

# BMJ Open Antibiotic prescribing on admission to patients with pneumonia and prior outpatient antibiotic treatment: a cohort study on clinical outcome

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## ABSTRACT

**Objective:** Most pneumonia treatment guidelines recommend that prior outpatient antibiotic treatment should be considered when planning inpatient antibiotic regimen. Our purpose was to study in patients admitted for community-acquired pneumonia the mode of continuing antibiotic treatment at the outpatient to inpatient transition and the subsequent clinical course.

**Design:** Retrospective cohort study.

**Setting:** Dutch PHARMO Record Linkage System.

**Participants:** 7323 patients aged >18 years and hospitalised with pneumonia in the Netherlands between 2004 and 2010.

**Main study parameter:** We identified all prescribed antibiotics prior to, during and after hospitalisation. In case of prior outpatient treatment, the continuation of antibiotic treatment on admission was categorised as: no atypical coverage > no atypical coverage; atypical coverage > atypical coverage; no atypical coverage > atypical coverage; and atypical coverage > no atypical coverage.

**Main outcome measures:** Length of hospital stay, in-hospital mortality and readmission within 30 days.

**Results:** Twenty-two per cent of the patients had received prior outpatient treatment, of which 408 (25%) patients were switched on admission to antibiotics with atypical coverage. There were no differences in length of hospital stay, in-hospital mortality or readmission rate between the four categories of patients with prior outpatient treatment. The adjusted HR for adding atypical coverage versus no atypical coverage was 0.91 (95% CI 0.55 to 1.51) for time to discharge. For in-hospital mortality and readmission within 30 days, the adjusted ORs were 1.09 (95% CI 0.85 to 1.34) and 0.59 (95% CI 0.30 to 1.18), respectively.

**Conclusions:** This study found no association between mode of continuing antibiotic treatment at the outpatient to inpatient transition and relevant clinical outcomes. In particular, adding atypical coverage in patients without prior atypical coverage did not influence the outcome.

## Strengths and limitations of this study

- Strength of the study is that we had the opportunity to conduct it using a nationwide database with long-standing validity for drug and outcomes research.
- Within that database, it was possible to identify a large cohort of more than 7000 patients admitted for pneumonia, and with both community pharmacy and in-hospital pharmacy data available. This resulted in very detailed information on routine care prescribing of antibiotic treatment on admission to patients with and without prior outpatient treatment, and the possibility to study this in relation to major clinical outcomes.
- A limitation is that we were not able to evaluate pneumonia severity as a potential confounder or effect modifier in our multivariable analyses. On the other hand, most treatment guidelines recommend adding atypical coverage after non-responsiveness to  $\beta$ -lactam treatment for mild pneumonia and combination therapy for severe pneumonia. In other words, this implies that all patients with prior  $\beta$ -lactam outpatient treatment should receive atypical coverage irrespective of disease severity. The present study does not support this.

## INTRODUCTION

In Europe, pneumonia is the primary cause of hospitalisation for over three million persons per year, with mortality rates reported between 5% and 20%.<sup>1</sup> The major aetiological cause of pneumonia is infection by *Streptococcus pneumoniae* or *Haemophilus influenzae*.<sup>2</sup> Given this aetiology, several European guidelines for management of non-severe community-acquired pneumonia (CAP) recommend  $\beta$ -lactam antibiotics as first choice empirical treatment; however, in case of non-responsiveness to these antibiotics, treatment for atypical pathogens should

be considered.<sup>2-4</sup> In more detail, the current British Thoracic Society (BTS) guideline recommends that monotherapy with a macrolide may be suitable for patients with moderate to severe CAP who have failed to respond to an adequate course of amoxicillin before admission, whereas the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guideline suggests that for patients with no need for intensive care admission, the choice of antimicrobial agents should be based on considerations of allergy, intolerance and previous use of penicillin, macrolides or quinolones. The Dutch Working Party on Antibiotic Policy (SWAB) guideline recommends that for patients with mild CAP who receive amoxicillin or penicillin as initial therapy but do not improve within 48 h, therapy should be switched to monotherapy with a macrolide or doxycycline. Although studies support the strategy to add atypical coverage after non-responsiveness to  $\beta$ -lactam antibiotics from a microbial perspective,<sup>5 6</sup> little is known about how this is handled in clinical practice. For example, how is initial inpatient treatment modified in case of patients presenting to the emergency department after non-responsiveness to prior outpatient treatment? Aim of this study is to identify patterns of antibiotic prescribing at the outpatient to inpatient transition of patients with CAP and to study associations between these patterns and the subsequent clinical course.

## METHODS

This is an observational study using data from the Dutch PHARMO Record Linkage System (PHARMO RLS founded in 1999; <http://www.pharmo.nl>). This database includes data from several healthcare providers, among which are hospital discharge records from hospital administration systems and drug dispensing records from community pharmacies and in-hospital pharmacies. Both in-hospital and community pharmacy data are available for approximately one million individuals in defined areas of the Netherlands. The computerised drug dispensing histories from community pharmacies contain data on the dispensed drug, dispensing date, type of prescriber, amount dispensed, prescribed dose regimens and the duration of use. The in-hospital pharmacy database includes data on inpatient medication orders (type of drug, dose, time of administration and duration of use). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification. The hospital records include detailed information concerning the primary (mandatory) and secondary (optional) discharge diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Permission to conduct the study was obtained from the PHARMO Institute for Drug Outcomes Research. Ethics approval was not applicable because all data in the PHARMO RLS are anonymous.

## Study patients

We constructed a cohort of participants of age 18 years and older, with an episode of hospitalisation for CAP between 1 January 2004 and 31 December 2010. Episodes of pneumonia were selected based on ICD-9 codes 481-487. Patients were included in the study cohort if they had in-hospital medication data available, had a history of at least 12 months in PHARMO RLS before the hospitalisation for pneumonia, were discharged to their home and had a follow-up in PHARMO RLS of at least 3 months after hospitalisation or in case of death, a follow-up until date of decease. If a patient experienced two or more episodes of pneumonia less than 30 days apart, only the first episode was selected. For each patient selected, all prescribed medications during hospital stay, and in the year prior to and 2 weeks after hospitalisation were captured.

## Clinical characteristics

For all patients, we retrieved age and gender, and defined the following comorbidities by means of dispensed medication and/or hospitalisations in the year prior to the studied episode of pneumonia: pulmonary disease (two or more dispensations for inhalation medication), diabetes (two or more dispensations for insulin or oral glucose-lowering drugs or hospitalisation with ICD-9 codes 249-250), congestive heart failure (two or more dispensations for digoxin together with a diuretic or hospitalisation with ICD-9 code 428), cerebrovascular accident (hospitalisation with ICD-9 codes 430-438). Furthermore, use of proton-pump inhibitors and corticosteroids was assessed (two or more dispensations in the year prior to the hospitalisation for pneumonia).

## Antibiotic usage

All prescribed antibiotics (ATC J01) in the 14 days before, during and after hospitalisation were identified at the patient level. Based on whether or not the patient had received antibiotic treatment in the 2 weeks prior to hospitalisation, patients were classified as 'with' or 'without' prior outpatient treatment. For patients who had received prior outpatient antibiotic treatment, the outpatient antibiotic regimen closest to the date of hospitalisation was identified. The antibiotic regimen prescribed at the day of hospitalisation was considered the initial inpatient regimen. In case of prior outpatient treatment, the transition from outpatient to inpatient antibiotic regimen was categorised as: no atypical coverage > no atypical coverage; atypical coverage > atypical coverage; no atypical coverage > atypical coverage; and atypical coverage > no atypical coverage. Tetracyclines, macrolides and quinolone antibiotics were considered antibiotic coverage of atypical pathogens. For all patients, subsequent modifications of antibiotic therapy during hospital stay were assessed with a modification defined as a change of agent or combination of agents (eg, different regimen). Dose adjustments or adjustment of administration route were not considered. Finally, the

total duration (in days) of antibiotic therapy was calculated for all patients (inpatient plus outpatient therapy).

### Clinical course

The following items were scored for each patient as descriptor of the clinical course: number of modifications of antibiotic treatment during hospital stay, length of hospital stay (in days), in-hospital mortality, and readmission within 30 days from discharge.

### Data analysis

The SPSS statistical package (V.20.0.0.1 for Mac) was used for the statistical analyses. Continuous data were expressed as the mean±SD or as the median (IQR) where appropriate. Sankey plots were constructed to visualise patterns of continuation of antibiotic treatment at the outpatient to inpatient transition. Multivariable regression analyses were conducted to examine whether mode of transition (four categories; see above) was associated with time to discharge (Cox regression), in-hospital death (logistic regression) or readmission (logistic regression). All patient characteristics were included in the regression models as potential confounders. Sensitivity analyses comprised the restriction to patients who were on outpatient treatment for more than 2 days before hospital admission and exclusion of patients who received outpatient antibiotics unusual in the treatment of CAP in primary care (cotrimoxazole, nitrofurantoin and quinolone antibiotics).<sup>7</sup> Significance was set at  $p < 0.05$  for all tests.

## RESULTS

The total study population comprised 7323 patients hospitalised for CAP of which 1613 (22%) had received prior outpatient antibiotic treatment. The mean age of the population was 64±25 years and 47% of the patients were male. Pulmonary disease, corticosteroid use and proton-pump inhibitor use was more prevalent in patients with prior outpatient treatment (table 1).

The majority of patients who received prior outpatient antibiotics had been prescribed amoxicillin/clavulanic acid (38%), followed by doxycycline (17%) and amoxicillin (14%). Amoxicillin/clavulanic acid was also the most prescribed initial inpatient antibiotic regimen. Table 2 shows the top 10 initial inpatient antibiotic regimens for patients with and without prior outpatient treatment. The median total duration of antibiotic treatment (inpatient plus outpatient) was 11 (IQR 8–15) days for the complete cohort, 15 (IQR 11–20) days for patients who received prior outpatient treatment and 10 (IQR 7–13) days for patients admitted without prior outpatient treatment.

Comparing the outpatient antibiotic regimens with the initial inpatient regimens revealed that 38% of the patients continued with no atypical coverage and 16% of the patients continued with atypical coverage, whereas 25% of the patients were switched to an antibiotic

**Table 1** Patient characteristics of patients with and without prior outpatient treatment

	Prior outpatient treatment 1613 (100%)	No prior outpatient treatment 5710 (100%)	p Value
Age (mean±SD)	64±25	63±25	0.62
Male gender	753 (47)	2430 (43)	0.003
Pulmonary disease	720 (45)	2141 (38)	<0.001
Diabetes	53 (3)	194 (3)	0.83
Heart failure	114 (7)	335 (6)	0.08
CVA	15 (1)	87 (2)	0.07
PPI use	594 (37)	1705 (30)	<0.001
Corticosteroid use	474 (29)	1305 (23)	<0.001

Data are presented as number (%), unless otherwise stated. CVA, cerebrovascular accident; PPI, proton-pump inhibitor.

regimen covering atypical pathogens, and 21% of the patients vice versa. Figure 1 shows the distribution of transitions between outpatient regimens and initial inpatient regimens. Twenty-three per cent of the patients were prescribed exactly the same antibiotic regimen as they had received before hospitalisation.

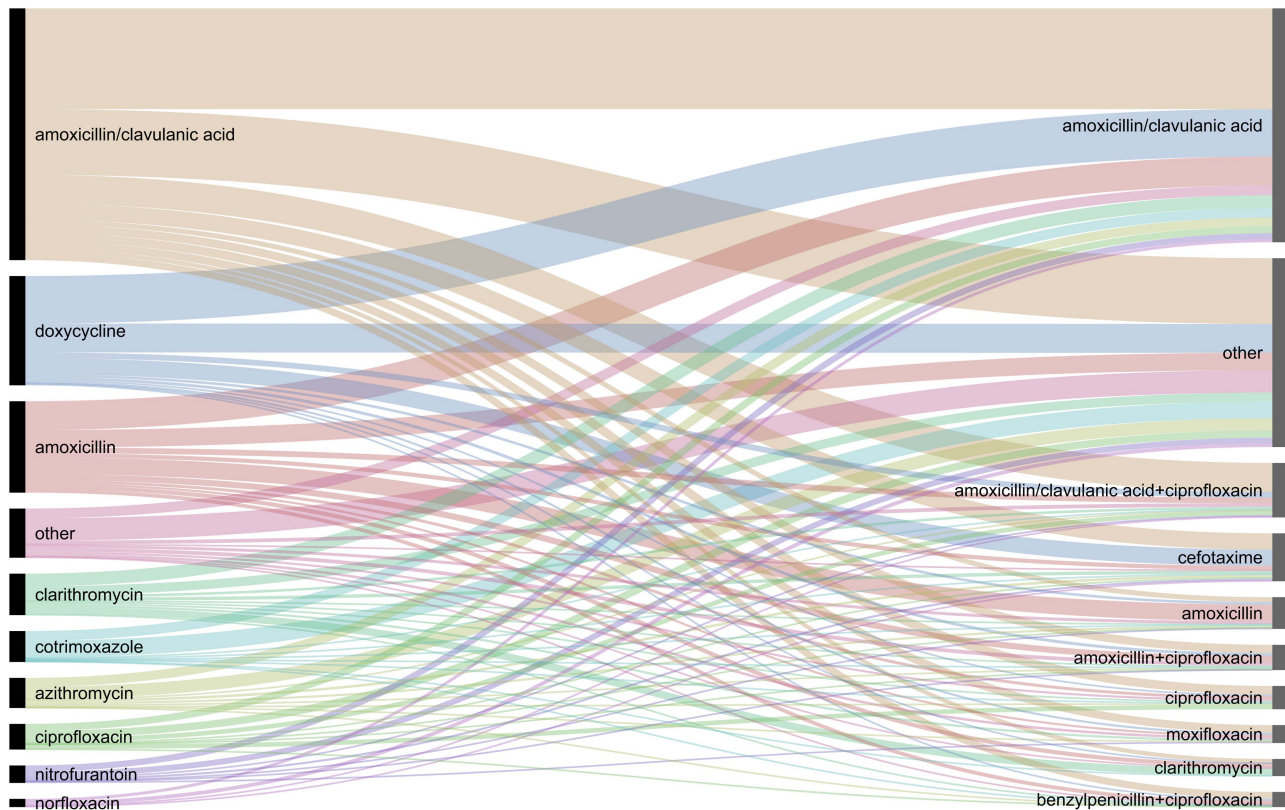
In table 3, the clinical course is shown for patients with and without prior outpatient treatment. Overall, median length of hospital stay was, although strictly statistically different, 7 days for both patients with and without prior outpatient treatment (median 7 (4–11) vs 7 (5–12) days;  $p = 0.008$ ). The frequency of any change in the initial antibiotic treatment was lower for patients without prior outpatient treatment (39% vs 43%;  $p = 0.009$ ). There was no difference in in-hospital mortality (6.6% vs 7.7%;  $p = 0.10$ ).

Within the patients with prior outpatient treatment, there were no differences in length of hospital stay,

**Table 2** Initial inpatient antibiotic regimens for patients with and without prior outpatient treatment

	Prior outpatient treatment N=1613 (100%)	No prior outpatient treatment N=5710 (100%)
Amoxicillin/clavulanic acid	576 (36)	2456 (43)
Amoxicillin	78 (5)	563 (10)
Amoxicillin/clavulanic acid + ciprofloxacin	134 (8)	473 (8)
Cefotaxime	118 (7)	345 (6)
Amoxicillin+ciprofloxacin	62 (4)	195 (3)
Benzyloxyphenylpenicillin+ciprofloxacin	37 (2)	172 (3)
Cefuroxime	27 (2)	125 (2)
Moxifloxacin	44 (3)	124 (2)
Ciprofloxacin	57 (4)	111 (2)
Clarithromycin	42 (3)	92 (2)

Data are presented as number (%).



**Figure 1** Sankey plot of antibiotic treatment at the outpatient to inpatient transition (n=1613 transitions). Left side: the top-10 outpatient regimens. Right side: initial inpatient regimens.

readmission rate or in-hospital mortality between the four identified categories (table 3). In the multivariable regression analyses (reference category: no atypical coverage > no atypical coverage), none of the transition categories were associated with time to hospital discharge (adjusted HRs 0.95 (95% CI 0.77 to 1.17), 1.09 (0.85 to 1.34) and 1.03 (0.82 to 1.28), respectively), in-hospital mortality (adjusted ORs 1.16 (0.66 to 2.02), 0.91 (0.55 to 1.51) and 0.95 (0.58 to 1.56), respectively), and readmission rate (adjusted ORs 0.79 (0.39 to 1.61), 0.59 (0.30 to 1.18) and 0.72 (0.39 to 1.35), respectively). For the latter two models, the Hosmer-Lemeshow goodness of fit test result and the area under the receiver operating characteristic curve (AUC) were  $p=0.23$  (AUC 0.721) and  $p=0.99$  (AUC 0.695). When the analyses were restricted to patients who were on antibiotic treatment for more than 2 days before hospital admission, this did not result in any significant changes in the calculated ORs. The same applies to the exclusion of patients with prior outpatient antibiotics unusual for the treatment of CAP in primary care (data not shown).

## DISCUSSION

This large observational study in over 7200 patients with CAP showed a large variation in outpatient and initial inpatient antibiotic regimens. In only a quarter of the

patients with prior outpatient treatment, atypical coverage was added to the initial inpatient therapy, but there was no association between mode of continuing of antibiotic treatment at the outpatient to inpatient transition and relevant subsequent clinical outcomes, like length of hospital stay, in-hospital mortality rate or readmission rate.

In general, protocols for empirical antimicrobial treatment are based on information about the most likely pathogens involved, prevalence of resistance in these pathogens and risks of unfavourable outcome when therapy is not appropriate. The latter is reflected in most guidelines by suggesting broader spectrum antibiotics in severe pneumonia.<sup>2 3</sup> Besides this, responsiveness to antibiotic treatment could act as a 'test therapeutique' or indirect microbiological examination, and can be used in addition to guide the antibiotic treatment regimen. The latter is, for example, incorporated in the British and Dutch pneumonia treatment guidelines by recommending that for patients with moderate to severe CAP and who received amoxicillin or penicillin as initial therapy but do not improve within 48 h, therapy should be switched to monotherapy with a macrolide or doxycycline; for patients with moderate to severe CAP and failure to improve despite 48 h treatment with a  $\beta$ -lactam antibiotic, an adequate dosage without evidence of abnormal absorption or non-compliance coverage for

**Table 3** Clinical course per category of outpatient to inpatient transition

Mode of transition	No prior outpatient treatment (n=5710) NA	Prior outpatient treatment (n=1613)			Atypical coverage > no atypical coverage N=340 (21)	p Value†
		No atypical coverage > no atypical coverage N=608 (38)	Atypical coverage > atypical coverage N=257 (16)	No atypical coverage > atypical coverage N=408 (25)		
Any change of antibiotic treatment	2240 (39)	242 (40)	118 (46)	193 (47)	138 (41)	0.009
Length of stay (median (IQR))	7 (4–11)	7 (5–12)	7 (4–10)	7 (5–11)	8 (5–12)	0.008
In-hospital mortality	376 (6.6)	50 (8.2)	20 (7.8)	26 (6.4)	29 (8.5)	0.10
Readmission	241 (4.2)	33 (5.4)	11 (4.3)	12 (2.9)	16 (4.7)	0.67

Data are presented as number (%), unless otherwise stated.  
 \*Prior versus no prior treatment.  
 †Within prior treatment group (four categories).

*Legionella* sp should be added.<sup>3 4</sup> That patients with pneumonia are hospitalised after prehospital antibiotic treatment is a common scenario with percentages reported in the recent literature between 17% and 26%.<sup>5 6 8 9</sup> In the present study, 22% of the patients had received antibiotic treatment before hospital admission.

To our knowledge, this study is the first study to show how antibiotic prescribing at the time of hospitalisation for pneumonia is affected by whether or not patients received prior outpatient treatment. The distribution of initial inpatient treatment regimens was very similar for patients with or without prior outpatient treatment. This suggests that choice of initial inpatient treatment is not to a great extent influenced by prior outpatient treatment. The Sankey plot also illustrated that there was no obvious pattern of adding atypical coverage in case of prior outpatient  $\beta$ -lactam treatment. But what are the clinical consequences? Overall, the present study showed no major impact of antibiotic prescribing practice at the outpatient to inpatient transition, neither on time to hospital discharge nor on in-hospital mortality and need for readmission. The median duration of hospital stay was 7 days in all categories identified. Although microbial examinations have confirmed increased prevalence of atypical organisms in patients hospitalised after prior outpatient  $\beta$ -lactam treatment,<sup>5 6</sup> the present study does not extend this finding towards major clinical consequences when atypical pathogens are not covered in the initial inpatient antibiotic treatment. In the present study, in 38% of the patients,  $\beta$ -lactam monotherapy was continued at admission without affecting prognosis. Possibly some atypical organisms are self-limiting irrespective of antibiotic treatment or alternatively, the current standard of care in hospitals timely modifies antibiotic treatment when necessary. The high incidence of modification of antibiotic treatment later during hospital stay in patients with prior outpatient treatment (on average 43%) could support such an explanation. Systematically searching for *Legionella pneumophila*, for example, might have provided a sufficient safety net to compensate not initiating combination therapy in the non-severely ill patients (assuming that combination therapy has been initiated in all patients with severe CAP). Such strategy corresponds to a large extent to the very recent randomised study of Garin *et al*<sup>10</sup> where patients with Pneumonia Severity Index (PSI) category IV pneumonia had delayed clinical stability with  $\beta$ -lactam monotherapy, but monotherapy was not inferior to combination therapy ( $\beta$ -lactam plus macrolide) in patients with PSI category I–III. Although patients with administration of any antibiotic for more than 24 h before admission were excluded from that study, its findings might thus extend to patients with prior outpatient treatment. Unfortunately, in the present study we could not explore this further because clinical information regarding disease severity at the time of admission was not available in the database as was the percentage of patients with atypical pathogens. Nonetheless, the

current recommendation to add atypical coverage in all patients with prior  $\beta$ -lactam outpatient therapy is not supported by the present study findings.

The present study also illustrates that when measuring the total duration of antibiotic exposure in patients with pneumonia, data should not be limited to outpatient or inpatient prescription data only. The median treatment duration was 11 days for all patients ( $n=7323$ ) and 15 days for patients who received prior outpatient treatment. For comparison: the median duration of hospital stay was 7 days. This means that the total antibiotic selective pressure of an episode of pneumonia is higher than only in-hospital exposure. Further, the recommended total duration of antibiotic treatment for pneumonia of 7–10 days was exceeded in more than half of the patients. The finding that median duration was 3 days longer than the length of hospital stay in patients without prior outpatient treatment also indicates that a large proportion of patients are being prescribed antibiotic treatment after discharge. Further research is definitely needed to address whether this holds any clinical benefits or not. Three days of antibiotic therapy has proven safe in mild to moderate severe CAP.<sup>11</sup>

Strength of the study is that we had the opportunity to conduct it using a nationwide database with long-standing validity for drug and outcomes research.<sup>12–13</sup> Within that database it was possible to identify a large cohort of patients with both community pharmacy and in-hospital pharmacy data available. However, there are also limitations in our study that need to be addressed. First, as discussed before, we were not able to assess pneumonia severity as a potential confounding factor, because detailed clinical information from the time of presentation at the emergency department was not available in the database. It is, therefore, not possible to exclude that mode of transition of antibiotic treatment is associated with clinical outcome in specific disease severity categories (eg, PSI categories I–III vs IV–V). Second, the reason for hospital referral was not available. It cannot be ruled out that factors other than non-responsiveness to antibiotic treatment were reason for referral in some patients. Finally, patients with pneumonia and their comorbidities were identified based on coded hospital discharge diagnoses and drug dispensing records. In general, this could introduce bias due to misclassification. However, previous studies from the Netherlands showed sufficient sensitivity and a high positive predictive value of 88% for ICD-9-CM coded hospital discharge diagnoses of CAP in hospital administration systems.<sup>14–15</sup> As data in the PHARMO RLS do also come from these systems, we consider that these results also apply to our present study data. The applied prescription-based proxies for comorbidities have also been validated in patients with pneumonia and showed varying robustness.<sup>16</sup> The proxies for pulmonary disease and diabetes were reliable but the performance for congestive heart failure was modest. By combining the prescription proxies with hospital

discharge diagnoses, we expect to have improved the validity of the identification of the comorbidities.

In conclusion, this study showed a large variation in antibiotic prescribing practice for CAP. Although the recommendation from guidelines to add atypical coverage after non-responsiveness to  $\beta$ -lactam treatment (and vice versa) had not been followed in many patients, there was no association with subsequent clinical outcome. Additional research is warranted for the observation that total duration of antibiotic treatment in daily practice exceeds the recommended duration by many days.

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**Contributors** EMWvdG and PDvdL designed the study, were involved in data analysis and interpretation, and drafted the work. JMP and SN were involved in data interpretation and revised the manuscript critically for important intellectual content. All authors had full access to the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript. PDvdL is the guarantor.

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