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Atypical coverage in community-acquired pneumonia after outpatient beta-lactam monotherapy

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ABSTRACT

Introduction: In adults hospitalized with community-acquired pneumonia (CAP) after >48 h of outpatient beta-lactam monotherapy, coverage of atypical pathogens is recommended based on expert opinion.
Methods: In a post-hoc analysis of a large study of CAP treatment we included patients who received beta-lactam monotherapy for >48 h before hospitalization. Length of hospital stay (LOS), 30-day mortality, and number of treatment escalations were compared for those that continued beta-lactam monotherapy and those that received atypical coverage at admission.
Results: Of 179 patients (median age 66 years (IQR 50–78), 100 (56%) male), 131 (73%) received additional atypical coverage at admission. These patients were younger, had less comorbidities, and longer symptom duration, compared to those that continued beta-lactam monotherapy. In crude analysis, median (IQR) LOS was 6 (4–8) and 6 (4–9) days, mortality was 2% and 4%, and treatment escalations occurred in 8 (17%) and 11 (8%) patients without and with atypical coverage, respectively. Adjusted effect ratios for absence of atypical coverage on LOS, mortality, and treatment escalation were 0.77 (95% CI 0.61–0.97), 0.37 (0.04–3.67), and 2.75 (0.94–8.09), respectively.
Conclusion: In adults hospitalized with CAP after >48 h of outpatient beta-lactam monotherapy, not starting antibiotics with atypical coverage was associated with a trend towards more treatment escalations, without evidence of increased LOS or mortality.

1. Introduction

The optimal empirical antibiotic treatment of community-acquired pneumonia (CAP) consists of the narrowest possible antimicrobial spectrum without compromising patient outcome. However, CAP may have different etiological causes requiring different antibiotic therapies, which are unknown when starting empirical treatment. Therefore, physicians must balance all-inclusiveness (that will stimulate resistance development) and insufficient treatment (that may worsen patient outcome). Clinical parameters cannot predict the causative pathogen [1–3]. The most debated question is whether atypical pathogens, such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila* must be covered empirically in all patients hospitalized with CAP [4,5]. Empirical treatment guidelines are based on the clinical severity of infection, local distribution of pathogens and resistance patterns of bacteria causing CAP, and failure of antibiotics prior to hospitalization. As general practitioners mostly prescribe beta-lactam antibiotics for lower respiratory tract infections, previous receipt of such antibiotics is a frequent reason to include empirical treatment for atypical pathogens when hospitalization for CAP is needed [3]. Empirical atypical coverage can include tetracyclines, macrolides, or fluoroquinolones. This guideline recommendation is based mainly on expert consensus. In a retrospective study, though, clinical outcome was comparable for those receiving

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and not receiving empirical atypical coverage after pre-hospitalization exposure to beta-lactam antibiotics [6]. Yet, in that study data could not be adjusted for disease severity and microbiology. The question whether atypical coverage is needed in CAP patients hospitalized to non-ICU wards that received beta-lactam monotherapy before hospitalization, therefore, remains to be answered.

2. Methods

2.1. Patients and setting

Data were used from a cluster-randomized trial evaluating empirical antibiotic treatment strategies described previously [7,8]. In short, seven hospitals in the Netherlands were randomized to three alternating empirical antibiotic treatment strategies for CAP, beta-lactam monotherapy, beta-lactam plus macrolide therapy, and fluoroquinolone monotherapy, during consecutive periods of four months. All patients hospitalized to a non-intensive care unit (non-ICU) ward with a working diagnosis of CAP were eligible for inclusion. A working diagnosis of CAP was defined as the presence of at least two 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, leucocytosis, C-reactive protein level more than 3 times the upper limit of the normal range, either of dyspnea, tachypnea, or hypoxemia, and new or increased infiltrate on chest radiography or CT scan) 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 non-respiratory source of infection were not considered to have a working diagnosis of CAP, nor were patients who had recently been hospitalized (for >48 h in the previous 2 weeks) or who resided in long-term care facilities. Treating physicians were instructed to treat CAP patients according to the allocated strategy, but deviations were allowed for medical reasons. Physicians were also allowed to switch antibiotic treatment if medically indicated, e.g. if the causing pathogen was identified or if patients deteriorated or failed to improve. Patients were prospectively included in the study after providing informed consent for the purpose of data collection. The study was approved by the Institutional Review Board of the University Medical Center Utrecht, the Netherlands.

The current analysis was restricted to patients receiving beta-lactam monotherapy as the last antibiotic treatment for >48 h prior to hospitalization. As these data were available per calendar day, we defined “>48 h” as three or more calendar days. Patients with two or more antibiotic-free calendar days between the end of outpatient antibiotic treatment and the day of hospitalization were not included, as we considered them not part of the study domain.

Patients were divided into two groups: those receiving and those not receiving atypical coverage at the time of hospitalization. As data on antibiotic treatment was available per calendar day, beta-lactam monotherapy was defined as receiving beta-lactams on the first calendar day of admission, and not receiving other antibiotics. If coverage of atypical pathogens was initiated on the second admission day, group assignment was based on the timing and rationales for treatment assignment provided in the medical records. E.g. if patients were hospitalized in the evening, a beta-lactam could be administered before midnight and a macrolide or fluoroquinolone was given the next morning, but this was already planned at the ER; such patients were classified as receiving empirical atypical coverage. However, if patients switched to atypical coverage the next calendar day based on new clinical or microbiological information, the empiric treatment was classified as no atypical coverage. All treatment episodes consisting of beta-lactam monotherapy (penicillin, amoxicillin (with or without clavulanic acid), cephalosporins, and carbapenems) were classified as absence of atypical coverage. Atypical coverage was categorized as receipt of a fluoroquinolone, macrolide, or tetracycline, or any combination of these with a beta-lactam. The decision to cover atypical pathogens was made by the treating physician.

2.2. Data collection

Data were collected from the medical records by trained research nurses and included demographics, comorbidities, severity indicators, laboratory results, antibiotic consumption, complications, and duration of hospitalizations. For assessment of disease severity we used the pneumonia severity index (PSI), a score consisting of 20 variables, and the CURB-65 score consisting of confusion, urea, respiratory rate, blood pressure, and age > 65 years; both scores developed to predict 30-day mortality [9,10]. The microbiological diagnostics were according to standard care practices and not dictated by protocol. Routine microbiological tests consisted of blood and sputum cultures and pneumococcal and legionella urinary antigen tests. Other tests including serology or polymerase chain reaction (PCR) tests of respiratory samples were requested at the discretion of the treating physician. Antibiotic treatment before admission was derived from the medical records or, if not documented, the patient was inquired by trained research nurses. Mortality status up to day 90 after admission was recorded from the medical charts. If in doubt, the mortality status of patients were checked electronically in the municipal personal records database except in one hospital,. In this hospital without electronic access to this database, research nurses contacted the general practitioner of each patient with an unknown status. In the Netherlands, every inhabitant is registered with a single general practitioner, who is routinely informed about important medical affairs.

2.3. Outcomes

The primary outcome was length of hospital stay (LOS) in days. Secondary outcome measures were all-cause 30-day mortality and treatment escalations. Treatment escalation was defined as antibiotic change for clinical deterioration/lack of improvement, or an identified pathogen not covered by the empirical treatment.

2.4. Statistical analysis

Common descriptive statistics were used to compare the two groups and differences were tested using the chi-squared or Fisher's exact test for proportions and Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. Differences in LOS were analyzed using a linear regression model with log-transformed LOS as the outcome. The exponential of the effect estimate is reported, which represents the relative change in LOS for patients continuing beta-lactam monotherapy compared to those receiving atypical coverage. All-cause 30-day mortality and treatment escalations were analyzed using a logistic regression model. Estimates are reported with 95% confidence intervals (CI) and a two-sided p-value <0.05 was considered statistically significant.

3. Results

Of 2283 patients included in the CAP-START study, 749 (32.8%) received any antibiotic prior to hospitalization and 179 (7.8%) received beta-lactam monotherapy prior to hospitalization for >48 h (Fig. 1). The median age was 66 years (interquartile range

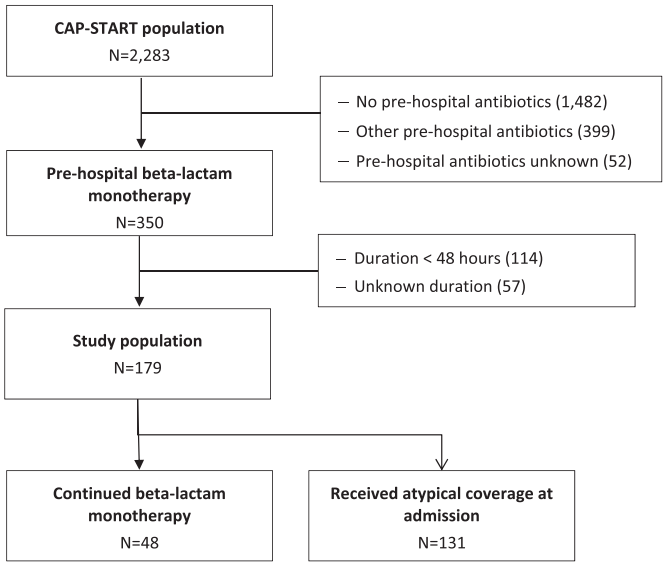

Fig. 1. Patient flowchart.

(IQR) 50–78) and 100 (56%) were male. At the moment of hospitalization beta-lactam monotherapy was continued in 48 (27%) patients and 131 (73%) received atypical coverage. Patients in the beta-lactam monotherapy group were older, had more comorbidity, and had longer symptom duration before admission compared to patients in the atypical coverage group, while clinical signs and symptoms at time of admission were comparable. There was no difference in the proportion of patients with sputum and blood cultures, however, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were more frequently performed in those receiving atypical coverage (Table 1).

3.1. Pathogens

The distribution of pathogens is provided in Table 2 for patients receiving empirical beta-lactam monotherapy or atypical coverage. To assess whether the microbiological data differs from the total CAP population, these data are also provided for patients without prior outpatient antibiotics (N = 1482). In the patients that received prior beta-lactam monotherapy for >48 h and that empirically received atypical coverage, a pathogen was less often detected, particularly *Streptococcus pneumoniae*, while atypical pathogens were detected in 12 (9.2%) of these patients compared to 23 (1.6%) of the patients without prior antibiotics. For patients that had received prior beta-lactam treatment for >48 h and continued beta-lactam treatment, the pathogen distribution was more comparable to those who had not received outpatient antibiotics, with an atypical pathogen detected in only 2 patients (4.2%) and a comparable proportion of patients with *S. pneumoniae*.

3.2. Antibiotic treatment and modifications

The most frequent beta-lactam prescribed prior to hospitalization was amoxicillin/clavulanic acid (n = 105, 59%) followed by amoxicillin (n = 70, 39%). The number of patients continuing beta-lactam monotherapy was 33/105 (31%) in those pre-treated with amoxicillin/clavulanic acid and 13/70 (19%) in those pre-treated with amoxicillin (Fig. 2). In patients continuing beta-lactam monotherapy, the empirical treatment consisted of amoxicillin/clavulanic acid monotherapy in 21 (44%), benzylpenicillin or amoxicillin monotherapy in 13 (27%), cephalosporin monotherapy in 9 (19%) and an aminoglycoside combined with a beta-lactam in 5 (10%) patients. A ranking of pre-admission, empirical, and final treatment regimens is provided in Table S1 in the Supplement.

Proportions of patients receiving beta-lactam monotherapy differed per hospital and for the three trial arms (Supplement Table S2). There was no clear effect of season on the choice of empirical treatment group (Supplement Fig. S1 and Table S4).

3.3. Effect of beta-lactam monotherapy on clinical outcomes

Median LOS was 6 (4–8) and 6 (IQR 4–9) days in the beta-lactam monotherapy group and the atypical coverage group, respectively. The adjusted relative effect of continuing beta-lactam monotherapy on LOS was 0.77 (0.61–0.97), indicating a 23% shorter LOS for patients that continued beta-lactam monotherapy (Table 3). After stratification for randomization arm, the effect estimates were in the same direction, ranging from 0.73 to 0.86 (Supplement Table S3).

Mortality within 30 days could not be assessed for one patient in the beta-lactam group who was discharged alive but was not a Dutch inhabitant and was lost to follow-up. One (2.1%) patient in the beta-lactam monotherapy group and 5 (3.8%) patients in the atypical coverage group died within 30 days (Table 3).

The single patient in the beta-lactam monotherapy group that died within 30 days was a 89 year old man with a history of cardiovascular disease, heart failure, and cerebrovascular disease. He was admitted with CAP with a PSI score of 139 (PSI class V, predicted 30-day mortality risk 26.7%). His pre-admission treatment consisted of amoxicillin/clavulanic acid for 3 days and this was continued during the admission. Microbiological evaluation included pneumococcal and legionella urinary antigen testing which were both negative. There were no complications and no therapy adjustments were made. He was discharged home after 10 days and died 7 days after discharge.

3.4. Treatment escalations

Treatment escalations occurred in 8 (16.7%) patients in the beta-lactam monotherapy group, with a median time to escalation of 2 days (range: 1–5). One patient switched from amoxicillin to amoxicillin-clavulanic acid after two days because of isolation of *Haemophilus influenzae* and *Moraxella catarrhalis* from sputum, two switched to ciprofloxacin because a pathogen was detected (*Klebsiella pneumoniae* from bronchoalveolar lavage after 5 days in one and *Legionella pneumophila* by the urinary antigen test after one day in the other patient), and five switched to different regimens with atypical coverage, two after one day and three after two days, because of clinical failure of the antibiotic treatment. In the atypical coverage group, 11 (8.4%) patients had a treatment escalation with a median time to escalation of 5 days (range: 1–9), all because of clinical failure. The adjusted odds ratio for treatment escalation in patients in whom beta-lactam monotherapy was continued was 2.75 (95% CI 0.94–8.09) (Table 3).

4. Discussion

This post-hoc analysis of 179 patients with CAP that had received >48 h of beta-lactam treatment prior to hospitalization to a non-ICU ward, did not reveal that continued treatment with beta-lactam monotherapy led to a worse clinical outcome compared to coverage of atypical pathogens. Apparently, possible detrimental effects of not routinely covering atypical pathogens were effectively prevented by early treatment escalation, which occurred in seven patients (15%). Patients that did receive atypical coverage were younger and – as a result – had lower severity scores. Except for a

Table 1
Baseline characteristics.

	Empirical treatment group		
	Beta-lactam monotherapy (N = 48)	Atypical coverage (N = 131)	P-value for difference
Demographics			
Age (median, IQR)	75 (63; 83)	64 (45; 76)	0.0015
Male gender	31 (65%)	69 (53%)	0.2106
Comorbidities			
Dependency in ADL	16 (33%)	28/130 (22%)	0.1547
Hospitalized in previous year	21 (44%)	39/130 (30%)	0.1227
Cardiovascular disease	13 (27%)	26 (20%)	0.4040
COPD or asthma	19 (40%)	33 (25%)	0.0904
Other chronic pulmonary disease	3 (6%)	10 (8%)	1.0000
Diabetes mellitus	8 (17%)	19 (15%)	0.9025
Cancer	8 (17%)	7 (5%)	0.0285
Prior antibiotic treatment			
Days of beta-lactam (median, IQR)	4 (4; 5)	4 (3; 6)	0.6192
Amoxicilline	13 (27%)	57 (44%)	0.0684
Amoxicillin-clavulanic acid	33 (69%)	72 (55%)	0.1367
Flucloxacillin	2 (4%)	1 (1%)	0.1756
Signs and symptoms			
Symptom duration (median, IQR)	6 (3; 7)	7 (4; 12)	0.0106
Temperature (median, IQR)	37.7 (37.1; 38.2)	38.0 (37.3; 38.6)	0.1630
Chills	3 (6%)	15 (11%)	0.4065
Vomiting/diarrhoea	4 (8%)	14 (11%)	0.7835
Confusion	2/35 (6%)	14/110 (13%)	0.3584
Systolic blood pressure <90 mmHg	0/47 (0%)	2/128 (2%)	1.0000
Diastolic blood pressure <60 mmHg	5/47 (11%)	11/128 (9%)	0.7680
Oxygen saturation <90%	10/43 (23%)	18/114 (16%)	0.3919
Respiratory rate >30/min	5/31 (16%)	12/85 (14%)	0.7726
Heart rate >125/min	4/46 (9%)	9/127 (7%)	0.7476
Leucocyte count (median, IQR)	10 (7; 13)	11 (8; 14)	0.0773
CRP (median, IQR)	110 (54; 165)	126 (69; 209)	0.0950
X-ray confirmed CAP	40 (83%)	112 (85%)	0.9025
CAP severity indices			
PSI score (median, IQR)	88 (64; 109)	74 (51; 95)	0.0171
CURB65 score (median, IQR)	1 (0; 2)	1 (0; 2)	0.0633
Microbiological testing			
Blood culture	34 (71%)	95 (73%)	0.9723
Sputum culture	23 (48%)	54 (41%)	0.5280
PUAT	35 (73%)	116 (89%)	0.0204
LUAT	33 (69%)	119 (91%)	0.0006

Abbreviations: IQR: interquartile range; ADL: activities of daily living; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; PSI: pneumonia severity index; CURB65: severity score consisting of confusion, urea, respiratory rate, blood pressure, and age<Roman> = </Roman>65; PUAT: pneumococcal urinary antigen test; LUAT: legionella urinary antigen test.

Table 2
Proven and probable pathogens.

	No prior treatment	>48 h of prior beta-lactam	
	(N = 1482)	Beta-lactam monotherapy (N = 48)	Atypical coverage (N = 131)
Streptococcus pneumoniae	266 (16.6%)	8 (15.1%)[a]	8 (6.0%)[b]
Staphylococcus aureus	48 (3.0%)	1 (1.9%)	1 (0.8%)
Other gram-positives	24 (1.5%)	0 (0.0%)	0 (0.0%)
Haemophilus influenzae	119 (7.4%)	2 (3.8%)	3 (2.3%)
Moraxella catarrhalis	29 (1.8%)	1 (1.9%)	0 (0.0%)
Escherichia coli	46 (2.9%)	1 (1.9%)	2 (1.5%)
Klebsiella pneumoniae	15 (0.9%)	1 (1.9%)	2 (1.5%)
Pseudomonas aeruginosa	22 (1.4%)	0 (0.0%)	1 (0.8%)
Other gram-negatives	53 (3.3%)	2 (3.8%)	4 (3.0%)
Legionella pneumophila	13 (0.8%)	1 (1.9%)[c]	1 (0.8%)[d]
Mycoplasma pneumoniae	7 (0.4%)	1 (1.9%)	11 (8.3%)[e]
Coxiella burnetti	1 (0.1%)	0 (0.0%)	0 (0.0%)
Mycobacteria	2 (0.1%)	0 (0.0%)	0 (0.0%)
Viruses	37 (2.3%)	2 (3.8%)	5 (3.8%)
Fungi/yeast	19 (1.2%)	2 (3.8%)	0 (0.0%)
No pathogen identified	904 (56.3%)	31 (58.5%)	95 (71.4%)

[a] In the beta-lactam monotherapy group 6 had a positive pneumococcal urinary antigen test on day 1.
[b] In the atypical coverage group 3 had a positive pneumococcal urinary antigen test on day 1.
[c] This patient had a positive Legionella urinary antigen test on day 2 and switched to ciprofloxacin.
[d] This patient had a positive Legionella urinary antigen test on day 1.
[e] 6 were based on serology, 4 on PCR, and 1 on serology and PCR.

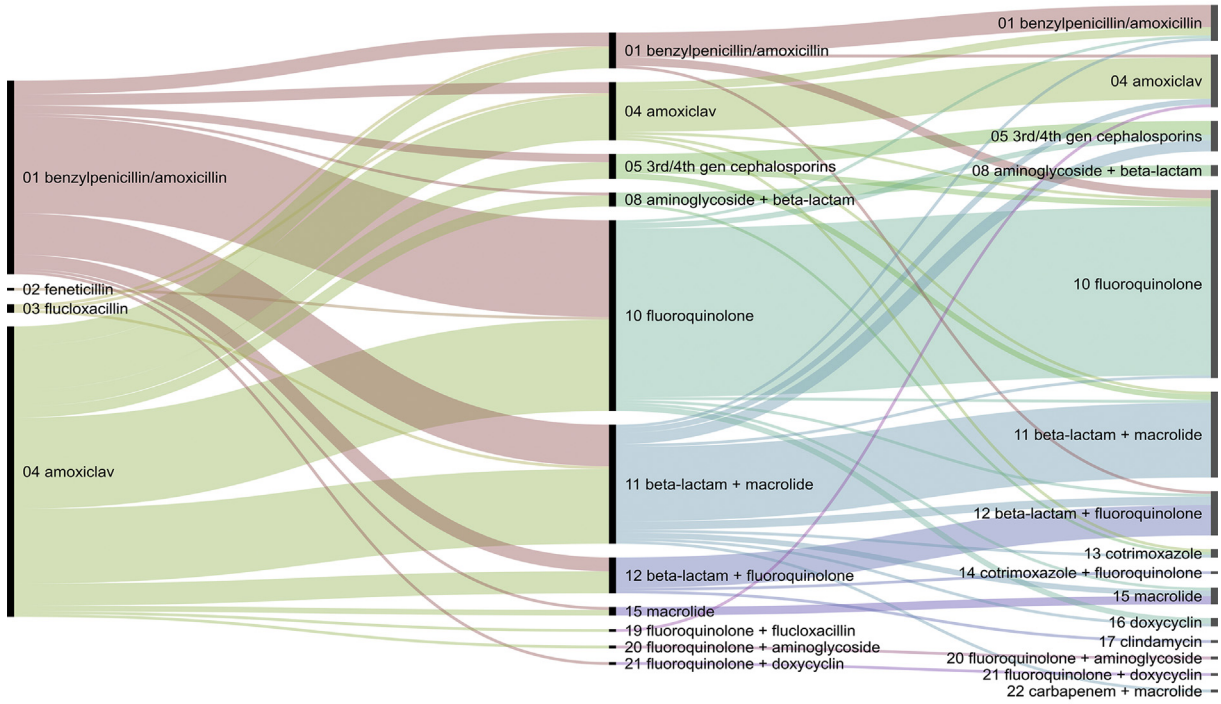

Fig. 2. Antibiotic treatment and modifications.
The first bar shows antibiotic treatment prior to hospitalization, the second bar shows treatment at time of admission, and the third bar shows "final" treatment. In patients with more than one in-hospital treatment modification, the first modification is shown in the third bar. Antibiotic treatment modifications per randomization arm are provided in Fig. S2 of the Supplementary Appendix.

Table 3
Outcomes.

Outcome parameter	Beta-lactam monotherapy (N = 48)	Atypical coverage (N = 131)	Crude effect[a]	p-value	Adjusted effect[a]	p-value
Clinical outcomes						
Length of hospital stay	6.0 (3.8–8.0)	6.0 (4.0–9.0)	0.87 (0.69–1.10)[b]	0.239	0.77 (0.61–0.97)[b]	0.027
30-day mortality	1 (2.1%)	5 (3.8%)	0.55 (0.06–4.81)	0.587	0.37 (0.04–3.67)	0.392
Antibiotic modifications						
Treatment escalation	8 (16.7%)	11 (8.4%)	2.18 (0.82–5.81)	0.118	2.75 (0.94–8.09)	0.066
Non-covered pathogen	3 (6.2%)	0 (0%)	NA		NA	
Clinical failure	5 (10.4%)	11 (8.4%)	1.27 (0.42–3.86)	0.675	1.40 (0.43–4.59)	0.578

[a] Odds ratios (95% CI) unless otherwise indicated. Adjusted for center, PSI-score, and history of COPD/asthma.
[b] Effect estimate indicates relative change in length of hospital stay.

higher prevalence of malignancies in those in which beta-lactam monotherapy was continued and a slightly longer symptom duration before admission in those receiving atypical coverage, both patient groups appeared comparable in clinical presentation and comorbidities. Our findings suggest that it is safe in at least part of the patients to continue beta-lactam monotherapy. These findings do not support current recommendations to include antibiotic coverage for atypical pathogens in this patient population, which are based on expert opinion only.

Due to its post-hoc nature this study has limitations. First, we did not systematically record the reasons for antibiotic choices in these patients, but some choices will have been motivated by the antibiotic allocation of the cluster-randomized trial. Other reasons might be age and symptom duration, perceived malabsorption of oral antibiotics as a reason to continue beta-lactam monotherapy intravenously (although only 8% of patients in the beta-lactam group had gastro-intestinal symptoms), practice differences between hospitals or other reasons to suspect a certain pathogen sensitive or not sensitive to beta-lactams. Furthermore, treating physicians may have been unaware of prior treatment with beta-lactams. The higher frequency of documented atypical pathogens in patients that received atypical coverage might reflect the ability of physicians to predict atypical pathogens, but could also reflect differences in testing practice or availability of testing results within one day, allowing pathogen-directed instead of empirical treatment. Indeed, pneumococcal and legionella urinary antigen tests were performed more frequently in patients receiving atypical coverage. Yet, of six patients with empirical atypical coverage and a positive pneumococcal antigen test, only three de-escalated to beta-lactam monotherapy, and of 118 patients with empirical atypical coverage and a negative legionella antigen test, only ten switched to beta-lactam monotherapy, including the three patients with a positive pneumococcal antigen test. Data on timing of any PCR test results were not collected.

Second, although the data are derived from a cluster-randomized trial of empirical antibiotic treatment strategies, adherence in this subgroup of previously treated patients was low in those randomized to beta-lactam monotherapy (Supplement

Table S2). We, therefore, as in observational studies, adjusted for known confounders in a multivariable analysis, but cannot exclude the possibility of residual confounding such as indication bias. Particularly, we had no information about the clinical course prior to hospital admission, which could be a relevant confounder. A per protocol analysis, restricted to patients treated according to the randomisation, was not performed because of the decreased sample size, and because it might have induced additional selection bias.

Third, although the point estimates for adjusted differences in clinical outcome were in favour of the beta-lactam monotherapy group, the low number of included patients precludes firm conclusions about the lack of a mortality difference. Finally, as clinicians were not blinded to therapy, they may have changed antibiotic therapy earlier in the course of clinical deterioration if the patient received beta-lactam monotherapy than in those receiving atypical coverage. Therefore, we may have overestimated the real need to escalate treatment in the beta-lactam monotherapy group. Of eight patients that continued beta-lactam monotherapy and where treatment was escalated, three had a therapy switch because of a documented pathogen, and five switched to atypical coverage due to clinical instability.

Strengths of our study are the prospective data collection on CAP severity and comorbidities, the availability of motivations for therapy adjustments and microbiological results to reliably classify antibiotic modifications, and the collection of all-cause mortality outside the hospital with a fixed follow-up duration. Also, the cluster-randomized comparison of different treatment strategies allowed us to perform a sensitivity analysis stratified for randomized allocation. This yielded a similar effect size during the beta-lactam monotherapy strategy as during each of the strategies with atypical coverage, suggesting that the cluster-randomization did not induce additional confounding bias.

The prospective recruitment of consecutive patients and inclusion of 70% of the eligible patients ensures the generalizability of our study findings to similar settings. The results may be less generalizable to settings where beta-lactam monotherapy is not the first-choice outpatient treatment for CAP or in settings with higher likelihood of *Legionella pneumophila* as causative pathogen. In the Netherlands, *Legionella pneumophila* is a rare CAP pathogen which makes a test-and-treat policy acceptable to ensure the safety of continuing beta-lactam monotherapy at admission for most of the patients.

Our study confirms previous observations of a higher prevalence of atypical pathogens and a lower prevalence of *S. pneumoniae* in patients previously treated with beta-lactams [11–13]. The lower prevalence will partly be due to successful outpatient treatment of pneumococcal infections, enriching the fraction with atypical pathogens among CAP-patients needing hospitalization, and partly to the decreased sensitivity of cultures after antibiotic treatment. However, in contrast to these previous studies, we found a low prevalence of *L. pneumophila*, despite a high proportion of patients being tested. This may explain our finding of comparable clinical outcome, as empirical coverage seems less important for other atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydophila* species, given their general mild course of disease.

Similar to a previous retrospective study based on health records, also performed in the Netherlands [6], we found no evidence of worse clinical outcome for the patients that continued treatment with beta-lactams. Our study extends these findings through adjustment for disease severity on presentation, information on all-cause mortality up to 30 days, preventing potential bias through competing events such as hospital discharge, evaluating reasons for antibiotic modifications and microbiological results, enabling accurate differentiation between escalations and other reasons for treatment modification. To the best of our knowledge, there are no other studies investigating the safety of continuing beta-lactam monotherapy in these patients.

Macrolides and fluoroquinolones are associated with increased development of resistance [14,15]. Therefore, the use of these agents should be limited to patients that truly benefit from them. A randomized controlled trial (RCT) would be the most reliable method to confirm the safety of continuing beta-lactam monotherapy in patients previously treated with beta-lactams. However, apart from logistical aspects, ethical constraints to randomization due to current expert opinion and guideline recommendation of optimal treatment will probably preclude such a study ever being performed. Alternatively, rapid diagnostic tests may be useful to detect pathogens not sensitive to beta-lactams in an early stage. This might provide an adequate safety net to escalate rapidly based on the test results, thus encouraging empirical beta-lactam monotherapy in all patients. As respiratory infections are the most important reason for in-hospital antibiotic treatment in all age groups, such a policy may have a substantial impact on the overall selective antibiotic pressure in hospitals [16]. The safety of this approach and effects on antibiotic consumption should be tested in future randomized trials.

In conclusion, in hospitalized CAP patients that have received >48 h of prior outpatient beta-lactam monotherapy, continuation of beta-lactam monotherapy was associated with a trend towards more treatment escalations, without evidence of increased LOS or mortality. The sample size of our study precludes strong conclusions regarding differences in mortality.

Summary of take home message

Beta-lactam monotherapy after outpatient beta-lactam treatment is not associated with worse outcome in hospitalized CAP.

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Conflicts of interest

CHvW reports consultation fees, presentation fees, and thesis print support from Pfizer. MJMB reports research grants and an educations grant from Pfizer, paid to institution. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2017.06.012.

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