ORIGINAL ARTICLE

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

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ABSTRACT

BACKGROUND

The choice of empirical antibiotic treatment for patients with clinically suspected community-acquired pneumonia (CAP) who are admitted to non–intensive care unit (ICU) hospital wards is complicated by the limited availability of evidence. We compared strategies of empirical treatment (allowing deviations for medical reasons) with beta-lactam monotherapy, beta-lactam–macrolide combination therapy, or fluoroquinolone monotherapy.

METHODS

In a cluster-randomized, crossover trial with strategies rotated in 4-month periods, we tested the noninferiority of the beta-lactam strategy to the beta-lactam–macrolide and fluoroquinolone strategies with respect to 90-day mortality, in an intention-to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

RESULTS

A total of 656 patients were included during the beta-lactam strategy periods, 739 during the beta-lactam–macrolide strategy periods, and 888 during the fluoroquinolone strategy periods, with rates of adherence to the strategy of 93.0%, 88.0%, and 92.7%, respectively. The median age of the patients was 70 years. The crude 90-day mortality was 9.0% (59 patients), 11.1% (82 patients), and 8.8% (78 patients), respectively, during these strategy periods. In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% confidence interval [CI], −0.6 to 4.4) with the beta-lactam–macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, −2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated noninferiority of the beta-lactam strategy. The median length of hospital stay was 6 days for all strategies, and the median time to starting oral treatment was 3 days (interquartile range, 0 to 4) with the fluoroquinolone strategy and 4 days (interquartile range, 3 to 5) with the other strategies.

CONCLUSIONS

Among patients with clinically suspected CAP admitted to non-ICU wards, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies with a beta-lactam–macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality. (Funded by the Netherlands Organization for Health Research and Development; CAP-START ClinicalTrials.gov number, NCT01660204.)

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Community-acquired pneumonia (CAP) is a leading cause of hospitalization and death worldwide.[1-3] Most guidelines recommend that antibiotic treatment be based on the severity of disease at presentation, assessed either on the basis of the level of care needed or on the basis of a prognostic risk score.[4-6] For patients with clinically suspected CAP who are admitted to a non–intensive-care-unit (ICU) ward, guidelines recommend either combination therapy with a beta-lactam plus a macrolide or plus ciprofloxacin or monotherapy with moxifloxacin or levofloxacin for empirical treatment. These guidelines have increased the use of macrolides and fluoroquinolones, although these antibiotic classes have been associated with increased development of resistance.[7,8] The evidence in support of these recommendations is limited.[9-13] The recommendation to add a macrolide to a beta-lactam is based on observational studies, which are prone to confounding by indication.[14] Although fluoroquinolones have been evaluated in randomized, controlled trials, their superiority over beta-lactam monotherapy has not been shown.[15,16] Moreover, the results of randomized, controlled trials may be affected by in-hospital antibiotic exposure that occurs before randomization[17,18] and often have restrictive inclusion criteria, which limit the generalizability of their results to daily practice.

We therefore assessed whether a strategy of preferred empirical treatment with beta-lactam monotherapy is noninferior to either preferred beta-lactam–macrolide combination therapy or preferred fluoroquinolone monotherapy, with regard to 90-day all-cause mortality among adults with clinically suspected CAP who are admitted to non-ICU wards. These strategies allowed for deviation from the assigned antibiotic therapy for medical reasons, so as not to compromise care. We performed a pragmatic, cluster-randomized, crossover trial to overcome confounding by indication and the effects of prerandomization antibiotic therapy.

Methods

Study Design and Oversight

The Community-Acquired Pneumonia — Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START) was performed in seven hospitals in the Netherlands, from February 2011 through August 2013 (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The design and rationale of the study have been described elsewhere,[18] and the data are reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) statements for cluster-randomized and noninferiority studies.[19,20] Additional study details are provided in the study protocol and statistical analysis plan, which are available at NEJM.org. The study protocol was approved by the ethics review board at the University Medical Center Utrecht (reference number 10/148), by the local institutional review boards, and by the antibiotic committee at each participating hospital.

Eligibility and Recruitment of Patients

Patients 18 years of age or older with clinically suspected CAP who required antibiotic treatment and hospitalization in a non-ICU ward were eligible for the study (Table 1). Patients with cystic fibrosis were not eligible. Hospital G (see the Supplementary Appendix) included only patients with a CURB-65 score greater than 2 (the CURB-65 score is calculated by assigning 1 point each for confusion, uremia [blood urea nitrogen ≥20 mg per deciliter], high respiratory rate [≥30 breaths per minute], low systolic blood pressure [<90 mm Hg] or diastolic blood pressure [≤60 mm Hg], and an age of 65 years or older, with a higher score indicating a higher risk of death within 30 days).[21] We used on-site training of research nurses throughout the study to ensure the standardization of case definitions.

Emergency department registries were screened daily for eligible patients by research nurses or physicians. Obtaining informed consent before intervention was deemed unnecessary, because patients did not undergo randomization individually, and all the antibiotics we studied are used in current practice.[22] Written informed consent obtained within 72 hours after admission was required for data collection.

Intervention

During consecutive periods of 4 months, beta-lactam monotherapy, beta-lactam with a macrolide, or fluoroquinolone monotherapy was used as the preferred empirical treatment for eligible patients. The order of strategies was randomized separately in each hospital, without washout periods. Patients were treated and assessed in ac-

Table 1. Definitions.

Case definitions
Community-acquired pneumonia (CAP) (working diagnosis): The presence of at least two of the diagnostic clinical criteria and in-hospital treatment with antibiotics for clinically suspected CAP as documented by the treating physician. Patients with two or more criteria and an obvious nonrespiratory source of infection were not considered to have a working diagnosis of CAP, nor were patients who had recently been hospitalized (for >48 hours in the previous 2 weeks) or who resided in long-term care facilities.
Radiologically confirmed CAP: A working diagnosis of CAP plus the presence of a new or increased infiltrate on chest radiography or computed tomography (CT) and at least two other clinical criteria.
Diagnostic clinical criteria
Cough
Production of purulent sputum or a change in the character of sputum
Temperature >38°C or <36.1°C
Auscultatory findings consistent with pneumonia, including rales, evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony), or both
Leukocytosis (>10×10^9 white cells per liter or >15% bands)
C-reactive protein level more than 3 times the upper limit of the normal range
Dyspnea, tachypnea, or hypoxemia
New or increased infiltrate on chest radiography or CT scan
Intervention strategies*
Beta-lactam strategy: Preferred empirical treatment with amoxicillin, amoxicillin plus clavulanate, or a third-generation cephalosporin. Penicillin was not allowed as empirical beta-lactam monotherapy.
Beta-lactam–macrolide strategy: Preferred empirical treatment with penicillin, amoxicillin, amoxicillin plus clavulanate, or a third-generation cephalosporin in combination with azithromycin, erythromycin, or clarithromycin
Fluoroquinolone strategy: Preferred empirical treatment with moxifloxacin or levofloxacin

* Strategies were based on the recommendations in the Dutch guideline on treatment of CAP that was available before the start of the study.[23]

cordance with the strategy that was applicable on the admission date. Clinicians were repeatedly informed of the current antibiotic strategy by local investigators and with the use of newsletters and presentations.

The antibiotics allowed during each treatment strategy period (Table 1) were based on the 2005 Dutch guideline.[23] Physicians were encouraged to apply the assigned treatment strategies for the full treatment of patients with suspected CAP, unless there were medical reasons not to, such as adverse events or de-escalation of antibiotic treatment (e.g., because of a switch to targeted treatment when a causative pathogen had been identified). Adherence to the strategy was defined as treatment in accordance with the assigned strategy or deviation from the strategy for medical reasons (i.e., motivated deviation), irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic. Adherence to the antibiotic was defined as initial treatment with the assigned antibiotic, irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic.

RANDOMIZATION

Computer-generated randomization was performed in blocks of six, each containing a sequence of the three antibiotic strategies. Hospitals were assigned to their sequence after approval of the study by the hospital antibiotic committee. Two hospitals that had closely collaborating medical staff were randomized as one cluster. All the hospitals planned to participate until the calculated sample size was met or for a maximum of 2 years (Fig. S1 in the Supplementary Appendix).

OUTCOMES

The primary outcome was all-cause mortality within 90 days after admission. The secondary outcomes were the time to starting oral treat-

ment, length of hospital stay, and occurrence of minor or major complications during the hospital stay. All outcomes were measured at the individual patient level.

DATA COLLECTION

Data on clinical presentation, laboratory and microbiologic test results, the antibiotic agents used, complications, and clinical outcome were retrieved from medical records. Nonroutine data were recorded by research nurses directly after the patient's inclusion. When the reasons for deviations from the assigned empirical treatment were not clear in the medical chart, research nurses requested information from responsible physicians. The 90-day mortality was determined from the patient record database of each participating hospital or from the municipal personal records database (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Details about the calculation of sample size are provided in the Supplementary Appendix. Analyses were performed in accordance with the intention-to-treat principle, with adjustment for clustering. Differences among the groups in 90-day mortality were assessed with the use of a mixed-effects logistic-regression analysis, including hospitals as a fixed effect and each strategy period per hospital as a random intercept.[24] We estimated absolute risk differences among strategies by averaging the computed individual risks for each treatment group, and confidence intervals were calculated with the use of 2000 bootstrapping samples.[25] Noninferiority was assessed in a one-sided test at a significance level of 0.05 with the use of two-sided 90% confidence intervals.

Differences in the length of hospital stay and the time to starting oral administration of antibiotics were tested with mixed-effects Cox proportional-hazards models.[26] The frequencies of major and minor complications were compared by means of mixed-effects multinomial regression. Post hoc analyses of the strategy-adherent and antibiotic-adherent populations were performed for all outcomes. We performed sensitivity analyses that included only patients with radiologically confirmed CAP (Table 1) and that assessed 30-day mortality instead of 90-day mortality, and we calculated two-sided 95% confidence intervals. Missing data were imputed by multiple imputation,[27] with the exception of data on respiratory rate, heart rate, and confusion at admission; the values for these variables were assumed to be normal when data were missing. The analyses were performed with the use of R software, version 3.0.2 (R Project for Statistical Computing).[28]

RESULTS

ENROLLMENT

A total of 3325 patients were eligible for inclusion in the study, and 2283 (69%) gave consent. The median age of the patients was 70 years (interquartile range, 59 to 79). Among the patients who were not included, the median age was 74 years (interquartile range, 63 to 83) during the beta-lactam strategy periods, 74 years (interquartile range, 61 to 82) during the beta-lactam–macrolide strategy periods, and 74 years (interquartile range, 61 to 83) during the fluoroquinolone strategy periods, and the reasons for noninclusion were similar across strategies (Fig. 1). The baseline characteristics of included patients were similar among strategy periods, and blood and sputum cultures and urinary antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed with similar frequency (Table 2). The microbial causes of CAP were similar in the three treatment groups. *S. pneumoniae* was the pathogen detected most frequently (in 15.9% of patients), followed by *Haemophilus influenzae* (in 6.8%); atypical pathogens were found in 2.1% of the patients (Table S1 in the Supplementary Appendix). Resistance to the initiated antibiotic treatment was highest with the beta-lactam strategy (Table S2 in the Supplementary Appendix).

Six hospitals completed 6 randomized strategy periods each; enrollment was discontinued in one hospital after 4.5 periods, when the intended number of patients per treatment group had been reached. Changeovers from one treatment strategy period to the next occurred as planned except in one hospital: because of unforeseen fluoroquinolone supply problems, 4 weeks of the first fluoroquinolone period were exchanged with the subsequent beta-lactam–macrolide period (Fig. S1 in the Supplementary Appendix).

STRATEGY ADHERENCE AND ANTIBIOTIC USE

Rates of adherence to the strategies and to antibiotic treatment are shown in Figure 1. Antibiotic use during each strategy period is summarized in Table S3 in the Supplementary Appendix, and

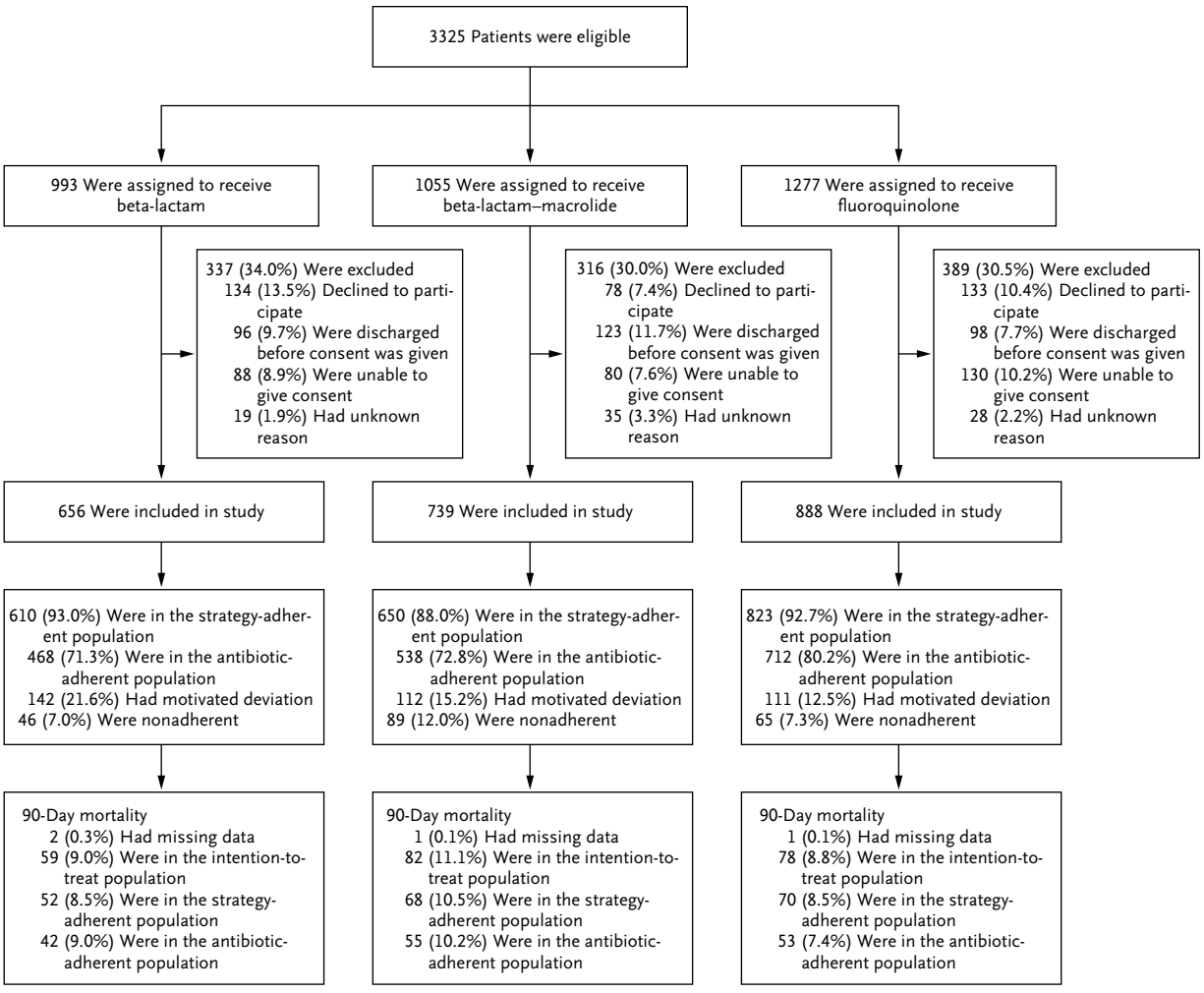


Figure 1. Inclusion of Patients, Rates of Adherence, and Mortality.

The strategy-adherent population was the population that underwent treatment in accordance with the assigned strategy or had deviation from the strategy for medical reasons (i.e., motivated deviation), irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic; the antibiotic-adherent population was the population that underwent initial treatment with the assigned antibiotic, irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic.

antibiotic adherence is summarized in Figure S3 in the Supplementary Appendix. The number of patients empirically treated with antibiotic coverage for atypical pathogens (i.e., macrolides, fluoroquinolones, and doxycycline) during the beta-lactam strategy periods was 67% less than the number treated with atypical coverage during the beta-lactam–macrolide strategy periods and 69% less than the number during the fluoroquinolone strategy periods, and the cumulative number of days with atypical coverage was 57% and 62% less, respectively.

Deviations were made for 565 patients (24.8%); a total of 200 of these deviations had no documented medical reason. The most frequent medical reasons for deviation from the beta-lactam strategy were the perceived need to cover atypical pathogens (53 patients, 8.1%), a contraindication to beta-lactams (21 patients, 3.2%), and a recent start of treatment with another antibiotic class or a lack of response to preadmission treatment with beta-lactams (27 patients, 4.1%) (Table S4 in the Supplementary Appendix). Among patients receiving the assigned therapy, switches to

Table 2. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Antibiotic Treatment Strategy		
	Beta-Lactam (N=656)	Beta-Lactam–Macrolide (N=739)	Fluoroquinolone (N=888)
Median age (interquartile range) — yr	70 (60–79)	70 (59–80)	71 (59–79)
Male sex — no. (%)	381 (58.1)	431 (58.3)	505 (56.9)
Median duration of symptoms (interquartile range) — days	3 (1–7)	3 (1–7)	3 (1–7)
Received antibiotics before admission — no./total no. (%)	219/637 (34.4)	227/721 (31.5)	303/873 (34.7)
Current smoker — no./total no. (%)	109/627 (17.4)	154/723 (21.3)	196/872 (22.5)
Past smoker — no./total no. (%)	379/627 (60.4)	398/723 (55.0)	490/872 (56.2)
Received influenza vaccination — no./total no. (%)	453/624 (72.6)	466/700 (66.6)	572/847 (67.5)
Received pneumococcal vaccination — no./total no. (%)			
PPSV23	16/594 (2.7)	18/671 (2.7)	13/822 (1.6)
PCV13	19/656 (2.9)	7/739 (0.9)	10/888 (1.1)
Dependency in ADL — no./total no. (%)†	199/637 (31.2)	200/714 (28.0)	257/870 (29.5)
Had one or more hospital stays in the previous year — no./total no. (%)	271/653 (41.5)	298/722 (41.3)	351/881 (39.8)
Had coexisting condition — no. (%)			
Cardiovascular disease	153 (23.3)	154 (20.8)	172 (19.4)
COPD or asthma	260 (39.6)	281 (38.0)	377 (42.5)
Other chronic pulmonary disease	64 (9.8)	97 (13.1)	61 (6.9)
Diabetes mellitus	118 (18.0)	101 (13.7)	161 (18.1)
Cancer‡	106 (16.2)	124 (16.8)	151 (17.0)
HIV/AIDS — no. (%)	3 (0.5)	6 (0.8)	6 (0.7)
Chronic renal failure or nephrotic syndrome	10 (1.5)	14 (1.9)	7 (0.8)
Receiving immunosuppressive therapy — no. (%)	59 (9.0)	57 (7.7)	93 (10.5)
Underwent organ or bone marrow transplantation — no. (%)	19 (2.9)	24 (3.2)	29 (3.3)
PSI score§¶	84.6±29.0	84.8±27.8	85.4±28.5
Median CURB-65 score (interquartile range)§‖	1 (1–2)	1 (1–2)	1 (1–2)
Had radiologically confirmed CAP — no. (%)	506 (77.1)	566 (76.6)	665 (74.9)
Blood culture obtained — no. (%)	508 (77.4)	559 (75.6)	670 (75.5)
Sputum culture obtained — no. (%)	306 (46.6)	347 (47.0)	390 (43.9)
PUAT performed — no. (%)	504 (76.8)	582 (78.8)	711 (80.1)
LUAT performed — no. (%)	492 (75.0)	574 (77.7)	668 (75.2)

* Plus–minus values are means ±SD. ADL denotes activities of daily living, COPD chronic obstructive pulmonary disease, LUAT legionella urinary antigen test, PCV13 13-valent pneumococcal conjugate vaccine (received in the Community Acquired Pneumonia Immunization Trial in Adults [CAPITA]), PPSV23 23-valent pneumococcal polysaccharide vaccine, PSI Pneumonia Severity Index, and PUAT pneumococcal urinary antigen test.

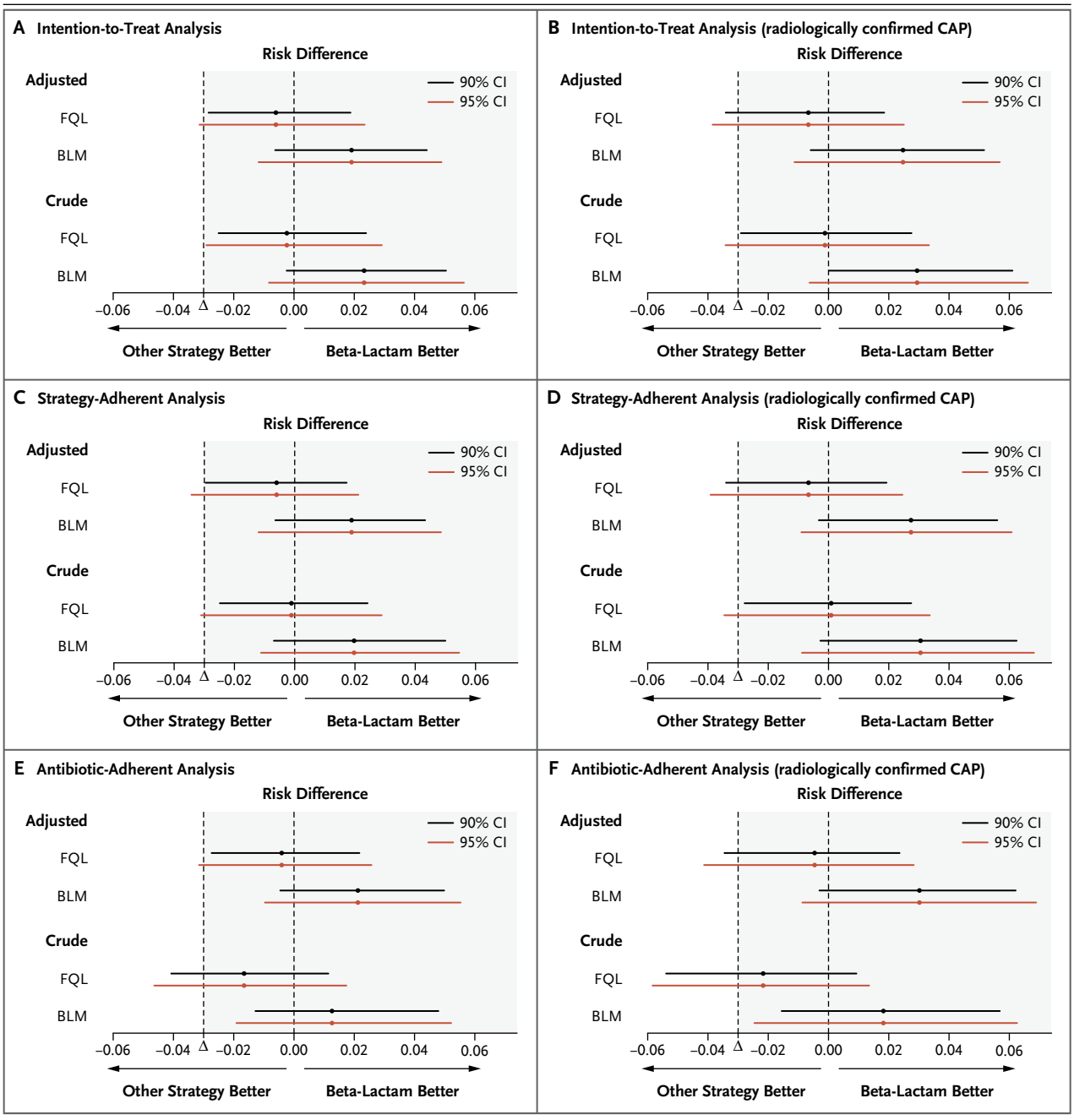
† This category includes patients who were not able to perform ADL autonomously.

‡ Active cancer was defined as a solid or hematologic cancer treated with radiotherapy or chemotherapy within the previous 5 years.

§ When data were missing, values were assumed to be normal. A total of 6.3% of data points used to calculate the PSI score had missing values, and 11.3% of data points used to calculate the CURB-65 score had missing values.

¶ The PSI score uses 20 clinical measures to predict risk of death within 30 days, with results ranging from 0.1% (in patients with a score of 0–50) to 27.0% (in patients with a score >131).

‖ The CURB-65 score is calculated by assigning 1 point each for confusion, uremia (blood urea nitrogen ≥20 mg per deciliter), high respiratory rate (≥30 breaths per minute), low systolic blood pressure (<90 mm Hg) or diastolic blood pressure (≤60 mm Hg), and an age of 65 years or older, with a higher score indicating a higher risk of death within 30 days.



other antibiotic classes because of perceived insufficient clinical recovery were made for 41 patients (8.8%) during the beta-lactam strategy periods, for 33 patients (6.1%) during the beta-lactam–macrolide strategy periods, and for 26 patients (3.7%) during the fluoroquinolone strategy periods. Other reasons for switching antibiotic classes are provided in Table S5 in the Supplementary Appendix.

PRIMARY OUTCOME

All-cause mortality at 90 days could not be assessed for four patients; these patients were included only in secondary analyses (Fig. 1). The absolute difference in the adjusted risk of death between the beta-lactam strategy and the beta-lactam–macrolide strategy was 1.9 percentage points (90% confidence interval [CI], −0.6 to 4.4) in favor of the beta-lactam strategy, and the

Figure 2 (facing page). Noninferiority Plots.
The noninferiority plots show crude and adjusted absolute risk differences for 90-day mortality associated with the beta-lactam–macrolide combination and fluoroquinolone monotherapy strategies, as compared with the beta-lactam monotherapy strategy, in analysis of the intention-to-treat population, the strategy-adherent population, and the antibiotic-adherent population, as well as for the sensitivity analysis including only patients with radiologically confirmed community-acquired pneumonia (CAP). To allow for one-sided testing of noninferiority, 90% confidence intervals were calculated (shown in black); 95% confidence intervals are also provided (shown in red). Confidence intervals within the gray-shaded area are noninferior. The crude analyses take into account cluster-period effects and center effects. The adjusted analyses are additionally corrected for Pneumonia Severity Index score (a score that uses 20 clinical measures, including age and sex, to predict the risk of death within 30 days, with results ranging from 0.1% [in patients with a score of 0–50] to 27.0% [in patients with a score >131]); smoking status; presence of chronic pulmonary diseases, chronic cardiovascular diseases, diabetes mellitus, or immunosuppression; previous treatment with antibiotics; and number of hospitalizations during the previous year. The analysis of the antibiotic-adherent population is further adjusted for duration of symptoms; dependency in activities of daily living; presence or absence of hematologic cancer, nonhematologic cancer, or immunosuppression; C-reactive protein level; whole-blood leukocyte count; and temperature at hospital admission. The noninferiority margin is –3 percentage points (shown as Δ). The intracluster correlation for cluster-period effects in the primary analysis was 4.5×10^{-7}. Exact numbers are provided in Table S6 in the Supplementary Appendix, and survival curves are shown in Figure S4 in the Supplementary Appendix. BLM denotes beta-lactam–macrolide combination therapy and FQL fluoroquinolone monotherapy.

absolute difference between the beta-lactam strategy and the fluoroquinolone strategy was –0.6 percentage points (90% CI, –2.8 to 1.9) in favor of the fluoroquinolone strategy. These confidence intervals do not include the prespecified margin of a 3–percentage-point higher 90-day mortality, thus demonstrating the noninferiority of the beta-lactam strategy to the beta-lactam–macrolide and fluoroquinolone strategies (Fig. 2).

In the strategy-adherent and antibiotic-adherent populations, the absolute adjusted risk differences were similar to those in the intention-to-treat population. Similar estimates were obtained in sensitivity analyses of patients with radiologically confirmed CAP and in analyses of 30-day mortality. The two-sided 95% confidence interval for the comparison of the beta-lactam strategy with the fluoroquinolone strategy crossed the noninferiority margin (Fig. 2, and Table S6, S7, and S8 in the Supplementary Appendix).

SECONDARY OUTCOMES

The median length of hospital stay was 6 days for all strategies, but the upper quartile was higher during the beta-lactam–macrolide strategy periods (Table 3). The median duration of intravenous treatment was 3 days during the fluoroquinolone strategy periods and 4 days during the other strategy periods (Table 3). The proportions of patients whose treatment started with oral antibiotics were 27% during the fluoroquinolone strategy periods, as compared with 13% and 10% during the beta-lactam and beta-lactam–macrolide strategy periods, respectively. There were no significant differences among the three strategies in the incidence of major or minor complications (Table 3).

DISCUSSION

In this pragmatic, cluster-randomized, crossover trial, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies of treatment with beta-lactam–macrolide combination therapy and with fluoroquinolone monotherapy among patients with suspected CAP who were admitted to non-ICU wards. Moreover, there were no clinically relevant differences among treatment strategies in the length of hospital stay or in reported complications. The median time to starting oral treatment was shorter with the fluoroquinolone strategy, mainly because more patients during those strategy periods started with oral empirical treatment at admission, but this did not result in a decreased length of hospital stay.

Our approach differs from those of previous studies in four aspects. First, this study addressed treatment strategies, rather than individual antibiotics, in the treatment of patients hospitalized with a clinical suspicion of CAP. To reflect daily medical practice, we allowed for deviations from the assigned therapy for medical reasons. To minimize confounding, all the patients were included in the intention-to-treat analysis. Although deviations and switches reduced the differences among treatment strategies, empirical atypical coverage was reduced by 67% during the

Table 3. Effects of Antibiotic Treatment Strategies on Secondary Outcomes.*

Outcome	Antibiotic Treatment Strategy		
	Beta-Lactam (N=656)	Beta-Lactam–Macrolide (N=739)	Fluoroquinolone (N=888)
Median length of stay (IQR) — days†	6 (4–8)	6 (4–10)	6 (4–8)
Rate ratio for discharge alive (95% CI)‡			
Intention-to-treat population			
Crude	Reference	0.86 (0.77–0.96)	1.03 (0.93–1.15)
Adjusted	Reference	0.87 (0.78–0.97)	1.04 (0.94–1.16)
Strategy-adherent population			
Crude	Reference	0.86 (0.77–0.96)	1.03 (0.93–1.15)
Adjusted	Reference	0.86 (0.77–0.97)	1.04 (0.93–1.16)
Antibiotic-adherent population			
Crude	Reference	0.84 (0.74–0.96)	1.04 (0.92–1.17)
Adjusted	Reference	0.84 (0.74–0.95)	1.03 (0.92–1.17)
Time to starting oral treatment§			
Receipt of oral antibiotics as initial in-hospital therapy — no. (%)	87 (13.3)	73 (9.9)	241 (27.1)
Median time receiving IV antibiotic treatment (IQR) — days	4 (3–5)	4 (3–5)	3 (0–4)
Rate ratio for starting oral treatment (95% CI)¶			
Intention-to-treat population			
Crude	Reference	0.95 (0.84–1.08)	1.28 (1.13–1.44)
Adjusted	Reference	0.97 (0.86–1.09)	1.29 (1.15–1.46)
Strategy-adherent population			
Crude	Reference	0.94 (0.82–1.07)	1.30 (1.15–1.48)
Adjusted	Reference	0.94 (0.83–1.08)	1.33 (1.17–1.51)
Antibiotic-adherent population			
Crude	Reference	0.93 (0.78–1.10)	1.47 (1.24–1.73)
Adjusted	Reference	0.93 (0.79–1.11)	1.52 (1.28–1.80)
Complications‖			
None — no. (%)	550 (83.8)	608 (82.3)	725 (81.6)
Minor — no. (%)	72 (11.0)	97 (13.1)	109 (12.3)
Major — no. (%)	32 (4.9)	42 (5.7)	47 (5.3)
Unknown — no. (%)	8 (1.2)	12 (1.6)	26 (2.9)
Odds ratio (95% CI)**			
Intention-to-treat population	Reference	1.06 (0.76–1.48)	1.02 (0.73–1.41)
Strategy-adherent population	Reference	1.06 (0.74–1.52)	1.03 (0.73–1.46)
Antibiotic-adherent population	Reference	1.20 (0.82–1.77)	1.03 (0.71–1.51)

* Crude analyses take into account cluster-period effects and center effects. Adjusted analyses are additionally corrected for PSI score (including age and sex); smoking status; presence of chronic pulmonary disease, chronic cardiovascular disease, diabetes mellitus, or immunosuppression; previous receipt of antibiotics; and number of hospitalizations in the previous year. IQR denotes interquartile range, and IV intravenous.

† The length of stay was unknown for 5 patients in the beta-lactam strategy group (0.8%), 2 patients in the beta-lactam–macrolide strategy group (0.3%), and 5 patients in the fluoroquinolone strategy group (0.6%), who were transferred to other hospitals.

‡ Rate ratios are from a Cox proportional-hazards model predicting the day of discharge as the event of interest. A rate ratio below 1 indicates a longer length of stay. The survival curve is shown in Figure S5 in the Supplementary Appendix.

§ The duration of intravenous treatment was unknown for 1 patient in the fluoroquinolone strategy group (0.1%) who was transferred to another hospital while receiving intravenous treatment.

¶ Rate ratios are from a Cox proportional-hazards model predicting the end of intravenous treatment or the start of oral treatment as the event of interest. A rate ratio below 1 indicates a longer duration of intravenous treatment. The survival curve is shown in Figure S6 in the Supplementary Appendix.

‖ Major complications include in-hospital death, respiratory insufficiency, ICU admission, organ failure, and septic shock. A detailed description of complications is provided in Table S9 in the Supplementary Appendix.

** Odds ratios (all crude analyses) are from a mixed-effects ordinal logistic-regression model with no, minor, or major complications as the dependent variable.

beta-lactam strategy periods as compared with the beta-lactam–macrolide strategy periods and by 69% during the beta-lactam strategy periods as compared with the fluoroquinolone strategy periods. The number of in-hospital days with atypical coverage was also reduced during the beta-lactam strategy periods, by 57% and 62%, respectively. In the post hoc analysis of the strategy-adherent and antibiotic-adherent populations, the beta-lactam strategy remained noninferior to the beta-lactam–macrolide strategy. In the crude analysis of the antibiotic-adherent population, the lower limit of the confidence interval crossed −3 percentage points for the comparison between beta-lactam and fluoroquinolone monotherapy; however, after adjustment for confounders, the lower limit of the confidence interval fell within the defined margins of noninferiority.

Second, we used a cluster-randomized design that allowed for an immediate start of the assigned empirical treatment strategy. The crossover component increased the efficiency of the trial by allowing comparisons of the effect of the strategies within each cluster and ensuring that all hospitals used all three strategies, a design that minimized the possibility of confounding. Despite the risk of selection bias that is inherent to cluster-randomized studies, the baseline characteristics of the patients were similar among strategies, and statistical adjustment for potential confounders changed the findings only minimally. Differential inclusion of patients across treatment groups was unlikely, given the similar age patterns for nonincluded patients and similar enrollment rates. We were not allowed to collect data on other characteristics of the patients who were not included. The pathogens found were similar among strategy groups, but the resistance of pathogens to the actual treatment was highest during the beta-lactam strategy periods. This did not appear to lead to a worse outcome, possibly because not all were proven causative pathogens and because of antibiotic switches.

Third, all patients for whom the antibiotic strategy might have been used in daily practice were eligible for enrollment, which increases the generalizability of the results. Although this could increase the heterogeneity of the population and the potential for bias toward noninferiority, the effect estimates were similar in the sensitivity analysis that included only patients with radiologically confirmed CAP.

Finally, the primary end point was 90-day all-cause mortality, because CAP is associated with high long-term mortality and this is a patient-relevant outcome that is not susceptible to observation bias.[17,29,30] An unplanned sensitivity analysis with 30-day mortality as the outcome yielded similar results. Among the secondary outcomes, complications, which were extracted from the medical records, might have been misclassified and subject to observation bias.

The noninferiority of the beta-lactam strategy to the beta-lactam–macrolide strategy was apparent in all analyses. These findings, together with the slightly longer length of hospital stay with the latter strategy, reported associations with the development of resistance,[7,8] and possible increased risks of cardiac events,[31,32] indicate that the addition of macrolides for empirical treatment of CAP should be reconsidered. In a recent randomized, controlled trial, the noninferiority of beta-lactam monotherapy to beta-lactam–macrolide combination therapy with respect to clinical stability at day 7 could not be shown, although superiority of the beta-lactam–macrolide combination therapy was not shown, either. Moreover, 30-day and 90-day all-cause mortality and length of hospital stay were similar with the two therapies.[33] Differences between that study and the current study include the strict criteria for eligibility and for switching therapy in cases of clinical deterioration in that study.

Some aspects of our study require explanation. In the noninferiority design, we used one-sided testing with an alpha significance level of 0.05. With 95% confidence intervals — that is, an alpha level of 0.025 — the noninferiority of beta-lactams to fluoroquinolones was not shown (Fig. 2); however, there was no clear trend toward superiority for fluoroquinolones in any of the other adjusted analyses.

Differences in the numbers of eligible patients per strategy resulted from cluster randomization. The beta-lactam and fluoroquinolone strategies were assigned more frequently during the 2011–2012 and 2012–2013 winter seasons, respectively, and more patients were hospitalized during 2012–2013 winter months. However, the proportions of patients included were similar throughout the seasons and among strategies (Fig. 1, and Fig. S2 in the Supplementary Appendix). Although a low incidence of atypical infections during the 2011–2012 winter season could have favored the beta-lactam strategy, na-

tional surveillance data showed a higher incidence of *Mycoplasma pneumoniae* infections, mostly CAP, during that period,[34] for which the beta-lactam strategy might have been less effective. The outbreak of Q fever in the Netherlands ended before the start of the current study,[35] and the distribution of pathogens was similar to those in other studies that have relied on routine microbiologic testing.[36-38]

Regional differences in microbial causes could reduce the generalizability of our findings. However, resistance of *S. pneumoniae* to penicillin,[39] which rarely occurs in the Netherlands, is unlikely to influence the outcome in patients with pneumonia treated with beta-lactam antibiotics.[40] The prevalence of *S. pneumoniae* resistance to macrolides was 4.2% in the Netherlands in 2011.[39] The incidence of legionella in this study was less than 1%. A higher incidence could influence the effectiveness of empirical treatment with beta-lactam monotherapy, which stresses the importance of rapid testing in patients with risk factors for Legionnaires' disease. In the current study, rapid urinary antigen testing for legionella was performed in 492 patients (75%) during the beta-lactam strategy periods; 5 of the patients (1%) tested positive, 2 of whom received ciprofloxacin empirically because of a high clinical suspicion. For the other 3 patients, antibiotic therapy was adjusted after test results became available. All 5 patients had a good clinical outcome. Higher incidences of community-acquired *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* infections would require the adaptation of all three treatment strategies.

In conclusion, among patients with suspected CAP who were admitted to non-ICU wards, we found that a strategy of preferred empirical treatment with beta-lactam monotherapy that allowed for deviations for medical reasons was noninferior to strategies with beta-lactam–macrolide combination therapy or fluoroquinolone monotherapy in terms of 90-day all-cause mortality. In addition, beta-lactam monotherapy was not associated with a longer length of hospital stay or a higher incidence of complications.

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