Predicting pneumococcal community-acquired pneumonia in the emergency department
Evaluation of clinical parameters

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Abstract

The aim of this study was to quantify the value of clinical predictors available in the emergency department (ED) in predicting *Streptococcus pneumoniae* as the cause of community-acquired pneumonia (CAP). A prospective, observational, cohort study of patients with CAP presenting in the ED was performed. Pneumococcal aetiology of CAP was based on either bacteraemia, or *S. pneumoniae* being cultured from sputum, or urinary immunochromatographic assay positivity, or positivity of a novel serotype-specific urinary antigen detection test. Multivariate logistic regression was used to identify independent predictors and various cut-off values of probability scores were used to evaluate the usefulness of the model. Three hundred and twenty-eight (31.0%) of 1057 patients with CAP had pneumococcal CAP. Nine independent predictors for pneumococcal pneumonia were identified, but the clinical utility of this prediction model was disappointing, because of low positive predictive values or a small yield. Clinical criteria have insufficient diagnostic capacity to predict pneumococcal CAP. Rapid antigen detection tests are needed to diagnose *S. pneumoniae* at the time of hospital admission.

Keywords: Community-acquired pneumonia, diagnosis, prediction rule, *Streptococcus pneumoniae*, urinary antigen test
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Introduction

Streptococcus pneumoniae is the most common causative pathogen of community-acquired pneumonia (CAP), being responsible for 20–38% of CAP cases, depending on the population, use of microbiological tests, and definition of 'causative pathogen' [1–4]. Antibiotic treatment recommendations for CAP have changed in recent years. The current treatment recommendations for CAP are based on the clinical severity of disease, rather than on the presumed aetiology, and recommend combinations of β-lactams and macrolides, or monotherapy with quinolones, for patients hospitalized with CAP [5–8]. This implies that most patients with pneumococcal pneumonia now receive broad-spectrum antibiotics. Extensive use of antibiotics could lead to superinfections with antibiotic-resistant pathogens or selection of antibiotic resistance, and will increase healthcare costs [9,10]. Ideally, patients with pneumococcal pneumonia would be treated with narrow-spectrum antibiotics, which would necessitate accurate prediction of pneumococcal CAP at the time of antibiotic prescription. Prediction of CAP aetiology at the time of clinical

presentation has been attempted before, with huge heterogeneity in approaches and results [11–16].

Recently, a new serotype-specific urinary antigen detection test (UAD) with high sensitivity and specificity has been clinically validated [17,18]. Using this test, in combination with the immunochromatographic assay (ICA) of BinaxNOW (Alere, Waltham, MA, USA), increased the proportion of patients diagnosed with pneumococcal CAP from 23.5% to 32.6%. With this optimized diagnostic approach for pneumococcal CAP, we aimed to develop a clinical prediction rule for diagnosing pneumococcal CAP in the emergency department (ED) in order to allow empirical treatment with narrow-spectrum antibiotics.

Materials and Methods

Patients

We conducted a prospective, observational, cohort study between January 2008 and April 2009. Adult patients (≥18 years) with a clinical suspicion of CAP presenting at the EDs of 23 Dutch hospitals were eligible. A clinical suspicion of CAP was defined as the presence of at least two of the following criteria: fever/hypothermia, cough/change in chronic coughing pattern, dyspnoea/tachypnoea/hypoxia, findings on percussion/auscultation consistent with pneumonia, leukocytosis/leukopenia, and/or shift to the left or an infiltrate(s) on the chest X-ray. Patients with recent hospitalization or residing in a nursing home, with known bronchial obstruction or a history of post-obstructive pneumonia, patients with primary lung cancer or another malignancy metastatic to the lungs, patients with AIDS, known or suspected *Pneumocystis jerovicii* pneumonia or known or suspected tuberculosis and unconscious patients were excluded. The study was approved by all local Research Ethics Committees, and written informed consent was obtained from all participants or family members.

A subset of the patients in this study with radiographically confirmed CAP and strict inclusion and exclusion criteria (n = 776) were used to validate the novel UAD [18].

Diagnostic approach

Standard diagnostic procedures included microbiological cultures of blood, sputum, and pleural fluid (if present), and, for study purposes, a urine sample was collected within 48 h after admission.

Urine samples were processed locally: samples were frozen at −70°C until being processed in the laboratory of Pfizer Vaccine Research (Pearl River, NY, USA). Here, both the UAD and the commercially available ICA (Alere) were performed batchwise by two technicians blinded to any clinical information. A third analyst interpreted the results when the first two analysts did not agree. The UAD is a Luminex technology-based multiplex urinary antigen detection assay that can simultaneously detect 13 different serotypes of *S. pneumoniae* by capturing serotype-specific polysaccharides secreted in human urine. In addition to an enhanced capacity to determine infections caused by one of those 13 pneumococcal serotypes (as compared with episodes yielding pneumococci from blood or other sterile body sites for serotyping), this test also has 41% higher sensitivity than the conventional ICA [17,18]. However, at the moment, this test is only available for research purposes.

Microbiological testing (blood, sputum cultures and BinaxNOW Legionella on urine, if clinically applicable) was performed in local laboratories according to local and manufacturers' protocols, with technicians unaware of the patient's clinical condition. When no urine sample was stored for central processing, the ICA results of the local laboratory were used to define aetiology.

Determinants

Data were collected from the medical chart, during admission or shortly afterwards, and documented in a standardized case record form by trained research nurses and/or physicians.The possible predictors were selected from the literature and because they were easily available in the ED (for a complete overview, see Table 2) [13,14,16]. Information on previous pneumococcal vaccination was also collected, but this was not considered to be a potential predictor, as it is rarely used in The Netherlands.

Definition of CAP

CAP was defined as the presence of an infiltrate on the chest X-ray at the moment of presentation to the ED, according to the judgement of the local radiologist together with at least two of the following signs or symptoms: cough, sputum production, temperature of >38°C or <36.1°C, auscultatory findings consistent with pneumonia, leukocytosis (>10.0 × 10^9 white blood cells (WBCs)/L) or leukopenia (<4.5 × 10^9 WBCs/L), a C-reactive protein level more than three times the upper limit of normal, hypoxaemia with P_{O_2} < 60 mmHg while the patient was breathing room air, or dyspnoea/tachypnoea.

The causative microorganism of CAP was considered to be 'definite' if it was cultured from blood or any other sterile fluid, or if the urinary antigen test was positive (either for *Legionella* or pneumococcal antigen with the ICA or with the UAD). A causative microorganism of CAP was considered to be 'probable' in the absence of a definite pathogen, and if it was