Strategies to optimise the treatment of community-acquired pneumonia

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CHAPTER 7

The extent of microbiological testing is associated with alteration of antibiotic therapy in adults with community-acquired pneumonia

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ABSTRACT

The aim of this study was to explore the relationship between the extent of microbiological testing and the frequency of antibiotic alteration in adults hospitalised with community-acquired pneumonia (CAP). We retrospectively studied 283 immunocompetent patients hospitalised with CAP. Information on microbiological testing and prescribed antibiotics was obtained. Patients were grouped according to the number of different microbiological tests performed within the first 2 days of admission (0–5 tests). Alteration rates were compared between these groups. Antimicrobial alteration was defined as a switch at day 3 of hospital stay to (1) a narrower spectrum antibiotics, or (2) a different class of antibiotics, or (3) a switch from dual therapy to monotherapy (4) or discontinuation of antibiotic treatment because the indication for antibiotic treatment did no longer exist. For each additional test performed, a stepwise increase in percentage of patients with altered antibiotic regimen ranging from 0 to 59% ($p = 0.001$) was found. Multivariate logistic regression analyses showed that performing PCR assay for atypical pathogens was most strongly associated with any alteration of antibiotic treatment (OR 2.6 (95% CI 1.4–4.9)) and with changes in atypical coverage specifically (OR 3.1 (95% CI 1.6–6.0). The extent of microbiological testing was positively associated with antibiotic alteration in adults hospitalised with CAP. Antibiotic treatment was most likely to be altered in patients in whom PCR assay for atypical pathogens was performed.

INTRODUCTION

Antimicrobial stewardship aims at encouraging appropriate antibiotic use, which should not only be effective but also limits toxic effects, induction of resistance and microbial selection.[1] This is of particular concern in the treatment of community-acquired pneumonia (CAP), which is one of the most common infectious diseases.[2]

Studies have shown that inappropriate therapy is associated with unfavourable outcomes.[3,4] One of the quality indicators of appropriate antibiotic use is alteration of antimicrobial treatment based on microbiological test results.[1] This may lead to reduced selective pressure for resistance and improved outcomes.[5–8]

Timely and adequate alteration of empiric antibiotics is only possible when actionable microbiological test results are available. However, in day-to-day clinical practice, no causative pathogen is found in over 60% of patients hospitalised with CAP. This is partially due to the limited yield of conventional diagnostics.[9] Newer and more rapid testing methods like urinary antigen tests (UAT) and PCR assays have been introduced in the past years.[10] It has been shown in a research setting that combining traditional sputum and blood cultures with these newer diagnostic tests can increase diagnostic yield up to 67% in patients with CAP.[11–13]

It is assumed that extensive microbiological testing results in an increased diagnostic yield and thereby facilitates more frequent alteration of antibiotic therapy. The aim of this study was to explore the relationship between the extent of microbiological testing and alteration of antibiotic therapy in adults hospitalised with CAP. The secondary objective was to assess the association between the extent of microbiological testing and clinical outcomes.

METHODS

Study design and patients

Adult patients who were hospitalised with CAP at the St. Antonius Hospital (an 850-bed non-academic teaching hospital in the Netherlands) between January 2013 and January 2017 were assessed.

CAP was defined as a new pulmonary infiltrate on chest X-ray in combination with two of the following findings: cough, sputum production, findings at auscultation indicative of pneumonia, body temperature > 38 °C or < 35 °C, C-reactive protein concentration > 15 mg/L and a white blood cell count > 10×10^9 cells/L or a leftward shift. Immunocompromised patients, either due to acquired or congenital immunodeficiencies or due to the use of immunosuppressive medication within 6 months of admission, were excluded, as were patients participating in a placebo-controlled trial evaluating

the effectiveness of adjunctive dexamethasone therapy in patients admitted with CAP (NCT01743755) for whom the diagnostic procedures were specified by the trial protocol. Furthermore, we excluded patients with empyema at admission, patients who were directly admitted to the intensive care unit and patients who died within 24 h of emergency room (ER) presentation. Eligibility for inclusion was based on radiology reports, laboratory results and patient history and physical examination as reported by the treating physician on the day of ER presentation. The study was approved by the Medical Ethics Committee of the St. Antonius Hospital (Nieuwegein).

Data collection

Patient medical records were checked to confirm that inclusion criteria were met, to collect data on any antibiotic use prior to hospital admission, to identify patients with a history of COPD and to determine the CURB-65 score (one point for each of the following criteria: confusion, urea > 7 mmol/L, respiratory rate > 30/min, blood pressure < 90 mmHg systolic or < 60 diastolic, age over 65 years) at time of hospital admission (day 1).[14]

Microbiological tests performed on day 1 and day 2 were selected for analyses using the General Laboratory Information Management System (GLIMS). The following five microbiological tests were included: (1) PCR assays on throat or nasal swabs for detection of respiratory viruses including influenza A; influenza B; parainfluenza viruses 1, 2 and 3; respiratory syncytial viruses type A and B; human metapneumovirus and rhinovirus; (2) PCR assays on throat swabs or on sputum samples for detection of atypical respiratory pathogens including *Coxiella burnetii*, *Legionella* species, *Chlamydophila psittaci* and *Mycoplasma pneumoniae*; (3) sputum cultures; (4) blood cultures and (5) UAT for the detection of *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* (BinaxNOW®).

Information on prescribed antibiotics was obtained using the Farmadatabase, a database in which all drugs prescribed during admission are registered.[15] All antibiotic prescriptions between January 2013 and January 2017 were extracted. Antibiotics prescribed during hospital admission were identified by matching admission dates to the date that the patient was screened for trial participation. A similar procedure was used to obtain data on all microbiological tests performed from GLIMS. All data were anonymised before analyses were performed.

Outcomes measures

The primary outcome was the percentage of patients whose initial antibiotic regimen had been altered by day 3 of hospital admission. Diagnostic yield was determined according to the number of microbiological tests performed. As secondary outcomes 30-day mortality, secondary intensive care unit (ICU) admission and length of hospital stay (LOS) were determined. Secondary ICU admission was defined as admission to the ICU after 24 h of hospital admission.

Data analyses

Alteration was defined as one of the following changes in antibiotic regimen: (1) switch to narrower spectrum antibiotics, or (2) switch to a different class of antibiotics, or (3) switch from dual therapy to monotherapy or (4) discontinuation of antibiotic treatment because the indication for antibiotic treatment did no longer exist. During the period in which patients were enrolled, the Dutch national guideline on the management of CAP advised to guide empirical antibiotic treatment according to the severity of disease. The antimicrobial spectrum varied from amoxicillin monotherapy for mild CAP to dual therapy with a cephalosporin plus atypical coverage for severe CAP (e.g. erythromycin or ciprofloxacin).[16]

To explore the association between the extent of microbiological testing and alteration of antibiotic treatment, patients were first divided into six groups according to the number of different microbiological tests performed within the first 2 days of hospital admission. The first group consisting of patients in whom no diagnostic tests were performed (0-test group), up to the last group consisting of patients in whom all five different tests were performed (5-test group). Subsequently, antibiotic regimens on the day of hospital admission and antibiotic regimens at day 3 of hospital admission were divided into six groups according to antibiotic classification: (1) a small spectrum penicillin with or without β-lactamase inhibitor, (2) a cephalosporin, (3) dual therapy combining a small spectrum penicillin with coverage of atypical pathogens (e.g. macrolide or fluoroquinolone), (4) dual therapy combining a cephalosporin with coverage of atypical pathogens, (5) monotherapy covering atypical pathogens and (6) other antibiotic classes or other combinations of antibiotic classes. Patients with altered antibiotic regimens by day 3 of admission were identified. The number and percentage of patients with altered antibiotic regimens on day 3 were calculated for each diagnostic test group.

Furthermore, we calculated the percentage of patients with at least one positive microbiological test result for the whole study population and for each of the diagnostic groups separately (0–5 tests). The diagnostic yield was compared between groups to determine its relationship with the extent of microbiological testing. A positive microbiological test was defined as (1) a positive PCR assay for respiratory viruses or atypical pathogens or a positive UAT, or (2) a pathogen identified by blood culture except for contamination as noted in the microbiology report or (3) a clinically relevant pathogen identified by sputum culture (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*). To explore the relationship between the number of microbiological tests performed by the end of day 2 and 30-day mortality and secondary ICU admission, patients were divided into two groups: one group in which limited microbiological testing was performed (0–2 tests) and one group in which extensive testing was performed (3–5 tests). For both

groups, the number and percentage of patients who died within 30 days of admission or were admitted to the ICU was calculated.

Overall descriptives are stated as number (%) for categorical data and mean (standard deviation (SD)) or median (interquartile range [IQR]) for continuous data. Categorical data was compared using Chi-squared tests or Fischer's exact tests, and continuous data was compared using an independent samples t-test or a Mann–Whitney U test as deemed appropriate. A p-value < 0.05 was considered significant.

Multivariable logistic regression analyses were performed to assess the association of each individual microbiological test with the outcomes: (1) any alteration of antibiotic therapy and (2) alterations in atypical coverage (discontinuation of or a switch to atypical coverage) adjusted for pneumonia severity (CURB-65 score).

RESULTS

Patient selection and baseline characteristics

A total of 390 patients with CAP were screened, of which 283 patients were found eligible for inclusion. The flowchart with reasons for exclusion is shown in Figure 1.

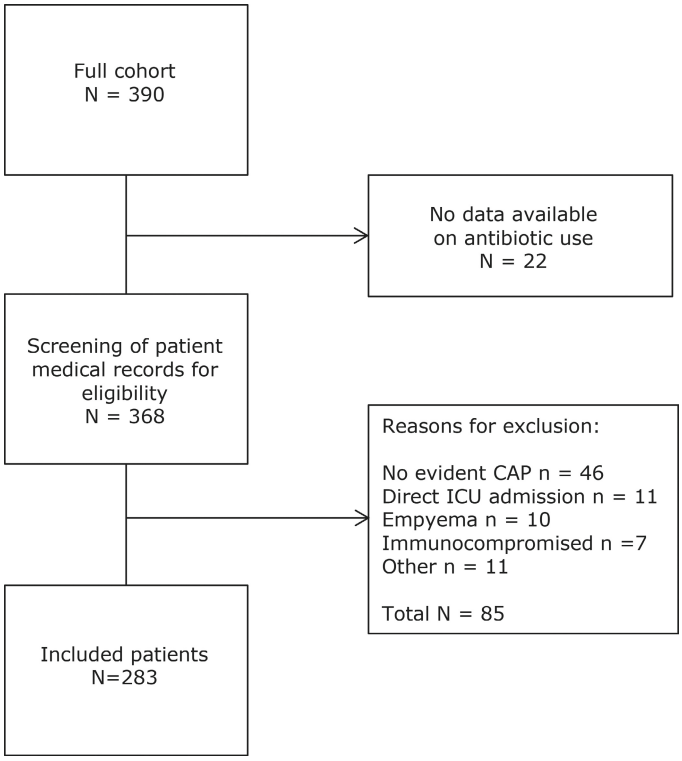

Figure 1 Patient selection flowchart

In Table 1, baseline characteristics are shown. The median CURB-65 score was 1 [IQR 1–2]. Antibiotics were prescribed to 32% of patients prior to admission. Baseline characteristics per group (0-test group to 5-test group) are shown in Supplementary Table 1.

Table 1 Baseline characteristics

Characteristic	
Median age, y [IQR]	70 [57–81]
Male, N (%)	151 (53)
History of COPD, N (%)	29 (10)
Antibiotic use prior to admission, N (%)	90 (32)
CURB-65 score, N (%)	
0	57 (20)
1	87 (31)
2	77 (27)
3	52 (18)
4	8 (3)
5	2 (1)
Initial antibiotic regimen, N (%)	
Small spectrum penicillin	130 (46)
Cephalosporin	35 (12)
Small spectrum penicillin with coverage of atypical pathogens	45 (16)
Cephalosporin with coverage of atypical pathogens	53 (19)
Antibiotics for atypical pathogens	11 (4)
Other	9 (3)

Microbiological testing

Blood cultures were performed in 224 (79%) patients, sputum culture in 109 (39%) patients, UAT in 231 (82%) patients and PCR for atypical pathogens in 70 (25%), and PCR for respiratory viruses was performed in 192 (68%) patients.

A pathogen was identified in 104 (37%) patients. There was a clear trend towards a higher pathogen identification rate in patients that did not use antibiotics prior to admission compared to those who did (40% vs. 29%, respectively, $p = 0.06$). As shown in Figure 2, there was a stepwise increase in the pathogen identification rate for each additional test performed ($p < 0.001$, Chi-squared test for trend). In descending order, the diagnostic yield of individual tests, if performed, was 33% for sputum cultures; 21% for PCR assay for respiratory viruses; 15% for UAT; 11% for PCR for atypical pathogens and 8% for blood cultures. The most frequently identified pathogen was *S. pneumonia* (17%) followed by *H. influenzae* (5%), influenza A virus (6%), *S. aureus* (3%) and *M. pneumoniae* (2%).

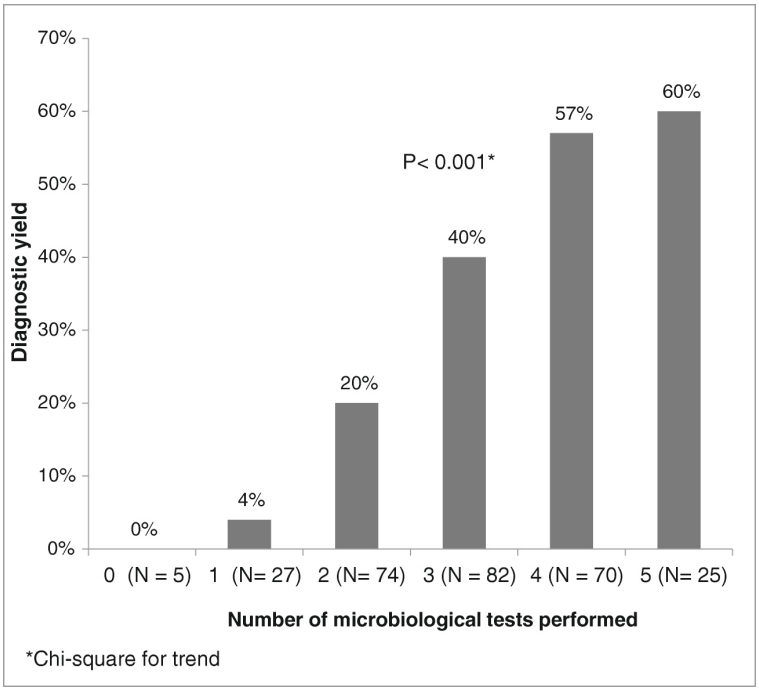

Figure 2 Number of performed microbiological tests and diagnostic yield

Antimicrobial alteration

Antibiotic regimens on day 1 and day 3 of admission are depicted in Figure 3. At day 3, 12 patients had already been admitted to the ICU, died or had been discharged. For these patients, no reliable data available on antibiotic use on day 3 could be retrieved. We therefore excluded them from further analyses concerning antibiotic alteration. Information on antibiotic use on day 3 of admission was available for 271 (96%) patients.

Antibiotic treatment was altered in 70 (26%) patients. Discontinuation of dual therapy (switch to monotherapy) was the most frequent change in antibiotic regimen (n = 53, 76%), followed by narrowing a cephalosporin to a small spectrum penicillin (n = 7, 10%). In 58 (21%) of the patients, the alteration involved removal or addition of atypical coverage. There was a stepwise increase in percentage of patients with an altered antibiotic regimen for each additional test performed (p = 0.001, Chi-squared test for trend) (Figure 4). In the multivariable analyses, performing a PCR assay for atypical pathogens was independently associated with both any alteration of antibiotic treatment on day 3 (OR 2.6 95% CI 1.4–4.9) and with an alteration regarding atypical coverage (OR 3.1 95% CI 1.6–6.0) (Table 2, Table 3).

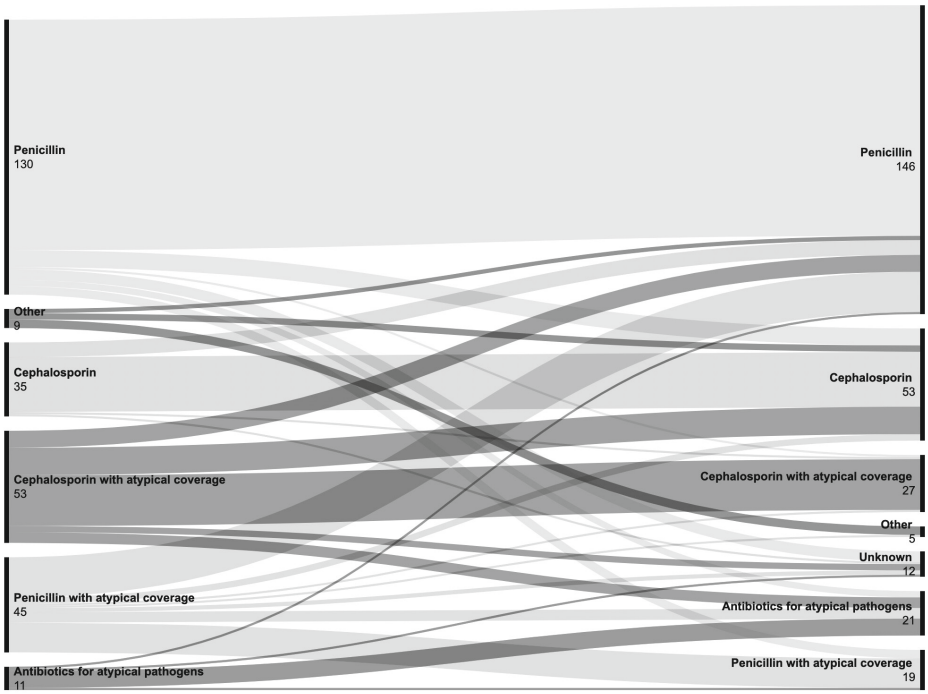

Figure 3 Antibiotic treatment and alterations. The first bar shows antibiotic treatment at the time of hospital admission, and the second bar shows antibiotic treatment at day 3 of hospital admission. The lines between both bars represent alteration in antibiotic regimens. Numbers represent the number of patients receiving a certain type of antibiotic

Table 2 Odds ratio for performing each individual microbiological test and any alteration of antibiotic treatment by day 3 of hospital admission

	Odds ratio (95% CI)	P value
Blood culture*	2.2 (1.0–4.9)	0.06
Sputum culture*	1.5 (0.8–2.8)	0.18
Urinary antigen test*	1.7 (0.7–4.0)	0.22
PCR for respiratory viruses*	0.8 (0.4–1.6)	0.53
PCR for atypical pathogens*	2.6 (1.4–4.9)	0.003
CURB-65 (≥ 2)**	1.7 (1.0–3.1)	0.06

*Reference category: test not performed within 2 days of admission
**Reference category: CURB-65 < 2

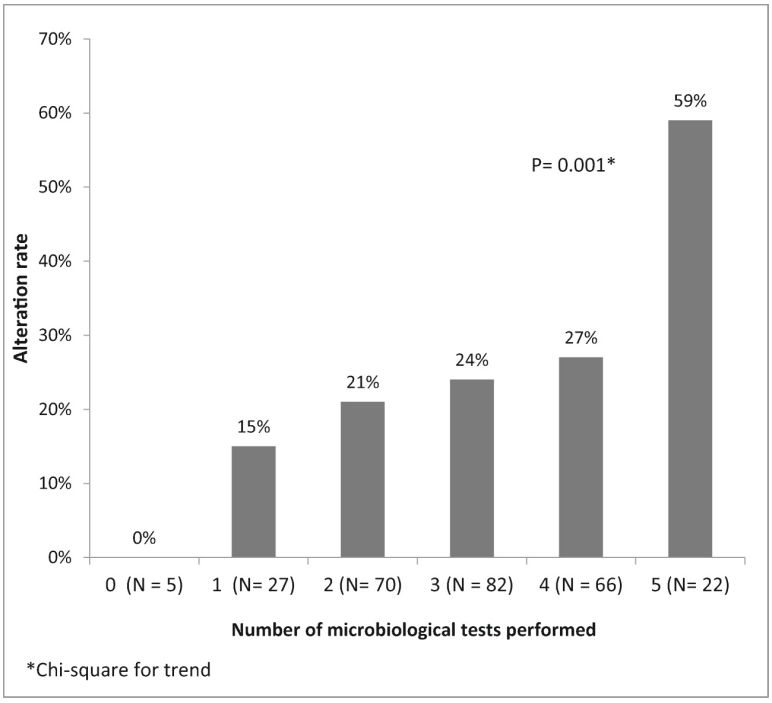

Figure 4 Number of microbiological tests performed and alteration rate

Table 3 Odds ratio for performing each individual microbiological test and alteration in atypical coverage by day 3 of hospital admission

	Odds ratio (95% CI)	P value
Blood culture*	1.8 (0.8–4.2)	0.18
Sputum culture*	1.5 (0.8–2.9)	0.21
Urinary antigen test*	2.2 (0.8–6.1)	0.13
PCR for respiratory viruses*	0.9 (0.5–1.9)	0.87
PCR for atypical pathogens*	3.1 (1.6–6.0)	0.001
CURB-65 (≥ 2)**	1.0 (0.5–1.8)	0.95

*Reference category: test not performed within 2 days of admission
**Reference category: CURB-65 < 2

Secondary outcomes

There was no significant difference between patients in whom 0–2 or 3–5 diagnostic tests were performed in either LOS nor negative outcomes (death within 30 days of admission and secondary ICU admission combined, due to low numbers) (Table 4).

Table 4 Number of microbiological tests performed and secondary endpoints

Number of tests	N	30-day mortality and/or secondary ICU admission, N (%)	Median LOS in days [IQR]
0-2	106	13 (12)	5 [3-8]
3-5	177	13 (7)*	6 [4-8]**
Total	283	226 (9)	5 [3-8]

*p = 0.158 (Chi-squared test): group with 0–2 performed tests compared to the group with 3–5 performed tests; **p = 0.126 (Mann–Whitney U): group with 0–2 performed tests compared to the group with 3–5 performed tests

DISCUSSION

The main finding of this study is the positive association between the number of microbiological tests performed within the first 2 days of hospital admission and the rate of antibiotic regimen alteration by day 3 in adults hospitalised with CAP. The antibiotic treatment alteration rate was almost three times higher by day 3 in patients in whom a PCR assay for atypical pathogens was performed. A change in atypical coverage was the most frequent alteration.

Regarding specific diagnostic tests, Oosterheert et al. investigated the addition of PCR assays for atypical pathogens and respiratory viruses to standard microbiological testing in day-to-day clinical practice in patients admitted with lower respiratory tract infections including, but not limited to, pneumonia.[17] The addition of these PCR assays to conventional diagnostics did increase diagnostic yield from 21 to 43%; however, antibiotic treatment was only modified based on PCR results in 11% of patients. We found a 26% overall alteration rate. A likely explanation for this difference is the higher frequency of dual therapy in our cohort (35% vs 16%) providing more opportunities for alterations.

More recently, Vestjens et al. retrospectively studied the association between the total costs of diagnostic testing and antimicrobial de-escalation in patients with CAP in three Dutch non-academic teaching hospitals.[18] It was demonstrated that the mean costs for microbiological testing per patient was the highest in the hospital where PCR assays were performed most frequently. In the study by Vestjens et al., the de-escalation rate was highest in the hospital with the lowest costs for testing. It was concluded that this seemingly counterintuitive finding could be explained by the presence of an automated iv-to-oral trigger alert in that specific hospital, guiding physicians to reconsider antibiotic regimens by drawing their attention to microbiological test results (including negative results). No such antibiotic stewardship intervention was in place in the hospital where the present study was performed.

However, to assess the potential added value of such an automated antibiotic stewardship intervention, we checked the medical records of the 15 patients receiving

dual therapy at admission, and in whom, a PCR assay for atypical pathogens was performed and whose antibiotic regimen was not altered, to assess the reasons for not switching antibiotic therapy. In the charts of four patients, the reason for continuing dual therapy was argued. However, in the 11 remaining patients, there was no note by the treating physician on the result of the PCR assay for atypical pathogens nor was a reason for continuing dual therapy argued. Considering that all these 11 patients had a negative PCR assay and did not have a positive UAT for Legionella implies that our observed frequency of alteration based on PCR is an underestimation of its true potential. It also supports the conclusion from Vestjens et al. that, apart from ordering a specific test, the way of communicating the results to physicians is also relevant towards the purpose of the test. Still, although its relatively (but decreasing) costliness compared to longer existing microbiological test methods, performing PCR assays for atypical pathogens clearly contributed to antibiotic therapy alteration in this single-centre study.

This study does have limitations, mainly due to its retrospective and single-centre design. First, we included the microbiological tests ordered on the day of hospital admission and the day after hospital admission. Inaccuracy of recorded time of sampling rendered it impossible to use a more exact timeframe (e.g. within 24 h or 48 h) in which microbiological tests were performed for every patient.

Second, we grouped patients receiving amoxicillin/clavulanic acid into the small spectrum penicillin group. As a result, we did not identify switches from amoxicillin/clavulanic acid to amoxicillin or penicillin as alteration. However, this only involved four patients with this scenario, making the impact on our findings rather small.

Third, due to low rates of antibiotic resistance in the Netherlands, guidelines for antibiotic treatment of CAP differ from countries with higher rates of resistance. As the antimicrobial resistance rates of *S. pneumoniae* for penicillin are low in the Netherlands, a small spectrum penicillin is the first line of treatment in patients with mild to moderate CAP.[16] Therefore, the number of patients receiving monotherapy with a small spectrum penicillin in our study is higher than it would be in other countries, thereby limiting the external validity of our findings for these countries. However, a strength of this study is that it reflects day-to-day clinical practice. Furthermore, our study included a well-defined cohort of patients with mainly mild to moderate–severe CAP. Median age, antibiotic use prior to hospital admission, level of pathogen identification and 30-day mortality were also very similar to those found in another large and recent Dutch cohort including non-ICU patients with CAP.[19]

In conclusion, for each additional microbiological test performed, we found a stepwise increase in alteration of antimicrobial therapy in patients admitted with CAP. Performing a PCR assay for atypical pathogens was most evidently associated with antibiotic alteration, most often being a switch from dual therapy to monotherapy.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 Baseline characteristics per group (0-5 tests)

Characteristic	0 tests	1 test	2 tests	3 tests	4 tests	5 tests
Median Age [IQR]	80 [50-89]	70 [60-81]	72 [62-84]	70[62-82]	68 [49-79]	66 [48-77]
Male N(%)	3 (60)	15 (56)	42 (57)	38 (46)	40 (57)	13 (52)
History of COPD N(%)	0 (0)	2 (7)	8 (11)	8 (10)	6 (9)	5 (20)
Antibiotic use prior to admission	1 (20)	9 (33)	20 (27)	27 (33)	22 (31)	11 (44)
Curb-65 score						
0	1 (20)	6 (22)	12 (16)	13 (16)	17 (24)	8 (32)
1	1 (20)	8 (30)	24 (32)	29 (35)	18 (26)	7 (28)
2	1 (20)	8 (30)	17 (23)	25 (31)	18 (26)	8 (32)
3	2 (40)	4 (15)	16 (22)	13 (16)	15 (21)	2 (8)
4	0 (0)	1 (4)	4 (5)	2 (2)	1 (1)	0 (0)
5	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)
Initial Antibiotic regimen N(%)						
Small spectrum penicillin	4 (80)	17 (63)	40 (54)	34 (42)	27 (39)	8 (32)
Cephalosporin	0 (0)	2 (7)	12 (16)	11 (13)	9 (13)	1 (4)
Small spectrum penicillin with coverage of atypical pathogens	1 (20)	2 (7)	6 (8)	13 (16)	16 (23)	7 (28)
Cephalosporin with coverage of atypical pathogens	0 (0)	3 (11)	11 (15)	17 (21)	13 (19)	9 (36)
Antibiotics for atypical pathogens	0 (0)	3 (27)	2 (18)	4 (36)	2 (18)	0 (0)
Other	0 (0)	0 (0)	3 (4)	3 (4)	3 (4)	0 (0)