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Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study

M M van der Eerden, F Vlapolder, C S de Graaff, T Groot, W Bronsveld, H M Jansen, W G Boersma

**Background:** There is much controversy about the ideal approach to the management of community acquired pneumonia (CAP). Recommendations differ from a pathogen directed approach to an empirical strategy with broad spectrum antibiotics.

**Methods:** In a prospective randomised open study performed between 1998 and 2000, a pathogen directed treatment (PDT) approach was compared with an empirical broad spectrum antibiotic treatment (EAT) strategy according to the ATS guidelines of 1993 in 262 hospitalised patients with CAP. Clinical efficacy was primarily determined by the length of hospital stay (LOS). Secondary outcome parameters for clinical efficacy were assessment of therapeutic failure on antibiotics, 30 day mortality, duration of antibiotic treatment, resolution of fever, side effects, and quality of life.

**Results:** Three hundred and three patients were enrolled in the study; 41 were excluded, leaving 262 with results available for analysis. No significant differences were found between the two treatment groups in LOS, 30 day mortality, clinical failure, or resolution of fever. Side effects, although they did not have a significant influence on the outcome parameters, occurred more frequently in patients in the EAT group than in those in the PDT group (60% vs 17%, 95% CI −0.5 to −0.3; p<0.001).

**Conclusions:** An EAT strategy with broad spectrum antibiotics for the management of hospitalised patients with CAP has comparable clinical efficacy to a PDT approach.

**METHODS**

**Patients**

A prospective randomised study was performed between December 1998 and November 2000 in the Departments of Pulmonary Diseases and Internal Medicine at the Medical Centre Alkmaar, a teaching hospital with 900 beds. The medical ethics committee of the hospital approved the study. Patients who fulfilled the following criteria were enrolled in the study after giving written informed consent: (1) age 18 years or over; (2) clinical presentation of an acute illness with one or more of the following symptoms suggesting CAP: presence of fever (≥38°C), dyspnoea, coughing (with or without expectoration of sputum), chest pain; (3) presence of new consolidation(s) on the chest radiograph. Patients were excluded from the study if one of the following criteria applied: presence of severe immunosuppression (HIV infection, high dose of immunosuppressive agents such as prednisone >35 mg/day, chemotherapy); presence of malignancy; pregnancy or breast feeding; documented severe allergy to antibiotics; presence of obstruction pneumonia; pneumonia within 8 days of hospital discharge.

**Abbreviations:** CAP, community acquired pneumonia; EAT, empirical broad spectrum antibiotic treatment; PDT, pathogen directed treatment.
As is common in our healthcare system, most of the patients first consulted their general practitioner (GP) and from this population a selected group was referred to our hospital. An assessment of disease severity was performed on admission using the pneumonia severity index (PSI) by one of the investigators (MMvdE). The treating physician was not aware of the PSI risk class stratification.

**Study design**

The patients were randomised on admission to one of the two treatment groups by means of cards in sealed envelopes. The empirical antibiotic treatment (EAT) group received antibiotic treatment according to the ATS guidelines of 1993. Beta-lactam/β-lactamase inhibitor plus erythromycin were given intravenously (IV). Ceftazidime and erythromycin IV were given to patients referred to the ICU. Physicians were blind to the outcome of microbial studies. The microbiologist reported the results to the treating physician in case of failure on antibiotic treatment or when a pathogen was identified that was inadequately covered according to microbial investigation by the empirical regimen.

The pathogen directed treatment (PDT) group received IV treatment directed at the pathogen suspected to be the causative agent, as reported from routine microbial investigation or from clinical presentation (table 1). The results of a Gram stain (presence of >25 polymorphonuclear leucocytes and <10 squamous cells at 100x magnification) from sputum or pleural fluid, pneumococcal antigen detection (latex agglutination; Murex Diagnostics, Dartford, UK) in sputum or pleural fluid, and *L pneumophila* serogroup 1 urinary antigen detection test (enzyme immunoassay, BinaxNOW, Binax, Portland, Maine, USA) could be obtained within 2 hours of admission 24 hours a day.

**Outcome**

Clinical efficacy was primarily determined by the assessment of LOS. No criteria for discharge were given to the treating physicians, nor were they informed about the contribution of LOS as an outcome parameter for this study. The investigator was not actively involved in nor interfered with the treatment of any of the patients.

Secondary outcome parameters included therapeutic failure on antibiotic treatment. Clinical failures were subdivided into patients showing an early failure after adequate or inadequate treatment and patients showing a late failure on antibiotic treatment. An early failure was defined as patients in whom signs and symptoms of pneumonia did not improve within 72 hours of antibiotic treatment and persisted or progressed thereafter. A late failure was defined as a patient in whom signs and symptoms of pneumonia returned after 72 hours of admission following an initially good response on antibiotic treatment or those who died before the 30 day follow up. When, in the case of a failure, no pathogen had been identified or when the subsequently isolated pathogen had not been appropriately treated (according to microbial results and antibiotic sensitivity patterns) from the start of treatment, this was termed a failure on inadequate treatment. Other secondary outcome parameters included 30 day mortality, duration of intravenous antibiotic treatment, total duration of antibiotic treatment, resolution of fever, presence of adverse events, and quality of life. Adverse events were reported by the treating physician as symptoms or signs that could not be attributed to the pneumonia after starting antibiotic treatment. A quality of life analysis was performed using the Short-Form 36 Health Survey (SF-36) scale and CAP Symptom Severity score (SSC). The SF-36 questionnaire was administered during treatment and at the follow up visits 1, 3, and 6 months after treatment. A higher SF-36 score reflected a higher sense of quality of life. The SSC included the presence of five symptoms (cough, dyspnoea, sputum production, pleuritic chest pain, and fatigue). The severity of each symptom was scored on a 6-point scale (from 0 = not present to 5 = severe). The SSC was calculated on days 1 and 7 of treatment and at follow up 1, 3, and 6 months after treatment. A lower SSC indicated a better quality of life. The SF-36 and SSC scores were calculated according to the method described by Metlay et al.

**Microbiological investigations**

For both groups a sputum specimen was obtained at admission for Gram staining, semi-quantitative culture, and *S pneumoniae* antigen detection testing; three sets of blood cultures were taken and, if clinical symptoms suggested, a urine sample for *L pneumophila* serogroup 1 antigen detection was obtained at admission, preferably before the start of antibiotic treatment. A bronchoalveolar lavage (BAL) specimen and protected specimen brush (PSB) with Gram stain, semi-quantitative culture, and *S pneumoniae* antigen detection were performed, after consent, when patients did not expectorate sputum within 24 hours of admission or in case of clinical failure. Thoracentesis with Gram staining, *S pneumoniae* antigen detection, and culture for aerobic and anaerobic bacteria was performed when pleural fluid was present. Blood samples for serology (Serion ELISA classic, Virion GmbH, Würzburg, Germany) were obtained on days 1 and 14 of treatment for the detection of antibodies to *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *L pneumophila* serogroup 1–7, influenza A and B virus, parainfluenza virus 1–3, respiratory syncytial virus (RSV), and adenovirus. After completing the study, all patients were analysed for the presence of *S pneumoniae* antigen (enzyme immunoassay, Binax-NOW, Binax, Portland, Maine, USA) in the urine samples obtained at admission.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Suspected pathogen</th>
<th>Recommended antibiotic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute illness, labor infiltrate, raised WBC with an increase in PMNs</td>
<td>Streptococcus pneumoniae</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Mild illness, headache, upper airway tract symptoms, young age, travel to southern Europe, contact with animals</td>
<td>Atypical bacterial pathogen*</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Co-morbid illness, alcohol abuse, aspiration</td>
<td><em>S pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Moraxella catarrhalis</em>, Gram negative <em>áéòia</em>, <em>Anàéòia</em>, <em>Staphylococcus aureus</em></td>
<td>Amoxicillin-clavulanate</td>
</tr>
<tr>
<td>Influenza epidemic</td>
<td></td>
<td>Fluclaxacin ± gentamicin</td>
</tr>
</tbody>
</table>

*WBC, white blood cells; PMN, polymorphonuclear leucocytes.

*Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae/pitacci*.
Definitive aetiology was defined as (1) identification of an aetiologic agent in the blood and/or pleural fluid; (2) detection of *L. pneumophila* spp antigen in the urine; (3) the presence of *S. pneumoniae* antigen in pleural fluid; and (4) a threefold increase in antibody titre of *L. pneumophila* serogroup 1–7, *M. pneumoniae*, *C. pneumoniae*, influenza A and B, parainfluenza virus 1–3, RSV or adenovirus according to the manufacturer. Presumptive aetiology was defined as (1) a positive sputum, BAL or PSB culture by semi-quantitative methods compatible with the organism(s) seen on a good Gram stain specimen, (2) detection of *S. pneumoniae* antigen in urine or sputum, BAL or PSB specimen; (3) a single raised IgM titre of ≥17 U/ml for *M. pneumoniae*.

**Statistical analysis**

The patient sample size was calculated from the following assumptions: a reduction in LOS for patients with CAP by 3.4 days (23%) following implementation of EAT and a mean LOS of 14.9 days in hospital with a standard deviation (SD) of 10.2 days. A sample size of 240 patients (120 per group) was found to be necessary to detect this difference with a power of 80% and an alpha error of 0.05.

An intention-to-treat analysis of the primary study outcomes was performed for all randomised patients. Furthermore, primary and secondary outcome parameters were measured for the evaluable study population. A Student’s *t* test was used to compare continuous data; differences in LOS were calculated with the Mann-Whitney test. A χ² test was used to compare categorical data between the two treatment groups. Results were expressed as mean (SD) values. Differences in outcome between the two treatment groups were calculated with 95% two-sided confidence intervals (95% CI). A p value of <0.05 was considered significant. Data were analysed using SPSS Version 11.5 for Windows (Chicago, USA).

**Table 2** Baseline characteristics of study patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PDT (n = 134)</th>
<th>EAT (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>62.0 (18.5)</td>
<td>66.7 (17.2)†</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (55)</td>
<td>67 (52)</td>
</tr>
<tr>
<td>Female</td>
<td>60 (45)</td>
<td>61 (48)</td>
</tr>
<tr>
<td>Nursing home residents, n (%)</td>
<td>3 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Outpatient antibiotic treatment, n (%)</td>
<td>39 (29)</td>
<td>29 (23)</td>
</tr>
<tr>
<td>Co-morbidity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>47 (35)</td>
<td>49 (38)</td>
</tr>
<tr>
<td>Asthma</td>
<td>10 (7)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9 (7)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>6 (4)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>13 (10)</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>0</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (10)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 cigarettes/day</td>
<td>25 (19)</td>
<td>35 (27)</td>
</tr>
<tr>
<td>&lt;10 cigarettes/day</td>
<td>8 (6)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>46 (34)</td>
<td>42 (32)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>54 (40)</td>
<td>45 (35)</td>
</tr>
<tr>
<td>Alcohol intake, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 units/day</td>
<td>5 (4)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Pneumonia severity index, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk class 1</td>
<td>15 (11)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Risk class 2</td>
<td>35 (26)</td>
<td>24 (19)</td>
</tr>
<tr>
<td>Risk class 3</td>
<td>31 (23)</td>
<td>33 (26)</td>
</tr>
<tr>
<td>Risk class 4</td>
<td>44 (33)</td>
<td>50 (39)</td>
</tr>
<tr>
<td>Risk class 5</td>
<td>9 (7)</td>
<td>13 (10)</td>
</tr>
</tbody>
</table>

PDT, pathogen directed treatment group; EAT, empirical antibiotic treatment group.

†P=0.03. No other significant differences in baseline values were found.

**Figure 1** Randomisation to treatment, withdrawal of informed consent, and follow up among 303 patients with community acquired pneumonia.
RESULTS
Baseline characteristics
Three hundred and three patients were included in the study; all were hospitalised. Thirty-five patients were initially misdiagnosed and six withdrew consent and were subsequently excluded from the study. The results from 262 patients were evaluable for analysis: of these, 134 were assigned to the PDT group and 128 to the EAT group (fig 1). Patients in the PDT group were significantly younger than those in the EAT group (mean age 62.0 years and 66.7 years, respectively; p = 0.03). Eighty-two patients (31%) stratified in risk class I and II were hospitalised; significantly more in the PDT group (n = 50 (37%)) than in the EAT group (n = 32 (25%); p = 0.03, table 2).

Aetiology
Overall, 196 microorganisms were identified. In 84 patients (63%) in the PDT group treatment could be directed at a presumptive or definite microbial diagnosis. A pathogen could not be identified in 50 patients (37%) in the PDT group treatment; of these, 49 patients (34%) were treated according to rapidly obtained microbial results, and in 11 of 72 patients (15%) who were treated according to a syndromic approach (p = 0.19; see fig S1 available on the Thorax website at http://www.thoraxjnl.com/supplemental). In the EAT group, mortality after inadequate treatment occurred in two patients infected with S aureus and in two other patients no pathogen could be identified (table 4).

No significant difference in mortality was seen between the different treatment groups in the intention-to-treat population or the evaluable study population (95% CI –1.9 to 3.7; p = 0.63; table 4).

In neither the intention-to-treat population nor the evaluable patient population was any significant difference found in clinical failures between the two treatment groups (95% CI –0.1 to 0.1; p = 0.66 and 95% CI –0.1 to 0.1; p = 0.74, respectively). In the evaluable population, 26 in the PDT group (19%) and 27 in the EAT group (21%) suffered a clinical failure on antibiotic treatment (table 4). In the PDT group, clinical failure occurred in 15 of 62 patients (24%) who were treated according to rapidly obtained microbial results, and in 11 of 72 patients (15%) who were treated according to a syndromic approach (p = 0.19; see fig S1 available on the Thorax website at http://www.thoraxjnl.com/supplemental). In the EAT group, mortality after inadequate treatment occurred in two patients infected with S aureus and in two other patients no pathogen could be identified (table 4).

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in the evaluable patient population (95% CI –0.14 to 0.01; p = 0.07 and 95% CI –0.14 to 0.01; p = 0.09, respectively; table 4). In the evaluable population, 10 patients (7%) in the PDT group died compared with 18 (14%) in the EAT group. Eleven patients in each group were referred to the ICU. From this subgroup, significantly more EAT patients than PDT patients died (10 (91%) v 5 (45%); 95% CI –0.84 to –0.07; p = 0.02). The real failures in the ICU group consisted of one PDT patient and two EAT patients who were treated inadequately and subsequently died (see table S1 available on the Thorax website at http://www.thoraxjnl.com/supplemental). A significant difference (p = 0.03) in mortality was observed in the PDT population between 72 patients (54%) who were treated according to a syndromic approach and 62 (46%) who received treatment directed at a pathogen suspected from rapid routine microbiological investigations (mortality rates 3% (n = 2) v 13% (n = 8), respectively; see fig S1 available on the Thorax website at http://www.thoraxjnl.com/supplemental).

Patients in both groups were treated for a mean period of 5 days with IV antibiotics and completed their treatment course after 10.8 days in the PDT group and 9.9 days in the EAT group. Patients were afebrile by day 3 of treatment (table 5).

### Antibiotic choice and adverse events

All patients except one in the PDT group were started on IV monotherapy. Penicillin G was used most frequently (n = 54 (40%)), followed by amoxicillin-clavulanate (n = 47 (35%)), erythromycin (n = 16 (12%)), amoxicillin (n = 9 (7%)), cefuroxime (n = 3 (2%)), and other (n = 5 (4%)). Antibiotic treatment was adapted in 25 patients (19%) in the PDT group to microbial culture results. Ten patients (7%) received two antibiotics during hospitalisation because of adaptation to culture results or clinical failure on monotherapy. Patients in the EAT group initially received a combination of erythromycin and amoxicillin-clavulanate (n = 112 (88%)), erythromycin + cefuroxime (n = 8 (6%)), doxycycline + amoxicillin-clavulanate...
(n = 1 (0.8%) or erythromycin + cefazidime (n = 7 (5%)) as IV antibiotic treatment (data not shown). Four patients referred to the ICU during treatment initially received erythromycin and amoxicillin-clavulanate, which was later replaced by erythromycin and cefazidime.

Significantly more adverse events were encountered in the EAT group than in the PDT group (77 patients (60%) v 23 patients (17%), 95% CI −0.5 to −0.3; p<0.001, table 5). The adverse events did not have any significant clinical influence on outcome parameters such as LOS, treatment failure, and mortality.

**DISCUSSION**

In this prospective randomised study no significant difference in outcome between a pathogen directed approach and an empirical strategy with broad spectrum antibiotics, as proposed by the ATS guidelines of 1993, was found in adult hospitalised patients with CAP. Only adverse events, although not clinically significant, occurred significantly more often in the EAT group than in the PDT group (p<0.001). Neither therapeutic regimen had any significant effect on LOS. It is known that there is a difference in LOS of patients with CAP between Europe and the USA.14–17 This may be explained by regional differences such as more economic pressure in the USA. Treatment of co-morbid illness, social factors and a lack of immediate outpatient supportive care facilities prolonged hospital stay in several cases in our study. These have also been observed in two other studies.15 16 It should be emphasised that, in this study, no criteria for discharge were given to the treating physician. The decision to discharge a patient from hospital was based on clinical judgement. However, we are of the opinion that a closer evaluation of hospital discharge criteria would have led to a reduction in LOS. Some authors have suggested that, in certain circumstances, a patient could be discharged directly after changing from IV to oral treatment.19–21

With regard to our secondary outcome parameters, both treatment strategies were successful in the evaluable patient population with only 6% and 4% early failures after inappropriate antibiotic prescriptions, as a result of which two (1%) and four (3%) patients died in the PDT and EAT groups, respectively. Patients in the EAT group were significantly older than those in the PDT group (p = 0.03), and this could have influenced the results as age is a known risk factor for mortality.18 The presence of significantly more low risk patients in the PDT population (p = 0.03) did not have a significant influence on the outcome parameters. In a subanalysis, a significant difference (p = 0.02) was found in mortality between PDT and EAT patients who had been admitted to the ICU (45% v 91%). It is difficult to explain the high mortality rate in EAT patients. One possible explanation is that, as the study was not designed to detect a difference in mortality in ICU patients, the relatively low number of ICU patients made it difficult to establish a firm conclusion about this population. Seven EAT patients (64%) received a combination of cefazidime and erythromycin and four (36%) initially received a combination of amoxicillin-clavulanate and erythromycin which was later switched to cefazidime and erythromycin when they were referred to the ICU. Gleason et al19 found a higher 30 day mortality rate after using a β-lactam/β-lactamase inhibitor plus macrolide compared with other antibiotics. In another study cephalosporin treatment was associated with a worse prognosis than treatment with penicillin.21 In the ATS guidelines of 2001 a clear distinction has been made between treatment of ICU patients with and without risk factors for *P aeruginosa* infection. Ceftriaxone and cefotaxime are currently the preferred cephalosporins for treating ICU patients without risk factors for *P aeruginosa* infection, instead of the other third generation cephalosporins with anti-

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blind, randomised study. Secondly, the study was powered according to LOS and not according to mortality. The reason for the choice of LOS was because of the lack of studies that investigated the effectiveness of implementing the ATS guidelines at the time we completed the study protocol. The only study on which we could base our power analysis was one which correlated the implementation of the ATS guidelines with LOS.11 We realised that LOS would be influenced by non-pneumonia factors such as treatment of co-morbidity or social circumstances. Given the observed mortality rates in our study, 322 patients in each group (644 patients in total) would be needed to show a significant difference in mortality between the two groups. For practical reasons this number of patients could not be included within the established period in which we performed our study. Thirdly, we implemented antibiotic treatment according to the 1993 ATS guidelines for the empirically treated group. New guidelines were presented in 2001 but are not essentially different for hospitalised patients with the exception of ICU patients. Another limitation is the admission of low risk patients (risk class I–II). In our study the presence of other active co-morbidities would be needed to show a significant difference in mortality.

In conclusion, we have attempted to compare two different treatment strategies in the management of CAP. Our results show that an empirical approach with broad spectrum antibiotics has comparable efficacy to a pathogen directed approach.

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Figure S1 and table S1 are available online at http://www.thoraxjnl.com/supplemental.

Authors’ affiliations
M M van der Eerden, C S de Graaff, W G Boersma, Department of Pulmonary Diseases, Medical Centre Alkmaar, Alkmaar, the Netherlands
F Vlaspolder, T Groot, Laboratory for Medical Microbiology, Medical Centre Alkmaar, Alkmaar, the Netherlands
W Bronsveld, Department of Internal Medicine, Medical Centre Alkmaar, Alkmaar, the Netherlands
H M Jansen, Department of Pulmonary Diseases, Academic Medical Centre, Amsterdam, the Netherlands

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