comparing de-escalated and non–de-escalated patients. This analysis, the list of the variables included in both IPW-PS together with the Hosmer-Lemeshow test and the receiver operating characteristic (ROC) curve, can be consulted in the Supplementary material, Appendix I. To deal with death as a competing risk, we performed a cause-specific Cox regression model with the variables that were univariately associated with the secondary outcomes adjusted by the IPW-PS for de-escalation. Cases were censored at death. The Cox proportional hazards model was used to perform multivariate survival analysis, which are reported as hazard ratio (HR) and 95% CI. To avoid immortal time bias, during the time between admission and the moment of antimicrobial de-escalation, patients were considered not de-escalated. Likewise, during the time from admission to clinical stability, patients were considered not clinically stable. The proportionality of risks in the Cox models was verified using the Schoenfeld residuals. The percentage of missing values among covariables were between 2% to 10%. Missing values were assumed at random. We used the function impute from Harrell miscellaneous R package to imput all missing values. A diagram of the statistical methods performed is provided as Supplementary material, Appendix L.

Results

A total of 3677 consecutive episodes of CAP were analysed. Microbiological results were positive in 1924 (52.3%) and non-positive in 1753 (47.7%). Study flowchart and further information regarding the distribution of the microbiological studies used to assess the aetiology of CAP is provided in the Supplementary material, Appendix D. As seen in Table 1, patients with positive microbiological tests more frequently presented chronic obstructive pulmonary disease and have received previous antibiotic therapy. Furthermore, signs of severity, like shock and intensive care unit (ICU) admission, were more common in patients with positive microbiological testing than those with non-positive results.

Antimicrobial de-escalation was performed in 648/1924 (33.7%) of patients with positive microbiological tests and in 179/1753 (10.2%) of those with non-positive results (OR, 4.46; 95% CI, 3.76–5.36). The median time to de-escalation was three days (interquartile range (IQR), 2–6) and was significantly longer in the group of patients with positive microbiological testing (4; IQR, 2–7 vs. 3; IQR, 2–5; OR, 2.21 (95% CI, 1.10–3.22)). Factors independently associated with antimicrobial de-escalation are detailed in Table 2, with positive microbiological testing (adjusted OR (AOR), 2.59 (95% CI, 1.96–3.41)) being one of the main associated factors. The combination of positive blood cultures, urinary antigen, and sputum culture (AOR, 2.07 (95% CI, 1.04–4.15)) followed by positive blood culture and urinary antigen (AOR, 2.03 (95% CI, 1.39–2.97)) were the results most frequently linked to antimicrobial de-escalation. Clinical stability at day 3 was more commonly present in the group of patients who underwent antimicrobial de-escalation (AOR, 1.76 (95% CI, 1.42–2.24)) than those who did not.

As shown in Table 3, quinolone monotherapy and the combination of β-lactam and macrolide were the more frequently empirical schemes used in the group of not de-escalated patients. Regarding directed therapy, β-lactam monotherapy was the preferred choice in the de-escalated group, whereas quinolone monotherapy was the main treatment in the group of not de-escalated patients. Broad spectrum antibiotics were more frequently used as directed therapy in the not de-escalated group (0.6% vs. 15.8%; OR, 0.26 (95% CI, 0.10–0.65)).

As displayed in the univariate analysis in Table 4, patients who underwent de-escalation presented lower 30-day case-fatality rates, less adverse events, and shorter hospital stay than patients who were not de-escalated. Nonetheless, after multivariate analysis adjustment, there were no differences between both groups regarding 30-day case-fatality rate (AHR, 0.44 (95% CI, 0.14–1.43)), adverse events (AHR, 0.77 (95% CI, 0.53–1.12)), or CAP recurrence (AHR, 0.65 (95% CI, 0.37–1.14)). Duration of antimicrobial IV therapy was significantly lower in the group of antimicrobial de-escalated patients (AHR, 0.85 (95% CI, 0.73–0.99)).

Discussion

In this large retrospective analysis of a prospectively collected cohort of non-immunosuppressed adults hospitalised with CAP, antimicrobial de-escalation was more often performed in patients with positive microbiological testing than in those with non-positive results, and it did not adversely affect relevant clinical outcomes.

The usefulness of routine microbiological testing for rationalising antibiotic use and improving CAP clinical outcomes continues to be a subject of controversy. Previous studies have mainly analysed the effect of a separate microbiological technique in antimicrobial de-escalation; the results obtained have been mixed probably due to the different diagnostic value of the various tests assessed [12,25,26]. Furthermore, some investigators [27] have reported that even with a reasonably high rate of aetiological diagnosis in hospitalised patients with lower respiratory tract infection, antimicrobial treatment was changed in 9% of patients. Interestingly, we found that even a relatively low rate of individual positive microbiological testing had an overall effect on antimicrobial de-escalation compared to patients with non-positive microbiological testing. Furthermore, we found higher rates of positive microbiological testing and antimicrobial de-escalation in patients admitted from 2005 to onwards (especially between 2005

Table 1
Univariate and multivariate analysis for clinical characteristics of patients with positive and non-positive microbiological testing

	Total (n = 3677)	Positive microbiological testing (n = 1924; 52.3%)	Non-positive microbiological testing (n = 1753; 47.7%)	OR (95% CI)	AOR (95% CI)
Age, median (IQR) (y)	69 (56–78)	68 (55–77)	70 (57–78)	1.00 (0.99–1.00)	0.99 (0.98–1.00)
Sex, female	1182 (32.1)	607 (31.5)	575 (32.8)	0.94 (0.82–1.08)	1.03 (0.83–1.26)
Current/former smoker	2210 (60.1)	1220 (63.4)	990 (56.5)	1.34 (1.17–1.52)	0.95 (0.84–1.08)
Influenza vaccination	1700 (46.2)	852 (44.3)	848 (48.4)	0.85 (0.74–0.97)	0.86 (0.70–1.06)
Pneumococcal vaccination	625 (17.0)	344 (17.9)	281 (16.0)	1.14 (0.06–1.36)	
Pre-hospital antibiotic therapy	807 (22.4)	347 (18.4)	460 (26.7)	0.62 (0.53–0.72)	0.69 (0.55–0.86)
Baseline conditions					
COPD	1064 (28.9)	611 (31.8)	453 (25.8)	1.34 (1.16–1.54)	1.33 (1.07–1.66)
Diabetes mellitus	807 (21.9)	410 (21.3)	397 (22.6)	0.92 (0.79–1.08)	
Chronic heart disease	948 (25.8)	467 (24.3)	481 (27.5)	0.85 (0.73–0.98)	
Cancer	361 (9.8)	210 (10.9)	151 (8.6)	1.30 (1.04–1.62)	1.38 (1.01–1.89)
Chronic kidney disease	356 (9.6)	186 (9.7)	170 (9.7)	1.00 (0.80–1.24)	0.97 (0.73–1.30)
Chronic hepatitis	299 (8.1)	191 (9.9)	108 (6.2)	1.68 (1.31–2.15)	1.44 (1.04–1.99)
Cerebrovascular disease	249 (6.7)	126 (6.5)	123 (7.0)	0.93 (0.72–1.20)	
Dementia	117 (3.1)	58 (3.0)	59 (3.4)	0.89 (0.62–1.29)	
Year of admission					
1995–1999	701 (19.1)	258 (13.4)	443 (25.3)	Ref.	
2000–2004	803 (21.8)	380 (19.8)	423 (24.1)	1.54 (1.25–1.90)	1.51 (1.03–2.22)
2005–2009	1250 (34.0)	792 (41.2)	458 (26.1)	2.97 (2.45–3.60)	1.56 (1.28–1.90)
2010–2017	923 (25.1)	494 (25.7)	429 (24.5)	1.98 (1.62–2.42)	1.65 (1.01–2.11)
Clinical features at admission					
Tachycardia (≥100 beats/min)	1689 (45.9)	1010 (52.5)	679 (38.7)	1.75 (1.53–1.99)	1.16 (0.96–1.40)
Tachypnoea (≥24 breath/min)	2551 (69.4)	1385 (72.0)	1166 (66.5)	1.29 (1.12–1.49)	1.20 (0.98–1.46)
Shock	227 (6.2)	172 (8.9)	55 (3.1)	3.02 (2.24–4.16)	1.66 (1.10–2.49)
Cough	3138 (85.7)	1679 (87.5)	1459 (83.7)	1.37 (1.14–1.65)	1.34 (1.01–1.77)
Productive cough	1738 (56.5)	1031 (59.4)	707 (52.6)	1.32 (1.14–1.52)	0.99 (0.89–1.22)
Clinical stability at day 3	2043 (55.6)	1172 (60.9)	871 (49.7)	1.58 (1.38–1.80)	0.98 (0.87–1.37)
Laboratory and radiological findings at admission					
Bilateral pneumonia	1009 (27.4)	586 (30.5)	423 (24.1)	1.38 (1.19–1.59)	1.16 (0.93–1.45)
Leukocytosis (≥12 × 109/L)	2025 (55.1)	1119 (58.2)	906 (51.7)	1.30 (1.14–1.48)	1.19 (0.98–1.44)
Respiratory insufficiency	2061 (56.1)	1153 (60.0)	908 (51.8)	1.39 (1.22–1.59)	1.06 (0.87–1.29)
Pleural effusion	125 (3.4)	76 (3.96)	49 (2.80)	1.43 (1.00–2.07)	0.89 (0.88–2.11)
Severity index scores					
PSI ≥4	631 (17.2)	370 (19.3)	261 (14.9)	1.36 (1.14–1.62)	0.86 (0.65–1.14)
SAPS ≥15	95 (2.6)	67 (3.5)	28 (1.6)	2.22 (1.44–3.53)	1.20 (0.57–2.54)
ICU admission	335 (9.1)	251 (13.0)	84 (4.8)	2.98 (2.31–3.87)	2.53 (1.69–3.79)

Data are presented as n (%) unless otherwise indicated.
COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; PSI score, Pneumonia Severity Index or PORT score; SAPS, Simplified Acute Physiology Score.

and 2009). This could be partially explained because of the effect of the urinary antigen tests and high-sensitivity viral PCR during the H1N1 influenza pandemic.

As previously reported [28], we found that patients with positive microbiological testing presented more severe forms of CAP with higher severity index scores and were more frequently admitted to the ICU. In this regard, it is important to stress that even in this situation of severe CAP, which may negatively affect the achievement of clinical stability, we found that positive microbiological testing was an important factor related to antimicrobial de-escalation. Prospective studies evaluating the application of a combined diagnostic and antimicrobial stewardship strategy stratifying by CAP severity might be needed.

Our study shows that, among other important factors such as ICU admission, clinical stability should be considered when evaluating the effect of microbiological testing on antimicrobial de-escalation and clinical outcomes. As other investigators have pointed out, it is likely that the lower mortality associated with antimicrobial de-escalation in observational studies might be due to bias [20]. In this regard, van Heijl et al. [29] conducted a study in which the effect of clinical stability was quantified using previous data from the literature to simulate clinical stability on day 3 and found that this variable strongly mediates the effect of de-escalation on mortality. Interestingly, our study found that when adjusting for clinical stability, de-escalation was not associated with any change in the 30-day case-fatality rate. We observed that clinical stability influences the effect of antibiotic de-escalation on other clinical outcomes. Therefore, adjusting for severity but also for clinical stability may be an important issue that should be addressed in future clinical trials assessing the effect of microbiological testing in antimicrobial de-escalation.

Our study has some limitations that should be acknowledged. Firstly, we did not assess healthcare prescribers' behavioural factors, which may have influenced the antibiotic de-escalation decision [30]. Secondly, patients' data were collected over a long period of time but multiplex viral PCR has only been available since 2009. Thirdly, our study was performed at a single institution with 24/7 availability of the microbiology laboratory and infectious disease consultation, and so our results may not be generalisable to all institutions. Finally, data regarding antimicrobial resistance were not recorded.

In summary, antimicrobial de-escalation was more frequently performed in patients with positive microbiological testing than in those with non-positive results. It did not negatively affect relevant clinical outcomes, including 30-day case-fatality rate, adverse events, and CAP recurrence. Our findings provide evidence of the importance of microbiological diagnosis in antimicrobial stewardship decision-making in hospitalised patients with CAP. Clinical trials evaluating comprehensive rapid diagnostic microbiological techniques and analysing the behaviour of prescribers are needed.

Table 2
Factors associated with antimicrobial de-escalation: univariate analysis and multivariate analysis after applying propensity score for positive microbiological testing

	Antimicrobial de-escalation (n = 827; 22.5%)	No de-escalation (n = 2850; 77.5%)	OR (95% CI)	AOR (95% CI)
Age, median (IQR) (y)	70 (57–79)	69 (56–78)	1.00 (1.00–1.01)	1.02 (0.99–1.01)
Sex, female	273 (33.0)	909 (31.9)	1.05 (0.89–1.24)	0.92 (0.74–1.15)
Current/former smoker	512 (61.9)	1698 (59.6)	1.10 (0.94–1.24)	
Influenza vaccination	404 (48.9)	1296 (45.5)	1.15 (0.98–1.29)	
Pneumococcal vaccination	171 (20.7)	454 (15.9)	1.38 (1.13–1.67)	1.24 (0.97–1.59)
Pre-hospital antibiotic therapy	132 (16.2)	675 (24.2)	0.61 (0.49–0.74)	0.77 (0.58–1.03)
Baseline conditions				
COPD	246 (29.7)	818 (28.7)	1.05 (0.89–1.25)	
Diabetes mellitus	184 (22.2)	623 (21.9)	1.02 (0.85–1.23)	
Chronic heart disease	219 (26.5)	729 (25.6)	1.05 (0.88–1.25)	
Cancer	97 (11.7)	264 (9.3)	1.30 (1.01–1.66)	1.08 (0.78–1.50)
Chronic kidney disease	101 (12.2)	254 (8.9)	1.42 (1.11–1.80)	1.36 (1.00–1.83)
Chronic hepatitis	77 (9.3)	222 (7.8)	1.22 (0.92–1.59)	
Cerebrovascular disease	65 (7.9)	184 (6.5)	1.24 (0.92–1.65)	
Dementia	29 (3.5)	88 (3.1)	1.14 (0.73–1.73)	
Year of admission				
1995–1999	60 (7.3)	641 (22.5)	Ref.	
2000–2004	120 (14.5)	683 (24.0)	1.87 (1.35–2.62)	2.20 (1.47–3–36)
2005–2009	380 (45.9)	870 (30.5)	4.65 (3.50–6.28)	4.34 (1.87–5.26)
2010–2017	267 (32.3)	656 (23.0)	4.34 (3.23–5.90)	4.56 (2.12–5.67)
Clinical features at admission				
Tachycardia (≥100 beats/min)	434 (52.5)	1255 (44.0)	1.40 (1.20–1.64)	1.03 (0.81–1.29)
Tachypnea (≥24 breaths/min)	572 (69.2)	1979 (69.4)	0.99 (0.84–1.17)	1.16 (0.93–1.44)
Shock	46 (5.6)	181 (6.35)	0.87 (0.62–1.20)	
Cough	721 (87.4)	2417 (85.2)	1.20 (0.96–1.52)	
Productive cough	417 (54.4)	1321 (57.1)	0.90 (0.76–1.06)	
Laboratory and radiological findings at admission				
Bilateral pneumonia	205 (24.8)	804 (28.2)	0.84 (0.70–1.00)	
Leukocytosis (≥12 × 109/L)	488 (59.0)	1537 (53.9)	1.23 (1.05-–1.44)	1.65 (0.98–1.89)
Respiratory insufficiency	453 (54.8)	1606 (56.4)	0.94 (0.80–1.10)	
Pleural effusion	18 (2.2)	106 (3.7)	0.57 (0.33–0.93)	
Clinical stability at day 3	618 (74.7)	1425 (50.8)	2.95 (2.49–3.52)	1.76 (1.42–2.24)
Positive microbiological testing	648 (78.4)	1276 (44.8)	4.47 (3.73–5.36)	2.59 (1.96–3.41)
All blood cultures	138 (16.7)	249 (8.7)	2.09 (1.67–2.62)	1.65 (1.27–2.13)
Only blood culture	36 (4.3)	96 (3.4)	1.31 (0.87–1.92)	
Only sputum culture	152 (18.4)	394 (13.8)	1.40 (1.14–1.72)	0.98 (0.89–1.32)
Only Legionella + *S. pneumoniae* urinary antigen	255 (30.8)	415 (14.5)	2.62 (2.19–3.14)	1.49 (1.22–1.81)
Blood culture + sputum culture	22 (2.7)	53 (1.9)	1.45 (0.86–2.37)	
Blood culture + urinary antigen	62 (7.5)	73 (2.6)	3.08 (2.17–4.37)	2.03 (1.39–2.97)
Sputum culture + urinary antigen	75 (9.2)	120 (4.2)	2.37 (1.76–3.18)	1.58 (1.14–2.17)
Blood culture + sputum culture + urinary antigen	18 (2.2)	26 (0.9)	2.33 (1.25–4.24)	2.07 (1.04–4.15)
Viral PCR	19 (2.3)	83 (2.9)	0.79 (0.46–1.28)	0.46 (0.20–0.79)
Positive serology (atypical agents)[a]	9 (1.1)	16 (0.6)	1.75 (0.70–4.02)	
Causative agent				
Streptococcus pneumoniae	461 (55.7)	799 (28.0)	3.23 (2.76–3.79)	1.69 (1.41–2.02)
Haemophilus influenzae	53 (6.4)	120 (4.2)	1.56 (1.11–2.17)	0.63 (0.26–1.54)
Legionella pneumophila	58 (7.0)	157 (5.5)	1.30 (0.94–1.76)	
Moraxella catarrhalis	2 (0.2)	7 (0.2)	1.04 (0.14–4.43)	
Other atypical bacteria[a]	9 (1.1)	16 (0.6)	1.96 (0.82–4.41)	
Gram negative bacilli	5 (0.6)	61 (2.1)	0.29 (0.10–0.65)	0.16 (0.05–0.50)
Staphylococcus aureus	0 (0)	34 (1.2)		
Virus	35 (4.2)	82 (2.9)	1.50 (0.99–2.22)	
Viral and bacterial coinfection	3 (0.4)	24 (0.8)	0.45 (0.10–1.29)	
Unknown	201 (24.3)	1550 (54.4)	0.27 (0.23–0.33)	0.32 (0.28–0.65)
Severity index at admission				
PSI ≥4	150 (18.2)	481 (16.9)	1.09 (0.89–1.33)	
SAPS ≥15	11 (1.3)	84 (2.9)	0.45 (0.23–0.81)	0.63 (0.26–1.54)
ICU admission	41 (5.0)	294 (10.3)	0.46 (0.32–0.63)	0.41 (0.25–0.67)

Data are presented as n (%) unless otherwise indicated.
COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; PSI score, Pneumonia Severity Index or PORT score; SAPS, Simplified Acute Physiology Score.
[a]Atypical community-acquired pneumonia (CAP) bacteria: *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Coxiella burnetiid, Legionella pneumophila.*

Table 3
Distribution of empirical and directed antimicrobial treatment between antimicrobial de-escalated patients and those who had no de-escalated

	Antimicrobial de-escalation (n = 827; 22.5%)	No de-escalation (n = 2850; 77.5%)	OR (95% CI)
Empirical antimicrobial treatment			
β-lactam + quinolone	334 (40.4)	1033 (36.2)	1.19 (1.00–1.40)
β-lactam monotherapy	343 (41.4)	762 (26.7)	1.94 (1.65–2.28)
Quinolone monotherapy	57 (6.9)	512 (18.0)	0.44 (0.27–0.67)
β-lactam + macrolide	22 (2.7)	168 (5.9)	0.26 (0.16–0.41)
Macrolide monotherapy	1 (0.1)	—	—
Broad spectrum β-lactam[a]	60 (7.3)	236 (8.3)	0.87 (0.65–1.16)
β-lactam + antiviral	10 (1.2)	139 (4.9)	0.24 (0.13–0.46)
Directed antimicrobial treatment			
β-lactam monotherapy[b]	725 (87.3)	541 (19.0)	30.34 (24.1–38.1)
β-lactam + quinolone	—	471 (16.5)	—
Quinolone monotherapy	57 (6.9)	893 (31.3)	0.04 (0.03–0.06)
β-lactam + macrolide	—	153 (5.40	—
Macrolide monotherapy	2 (0.2)	65 (2.3)	0.10 (0.03–0.43)
Broad spectrum antibiotics[c]	5 (0.6)	450 (15.8)	0.26 (0.10–0.65)
Antivirals	35 (4.2)	0	—
β-lactam + antiviral	3 (0.4)	132 (4.6)	0.01 (0.02–0.24)
Other[d]	0	145 (5.1)	—

Data are presented as n (%) unless otherwise indicated.
[a] Broad spectrum β-lactam antibiotics: included cefepime, piperacillin/tazobactam, meropenem, imipenem, ertapenem and amikacin, tobramycin, gentamycin, colistin.
[b] The 541 patients in the non–de-escalation group received treatment with ceftriaxone. In the case of the de-escalation group, the distribution was as follows: 364 received amoxycilin, 289 received amoxycilin/clavulanic, and 72 received penicillin.
[c] Broad spectrum antibiotics included cefepime, piperacillin/tazobactam, meropenem, imipenem, ertapenem, amikacin, tobramycin, gentamycin, colistin.
[d] Other antibiotics included 95 cases treated with macrolide and quinolone combination, 34 cases treated with linezolid, and 5 cases treated with vancomycin.

Table 4
Univariate and multivariate analysis for secondary clinical outcomes associated with antimicrobial de-escalation after applying adjusted cause-specific Cox regression model

	Total (n = 3677)	Antimicrobial de-escalation (n = 827; 22.5%)	No de-escalation (n = 2850; 77.5%)	OR (95% CI)	AHR (95% CI)
30-day case-fatality rate	142 (3.8)	12 (1.5)	130 (4.6)	0.31 (0.17–0.56)	0.44 (0.14–1.43)
Duration of antimicrobial intravenous therapy, median (IQR) (days)	4 (2–6)	4 (2–6)	4 (2–7)	0.85 (0.71–1.03)	0.85 (0.73–0.99)
Total duration of antimicrobial therapy, median (IQR) (days)	11 (9–15)	11 (9–13)	11 (10–15)	0.80 (0.61–1.06)	1.11 (0.94–1.31)
Adverse event	445 (12.1)	73 (8.8)	372 (13.1)	0.68 (0.50–0.93)	0.77 (0.53–1.12)
Rash	62 (1.7)	7 (0.8)	55 (1.9)	0.32 (0.11–0.77)	—
Hepatitis	33 (0.9)	2 (0.2)	31 (1.1)	0.20 (0.01–1.07)	—
Gastrointestinal	61 (1.7)	11 (1.3)	50 (1.8)	0.78 (0.34–1.66)	—
Renal	7 (0.2)	0	7 (0.2)	—	—
Phlebitis	238 (6.5)	41 (5.0)	197 (6.9)	0.79 (0.52–1.19)	—
Length of hospital stay, median (IQR) (days)	7 (5–11)	7 (5–9)	8 (5–11)	0.65 (0.56–0.85)	0.92 (0.79–1.08)
CAP recurrence	95 (2.6)	24 (2.9)	71 (2.5)	0.87 (0.51–1.43)	0.65 (0.37–1.14)

Data are presented as n (%) unless otherwise indicated.
AHR, adjusted hazard ratio; CAP, community-acquired pneumonia; IQR, interquartile range.

Transparency declaration

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Author's contributions

GAA, AR, and CG contributed to the concept and design of the study. The inclusion, data collection and interpretation were performed by GAA and AR. Microbiological data was supervised by CA, LC, and JN. EGL, NP, and CT supervised and performed statistical analysis. CG, AR, and JC contributed greatly to the writing of this paper. All authors have read and approved the final version of this manuscript.

Access to data

Data collected for the study—including de-identified individual participant data and a data dictionary defining each field in the set—will be made available to researchers who provide a methodologically sound proposal to the corresponding author and a signed data access agreement.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.06.021.

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