PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Prior outpatient antibiotic use as predictor for microbial aetiology of community-acquired pneumonia: hospital-based study

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Abstract

Objective The causative micro-organism in community-acquired pneumonia (CAP) is often difficult to predict. Different studies have examined chronic morbidity and clinical symptoms as predictors for microbial aetiology of pneumonia. The aim of our study was to assess whether prior outpatient antimicrobial treatment is predictive for determining the microbial aetiology of CAP.

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Methods This was a hospital-based prospective observational study including all patients admitted with CAP between 1 October 2004 and 1 August 2006. Microbial investigations included sputum, blood culture, sputum PCR, antigen testing and serology. Exposure to antimicrobial drugs prior to hospital admission was ascertained through community pharmacy dispensing records. Multivariate logistic regression analysis was conducted to assess whether prior outpatient antimicrobial treatment is a predictor of microbial aetiology. Patient demographics, co-morbidities and pneumonia severity were considered to be other potential predictors.

Results Overall, 201 patients were included in the study. The microbial aetiology was determined in 64% of the patients. The five most prevalent pathogens were *Streptococcus pneumoniae*, *Heamophilus influenzae*, *Legionella spp.*, *Mycoplasma pneumoniae* and Influenza virus A+B. Forty-seven of the patients (23%) had received initial antimicrobial treatment as outpatients. Multivariate analyses revealed that initial outpatient beta-lactam treatment was associated with a threefold increased chance of finding atypical pathogens and a threefold decreased probability of pneumococcal infection; the corresponding odds ratios were 3.51 (95% CI 1.25–9.99) and 0.30 (95% CI 0.10–0.90), respectively. Patients who received macrolides prior to hospitalisation had an increased probability of viral pneumonia.

Conclusion Prior outpatient antimicrobial therapy has a predictive value in the diagnostic workup aimed at identifying the causative pathogen and planning corresponding antimicrobial treatment in patients hospitalised for pneumonia.

Keywords Aetiology · Antibiotics · Diagnosis · Outcome assessment · Pneumonia

Introduction

Community-acquired pneumonia (CAP) remains a major reason for hospital admission and a common cause of death in developed countries [1, 2]. The initial management of patients hospitalised with pneumonia consists mostly of empirical antimicrobial treatment [3, 4]. Determination of the appropriate antimicrobial treatment is essential as inadequate antimicrobial treatment, generally defined as microbial ineffective therapy against the causative pathogen, can negatively influence patient outcome [5]. Because it is not always possible to identify the causative pathogen, especially during the first days following hospitalisation, many studies have focussed on other parameters suggestive of the causative pathogen. The most frequently studied parameters for this purpose are patient characteristics (age and co-morbidities) and clinical signs [6, 7], although nonresponsiveness to prior outpatient antimicrobial treatment has also been suggested as a predictor of the aetiology of pneumonia. However, to date, this latter parameter has not been comprehensively quantified and documented. The aim of the study reported here was to assess whether prior outpatient antimicrobial treatment is a predictor of microbial aetiology in patients admitted to hospital for CAP.

Methods

The study was conducted in the St. Antonius Hospital, a 600-bed teaching hospital in Nieuwegein, The Netherlands.

Patient population

This was a prospective observational study of patients with confirmed pneumonia admitted between October 1, 2004 and August 1, 2006. Pneumonia was defined as a new or progressive infiltrate on a chest X-ray plus at least two of the following criteria: cough, sputum production, temperature >38°C or <35°C, ausculatory findings consistent with pneumonia, leucocytosis or leucopenia (>10 g/l, <4 g/l or >10% rods in leucocyte differentiation), C-reactive protein >3 times the upper reference value for normal. Patients who were immune compromised (systemic steroid use at admission (prednisone equivalent >20 mg/daily for more than 3 days), haematological malignancies and other immunosuppressive therapy) were excluded. The study was approved by the local Medical Ethics Committee, and informed consent was obtained from each patient.

Microbial aetiology workup

At least two blood cultures were performed, and sputum was taken for Gram-staining and culture and subsequently analysed by Taqman real-time PCR for *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydophyla psittaci* [8]. Pharyngeal samples were taken for viral culture. Urine was sampled for antigen testing on *Streptococcus pneumoniae* and *L.pneumophila* (Binax NOW; Binax, Scarborough, ME) [9, 10]. In addition, serum samples taken on the day of admission and on day 10 were analysed in pairs for detection of a fourfold rise of antibodies to respiratory viruses, *Coxiella burnetii*, *M. pneumoniae*, and *C. psittaci* by complement fixation assay [11]. For each patient, the total workup was completed, and the microbiology department was blinded to data on outpatient antibacterial drug use. When both viruses and bacteria were identified in a patient, the search prevailed for a definite aetiology for the bacteria.

Exposure to antimicrobial therapy

Data on outpatient antimicrobial drug use were acquired through community pharmacy dispensing records that captured all drug exposures the year prior to hospital admission. A patient was considered to be exposed to an antimicrobial drug when a prescription was filled within 14 days prior to hospitalisation. The name, dosage and amount of antimicrobial drug dispensed were also ascertained. The prescribed antimicrobial drug was classified as appropriate or inappropriate in accordance with current Dutch guidelines on the initial treatment of patients with suspected pneumonia [12, 13].

Co-morbidity assessment

In addition to outpatient antimicrobial drug use, co-morbidities and other relevant patient characteristics were identified to address factors related with the aetiology of CAP. Co-morbidities were defined based on the presence of conditions for which the patient was under active medical supervision or was receiving treatment at the time of hospital admission. The co-morbidities evaluated were pulmonary diseases (chronic obstructive pulmonary disease or treated asthma), congestive heart failure, diabetes (both type I and type II), history of stroke and end-stage renal disease (serum creatinine >150 μmol/l). The patients were also classified according to the Pneumonia Severity Index (PSI) developed by Fine et al. [14]. This index classifies patients into five categories of predicted mortality risk (with the fifth category being that of highest mortality risk). The outpatient use of oral corticosteroids and gastric acid-suppressing drugs was also ascertained.

Statistical analysis

The SPSS statistical package (ver. 12.0.1 for Windows; SPSS, Chicago, IL) was used for the statistical analyses.

Continuous data were expressed as the mean ± SD or as the median (interquartile range) where appropriate. To study the association between prior outpatient antimicrobial treatment and the aetiology of pneumonia, we applied multivariate logistic regression analyses. The analyses were conducted for overall aetiology and relevant pathogens separately. All baseline characteristics were considered potential predictors. Potential predictors were included in the multivariate model when they were retained after backward stepwise elimination. Significance was set at a p value < 0.05. The model's performance (goodness-of-fit and discriminative ability) was tested by performing the Hosmer and Lemeshow test and calculating the area under the receiver operator characteristic (ROC) curve.

Results

In total, 201 patients with pneumonia were included in the study. The mean age of the patients was 63±17 years, and 124 patients were male. Three patients (1%) were admitted from a nursing home. Pneumonia severity as well as co-morbid illnesses are summarised in Table 1. The overall median duration of the hospital stay was 10 days [7 –14],

Table 1 Demographics, co-morbidities and pneumonia severity index of 201 patients with community-acquired pneumonia (CAP)

Characteristic	n (%)
Age (Years)	
<60	74 (37)
60–69	39 (19)
70–79	50 (25)
>80	38 (19)
Gender	
Male	124 (62)
Female	77 (38)
Co-morbidities	
Pulmonary diseases	71 (35)
Heart failure	18 (9)
Diabetes	35 (17)
History of stroke	17 (9)
End-stage renal disease	10 (5)
Nursing home resident	3 (1)
Co-medication	
Oral corticosteroids	58 (29)
Gastric acid suppressing drugs	61 (30)
Fine score at admission[a]	
I	30 (15)
II	34 (17)
III	53 (26)
IV	56 (28)
V	28 (14)

[a] Fine et al. [14]

Table 2 Outpatient antibiotics utilization profile prior to hospitalisation for CAP

Type of antimicrobial drug	Number of users (%)[a]	Appropriate[b]
Amoxycillin/clavulanic acid	18 (38)	Yes
Amoxycillin	12 (26)	Yes
Doxycycline	7 (15)	Yes
Clarithromycin	5 (11)	Yes
Co-trimoxazole	4 (8)	No
Ciprofloxacin	2 (4)	No
Norfloxacin	1 (2)	No
Azithromycin	1 (2)	Yes

[a] Total percentage exceeds 100% because some patients (n=3) had two prescriptions
[b] Based on current Dutch guidelines NVALT and SWAB [12, 13]

and 21 patients were admitted to the intensive care ward. During the hospital stay, ten patients died, all due to pneumonia. The overall 28-day mortality rate was 5%. Forty-seven patients (23%) had received antimicrobial treatment in the 14-day time-window prior to hospital admission. The antimicrobial drugs dispensed to these patients are summarised in Table 2.

The majority of the patients (79%) had their prescription filled within 4 days prior to hospital admission, and 85% of the prescribed antimicrobial drugs complied with current Dutch guidelines [12, 13]. A microbial aetiology could be determined in 128 (64%) of the patients. Table 3 shows the results of different tests used to determine the aetiological diagnosis of CAP.

Fewer causative pathogens were found in the population hospitalised following prior outpatient antimicrobial treatment than in patients without prior antimicrobial treatment [57 vs. 66%; crude odds ratio (OR) 0.71, 95% confidence interval (CI) 0.36–1.38]. In patients with prior beta-lactam treatment, aetiology in the group comprising atypical bacterial pathogens was more probable (eight of 29 cases, 28%; crude OR 4.66, 95% CI 1.73–12.56). The aetiology of *S. pneumoniae* was less prevalent in patients with prior beta-lactam antimicrobial treatment (four of 29 cases, 14%; crude OR 0.33, 95% CI 0.11–0.99). In multivariate analyses, these associations remained significant (OR 3.51, 95% CI 1.25–9.99 and OR 0.30, 95% CI 0.10–0.90, respectively) (Table 4). Additional significant predictors included in these models were heart failure, pulmonary comorbidity, pneumonia severity index and the use of gastric acid suppressing drugs. The goodness-of-fit of both multivariate models was good, with a p value of 0.899 (Hosmer and Lemeshow test) for the model predicting pneumococcal pneumonia and a p value of 0.995 for the model predicting pneumonia of an atypical aetiology. The corresponding areas under the ROC curve were 0.62 and 0.67, respectively.

Table 3 Results of of different tests used to determine the aetiology of CAP

	Sputum culture	Sputum PCR	Antigen testing	Blood culture	Serology	Viral culture
Number of samples	148	78	183	182	130	88
Number of positive samples	78	14	36	19	38	14
Percentage of positive samples	53	18	20	10	29	16
Streptococcus pneumoniae	33	–	30	17	–	–
Gram-negative strain						
Heamophilus influenzae	19	–	–	0	–	–
Other	10	–	–	1	–	–
Atypical						
Mycoplasma pneumoniae	–	7	–	–	8	–
Legionella spp.	1	5	6	–	7	–
Other	–	2	–	–	1	–
Viral	–	–	–	–	22	14
Other						
S. aureus	6	–	–	1	–	–
Gram-positive other	2	–	–	0	–	–

In patients aged <60 years without co-morbidities, the aetiology of atypical bacterial pathogens was more prevalent (OR 4.64, 95% CI 1.72–12.56). Pulmonary co-morbidity was associated with the finding of *S. pneumoniae* and *H. influenzae* as causative pathogens (OR 1.87, 95% CI 1.00–3.47; OR 3.72, 95% CI 1.20–11.57, respectively). Patients who received macrolides prior to hospitalisation had an increased probability of viral pneumonia (two of five cases, 40%) (crude OR 8.67, 95% CI 1.34–56.23).

Discussion

The results of our study show that among patients admitted for CAP, a threefold decreased chance of having a *S. pneumoniae* infection and a threefold increased probability of having pneumonia of atypical aetiology were associated with the patient having received an initial beta-lactam treatment as an outpatient. These findings indicate that information on prior outpatient antimicrobial therapy has a predictive value in the diagnostic workup aimed at identifying the causative pathogen and planning the corresponding treatment in patients with pneumonia.

The initial management of patients hospitalised with pneumonia has been under constant study in different settings during the past decades. The choice of antimicrobial treatment, time to first antimicrobial drug administration and route of administration have all appeared to be relevant factors associated with the outcome of pneumonia [15–17]. A knowledge of the predominant microbial patterns in CAP is therefore essential when choosing an essential empirical antimicrobial treatment. Previous studies have found that *S. pneumoniae*, *H. influenzae*, Influenza virus A and B, *Legionella spp.* and *C. pneumoniae* are the most frequent pathogens in CAP [13], which is in

accordance with our results. Because *S. pneumoniae* is the most frequently appearing pathogen, the administration of beta-lactam antibiotics is the initial empirical antimicrobial treatment of choice in the treatment guidelines on CAP [3, 12, 13]. Beta-lactam antibiotics, however, do not cover *Legionella spp.*, *C. pneumoniae* and *M. pneumoniae*, the so-called atypical pathogens. Therefore, patients with pneumonia of atypical aetiology who are treated with beta-lactam antibiotics as an outpatient will probably not respond to treatment, with the possible consequence being a deterioration of the situation and subsequent hospital admission. Our finding of an increased prevalence of

Table 4 Odds ratios (OR) for aetiology and prior outpatient beta-lactam treatment in patients admitted to hospital for CAP

Aetiology	Prior outpatient beta-lactam treatment (*n* = no. of patients)		OR (95% CI)
	Yes (%)	No (%)	
Total no. of samples	29 (100)	172 (100)	
Univariate			
Pneumococcal	4 (14)	56 (33)	0.33 (0.10–0.99)
Atypical	8 (28)	13 (8)	4.66 (1.72–12.56)
Viral	2 (7)	14 (8)	0.84 (0.18–3.89)
Gram-negative strains	2 (7)	21 (12)	0.53 (0.12–2.40)
Other	1 (3)	7 (4)	0.84 (0.10–7.11)
Unidentified	12 (41)	61 (36)	1.28 (0.58–2.87)
Multivariate			
Pneumococcal	–	–	0.30 (0.10–0.90)[a]
Atypical	–	–	3.51 (1.25–9.99)[b]

OR, Odds ratio; CI, confidence Interval
[a] Adjusted for heart failure and use of gastric acid suppressing drugs
[b] Adjusted for pulmonary diseases and pneumonia severity index

atypical pathogens in patients with prior outpatient beta-lactam treatment supports such an explanation, but also confirms what has already been suggested in the different guidelines for the management of community-acquired pneumonia in adults [13, 18]. These guidelines state that following the failure of the initial empirical treatment with beta-lactam antibiotics, the microbiological examination should be reassessed with a view to excluding the less common pathogens, such as atypical pathogens, and that antimicrobial treatment covering atypical pathogens should be considered. Our study supports the choice of antimicrobial treatment covering atypical pathogens (e.g. macrolides) for all patients with CAP who are admitted to hospital after prior treatment with beta-lactam antibiotics. However, whether this protocol will result in improved clinical outcome should be subject to additional study.

The observed reduction in the frequency of *S. pneumoniae* in patients who received prior outpatient antimicrobial treatment could also be due to a failure to detect the organisms in cultures. This could mask *S. pneumoniae* as the causative pathogen. However, we believe that this explanation is less plausible, especially since we also used antigen testing to identify the causative pathogen [19]. In addition, such a mechanism can not explain the finding of an increased probability of pneumonia caused by atypical pathogens. To the best of our knowledge, our study is the first to specifically document and quantify the failure of initial outpatient antibiotic treatment as a predictor of the microbial aetiology of CAP.

This study was conducted in a single teaching hospital in The Netherlands, but we believe that the conclusions drawn will apply to other settings. First, the percentage of identified aetiology (64% in this study) is in agreement with that of other studies using similar microbiological techniques [20–22]. Second, our patient characteristics comply to a great extent with a previous nationwide study on prior outpatient antibacterial therapy as a prognostic factor for mortality in patients hospitalised for pneumonia [23]. In that large database study, the percentage of patients hospitalised after initial outpatient antimicrobial treatment was almost identical to that observed in our study (27 vs. 23%, respectively). In addition, age distribution, co-morbidities and the antibiotic utilisation profile of the outpatients were very similar as were the median duration of hospital stay and in-hospital mortality. Unfortunately, due to limited numbers, we were unable to study an association between prior outpatient antimicrobial treatment and mortality in our study. A very reassuring finding was that 85% of all outpatient antibiotic prescriptions complied with national guidelines on the initial treatment of adults with suspected pneumonia. This reduces the possibility that the findings, rather than being associated with antibiotics, might reflect the diagnostic acumen of the physicians who saw the patients in primary care. However, we cannot rule out the possibility that typical signs of infection with atypical pathogens may have been missed by primary care physicians.

As well as finding a relation between prior antimicrobial treatment and aetiology, we also found an association between aetiology and age and pulmonary co-morbidity. Patients aged <60 years without co-morbidities were more likely to have an aetiology comprising viral or atypical bacterial pathogens, and pulmonary co-morbidity was independently associated with *S. pneumoniae* and *H. influenzae* as causative pathogens. These findings confirm the results of previous studies on the impact of age and co-morbidity on the microbial aetiology of CAP [6]. A limitation of the present study, however, is that we were not able to adjust for smoking habits and alcohol intake of the patients. Previous studies on determinants for pneumonia aetiology found that these factors are significant predictors of pneumococcal infection [6, 7]. On the other hand, we do not expect prior antimicrobial therapy and smoking and alcohol intake to coincide in such a way that this would result in a null effect when all the information is available.

In conclusion, among patients admitted for pneumonia, whether or not a patient has received prior antimicrobial therapy as an outpatient provides relevant information in the diagnostic workup, in particular in terms of identifying the causative pathogen and planning the initial treatment at the time of hospital admission. This finding supports a further strengthening of the continuity of care at the interface between the extramural and hospitalised settings.

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