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Community-acquired *Haemophilus influenzae* pneumonia – New insights from the CAPNETZ study

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Summary *Objectives:* We aimed to identify clinical characteristics and to assess effectiveness of different initial antibiotic regimens in adult patients with community-acquired pneumonia (CAP) caused by *Haemophilus influenzae*.
Methods: Characteristics were compared between patients with *H. influenzae* monoinfection versus CAP of other and unknown aetiology enrolled by the German prospective cohort study CAPNETZ. Impact of initial antibiotic treatment on "early clinical response" according to FDA criteria and overall clinical cure were analysed.
Results: H. influenzae was found in 176 out of 2790 patients with pathogen detection (6.3%). Characteristics significantly associated with a *H. influenzae* CAP ($p < 0.017$) included purulent sputum, prior pneumococcal vaccination and respiratory co-morbidities. Early clinical response rates on day 4 did not differ between patients receiving any mono- versus combination therapy (85.9% versus 88%), but were numerically higher for regimens including any fluoroquinolone (96.7%) and lower under macrolide monotherapy (70%). Initial CURB-65 score and chronic liver disease were identified as negative predictors for "early clinical response". At day 14, overall clinical cure was 91.9%.
Conclusions: H. influenzae was a common CAP pathogen, particularly in patients with previous pneumococcal vaccination and respiratory co-morbidities. Severity of illness and chronic liver disease were associated with a lower rate of "early clinical response".

Introduction

Haemophilus influenzae can be divided into encapsulated (with six distinct serotypes a—f on the basis of capsular polysaccharides) and non-encapsulated (or non-serotypeable by conventional antiserum agglutination, NTHi) strains. NTHi causes a broad range of community-acquired non-invasive mucosal infections including community-acquired pneumonia (CAP),[1] particularly in elderly patients,[2,3] patients with respiratory co-morbidities,[3] or patients with recurrent pneumonia.[4,5] NTHi was documented as a major cause of invasive disease in adults even before the introduction of the *H. influenzae* type b polysaccharide conjugate vaccine in 1987.[6,7]

H. influenzae pneumonia poses a therapeutic challenge, particularly because intrinsic efflux resistance mechanisms limit the activity of macrolides and ketolides.[8—10] Despite *H. influenzae* being reported as "susceptible" to azithromycin by current National Committee for Clinical Laboratory Standards breakpoints, several studies have found bacteriologic eradication failure of macrolides up to 61% in children with acute otitis, a rate similar to that obtained with placebo.[11,12]

Furthermore, β-lactamase production is highly prevalent in up to 55% of *H. influenzae* and is associated with resistance to aminopenicillins.[13] Strains with alterations in penicillin-binding proteins, particularly PBP3 (β-lactamase-negative ampicillin-resistant and β-lactamase-positive amoxicillin/clavulanic acid-resistant), are also increasing in prevalence.[13] Therefore, empirical antimicrobial treatment of CAP for outpatients,[14,15] particularly monotherapy with beta-lactams or macrolides, might achieve only limited activity against *H. influenzae*. However, prospective studies comparing treatment outcomes between different empirical regimens for CAP due to *H. influenzae* are lacking.

This prospective study aimed to determine characteristics, severity of disease and mortality in adult patients with CAP caused by *H. influenzae* monoinfection, compared to patients with CAP of other or unknown aetiology. To assess effectiveness of initial antimicrobial treatment, clinical outcomes on day 4 (i.e. "early clinical stability" according to FDA definitions) and day 14 were analysed in patients with *H. influenzae* monoinfection stratified to different empirical regimens.

Material and methods

Patient population

A detailed description of the CAPNETZ methodology is given elsewhere.[16] Noteworthy, inclusion criteria for patients were age ≥18 years and community-acquired pneumonia confirmed by radiological proof of a new lung infiltrate plus ≥ one of the following: cough, purulent (off-white, yellow or green and opaque) sputum, fever (≥38.3 °C), and auscultatory findings consistent with pneumonia. Patients who had been hospitalized during 28 days preceding the study and patients with severe immunosuppression or with active tuberculosis were excluded. The enrolment period comprised 10 years and 9 months from October 2002 to July 2013.

This prospective multicentre study (German Clinical Trials Register: DRKS00005274) was approved by the ethical review board of each participating clinical centre (Reference number of leading Ethics Committee "Medical Faculty of Otto-von-Guericke-University in Magdeburg": 104/01, see acknowledgement or www.capnetz.de for participating centres) and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrolment in the study.

Data collection

All demographic, clinical and diagnostic patient data and comorbidities were recorded using standardised Internet-based data sheets created by 2mt1 (Ulm, Germany).

Patients' characteristics were documented including demographics, smoking history and chronic co-morbidities

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