Clinical End Points of Therapy for Patients with Mild Community-Acquired Pneumonia

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Approximately 80% of patients with community-acquired pneumonia receive treatment as outpatients. The question is what are valid, reproducible, and quantifiable clinical end points that can be used in prospective clinical trials of the safety and efficacy of antibacterials. Patient-reported outcomes and measurements of time to end point are reasonable methods that, according to the limited data available, appear to work in clinical trials of therapy for mild-to-moderate community-acquired pneumonia among outpatients.

Each year, there are ≥4 million new cases of community-acquired pneumonia (CAP) in the United States [1]. Approximately 80% of the patients have mild disease (pneumonia severity index risk class, I) and receive treatment as outpatients [2]. Although the mortality risk for patients with mild CAP who receive treatment as outpatients is <1%, the disease causes significant morbidity and expense [3].

Outpatients with documented CAP are a target population for enrollment in clinical trials of antibacterial agents. This article suggests appropriate clinical end points (outcomes) that can be used to ascertain the benefit or lack of benefit of the antibacterial therapy administered.

GENERAL REQUIREMENTS

Everyone agrees that clinical trials should have well-defined end points that are reliable, valid, responsive, and acceptable [4, 5]. Reliability requires consistency, stability over time, and reproducibility among observers. Validity requires that there is a direct relationship between the end point measured and the clinical outcome for the disease being studied. An outcome measure should be responsive to both a favorable and an unfavorable clinical response. Clinical end points have to be acceptable to both patients and health care providers. Lastly, end points, or outcome measurements, should be relevant to existing standards of clinical practice.

NOT RECOMMENDED CLINICAL END POINTS FOR OUTPATIENTS WITH MILD CAP

Mortality. Mortality is easy to measure and obviously important. However, because so few outpatients with CAP die, mortality is not a sensitive measurement of treatment failure in this population.

Return to “normal” activities of daily living. Because of the many uncontrollable variables involved in the end point of return to normal activities of daily living, this measurement is not recommended. Styles of clinical practice, influences of insurance coverages, patient motivations, and country-to-country variations are too inconsistent to allow reliable, valid, and reproducible measurements.

Microbiological response. Classically, “eradication” of the pathogen causing the pneumonia was an often used end point. Even after aggressive attempts to identify an etiologic agent or agents, the etiology of CAP is found for only 20% of patients. Physicians judge treatment response by clinical and not microbiological criteria. Rarely are there end-of-therapy microbiological data. Thus, “presumed eradication” makes no sense as a measure of treatment success [4]. On the other hand,
microbiological data are very helpful in the documentation of a clinical failure of therapy.

**Chest radiography.** An infiltrate on a chest radiograph is an absolute criteria for entry into a clinical trial of a treatment for CAP. However, resolution of the infiltrate lags behind other clinical end points, such that the patient is clinically cured despite persistent infiltrates on radiographs. In a recent study of 288 hospitalized patients with CAP, at day 7 of therapy, 56% of patients were judged to have clinically improved, whereas the findings of chest radiography were “improved” for only 25% [6]. By 28 days after trial entry, 78% of the patients were clinically cured, and yet the chest radiograph was “improved” for only 53%.

**Admission to the hospital.** Some trials have used the proportion of patients admitted to the hospital as an outcome measure. Unfortunately, it is not possible to control provider bias, differences in social support, and other variables.

### RECOMMENDED CLINICAL END POINTS FOR OUTPATIENTS WITH MILD CAP

#### Historical perspective. In 1957, Petersdorf et al. [7] reported the results of a clinical trial detailing the influence of aspirin on the clinical response of pneumococcal pneumonia to intramuscular penicillin G. Of interest, the investigators used both patient-reported outcomes (PROs) and time-to-response as end-point measurements.

A symptom grading system was generated, and 2 blinded physician investigators independently asked patients their subjective response to 4 symptoms (general feeling, appetite, cough, and pain) on a 0 to 4 scale. This approach is the harbinger of the modern PRO end-point measurement described below.

Petersdorf et al. [7] also performed analyses of time to clinical stability. Time to resolution of subjective symptoms and pertinent objective clinical features (e.g., fever) were reported each day for the first 5 days of therapy as the percentage of asymptomatic and afebrile patients.

**PROs.** The goal of PROs is to capture the facets of illness outcome that are important to patients [4, 8]. Data collection requires direct interaction with patients and, as such, introduces a host of potential variables. To ensure the quality of the data and of the collection process, the tools of psychometrics are applied.

Psychometrics is the branch of psychology that designs, administers, and interprets quantitative tests that are used for the measurement of such psychological variables as intelligence, aptitude, and personality traits. A proposed relevant questionnaire with a numerical scale is generated in concert with patients and physicians. The questions (measurements) are accepted as scientifically acceptable only after comprehensive testing to demonstrate reliability, validity, and responsiveness.

**Validated CAP symptom questionnaire.** Torres et al. [9] conducted a prospective, randomized, double-blind, multicenter, multicountry trial that compared the effectiveness of moxifloxacin with that of standard antimicrobial regimens for outpatients with CAP. The “standard” oral regimens comprised amoxicillin, clarithromycin, or both drugs. Approximately 80% of all enrolled patients were in pneumonia severity index risk classes I–III.

An 18-point symptom questionnaire (CAP-Sym) was generated to assess the “bothersomeness” of CAP-related symptoms during the past 24 h by use of a 6-point Likert scale [8]. “Gold standard” psychometric methods were used to comprehensively evaluate the acceptability, reliability, responsiveness, and validity of the questionnaire. The study was implemented at 64 centers in 13 countries. The questionnaire was developed in English and then was translated into 12 other languages.

Both the questions and the interview process were standardized. Patients were interviewed before therapy (days 0–5), during therapy (days 7–10), and after completion of up to 14 days of therapy (days 28–35). The patient interview script and the 18-point symptom questionnaire are reproduced in figure 1.

The intention-to-treat analysis population comprised 233 patients in the moxifloxacin arm and 244 patients in the standard treatment arm. Despite the range of pneumonia severity index risk classes, 99% of patients completed the baseline interview in both treatment groups, and 93% of the moxifloxacin arm and 95% of the standard treatment arm completed all 3 interviews (table 1). The mean baseline scores for the CAP symptoms were in the 30s and thus were consistent with mild pneumonia because the maximum possible score is 90. Considering the inclusion of a range of pneumonia severity index risk classes and an age range of 11–88 years, the CAP-Sym score SD was modest and consistently in the range of 11–14.

**PROs in other pneumonia studies.** One other reported clinical trial used a “pneumonia-specific symptom score” on a short-form health survey (SF-12) [10]. Oral clarithromycin was compared with oral gatifloxacin. Of interest, questions included items relating to adverse drug effects. The degree of standardization of the interview process is not clear.

In contrast to the international study described above, more symptom scores were determined early in the course of illness in this trial. This is desirable because evidence suggests that the effect of drug treatment for pneumococcal pneumonia is demonstrable within the first few days.

There were no differences in the PRO pneumonia-symptom scores between treatment arms. There were more complaints of “bad taste” among patients given clarithromycin (49%) than among those given gatifloxacin (28%) (P = .007).

**Current status of PROs.** To my knowledge, PROs have not, to date, been the means of assessing the primary end point in a US Food and Drug Administration new drug application seeking approval for use to treat CAP. PROs have been included
Introduction to the CAP-Symptom Questionnaire to be read to the patient.

Patients with pneumonia sometimes experience symptoms or problems which we are evaluating as part of the study in which you are currently participating. We would therefore like to ask you a few questions about your own current experience in that respect. I am going to read you a list of symptoms or problems.

For each of them, I will ask you the extent to which the symptom/problem has bothered you in the past 24 hours: not at all, a little, moderately, quite a bit or extremely. If you have not had the symptom/problem in the past 24 hours, please let me know.

Overall, the interview will only take a few minutes and the questions are simple to answer. Please remember that you should answer in reference to what happened in the past 24 hours. Thank you very much in advance for your participation.

*Please read each item to patient and circle the number that corresponds to how much the patient has been bothered by the symptom/problem IN THE PAST 24 HOURS.*

<table>
<thead>
<tr>
<th>In the past 24 hours, how much have you been bothered by:</th>
<th>Patient did not have the symptom/problem</th>
<th>Patient had the symptom/problem and it bothered him/her...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not at all</td>
<td>A little</td>
</tr>
<tr>
<td>'1. Coughing?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'2. Chest pains?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'3. Shortness of breath'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'4. Coughing up phlegm/sputum (secretion from the chest)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'5. Coughing up blood?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'6. Sweating?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'7. Chills?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'8. Headache?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'9. Nausea?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'10. Vomiting?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'11. Diarrhea?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'12. Stomach pain?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'13. Muscle pain?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'14. Lack of appetite?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'15. Trouble concentrating?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'16. Trouble thinking?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'17. Trouble sleeping?'</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>'18. Fatigue?'</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 1. Interview script and 18-point symptom questionnaire for patients with community-acquired pneumonia (CAP). *Items that are included in the 12-point symptom questionnaire. Reproduced from [8], with permission from the American College of Chest Physicians.
in clinical trials of many drug classes in fields other than infectious diseases. The value of PROs as end-point measurements is reflected in a draft guidance published by the US Food and Drug Administration for industry entitled “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” [11]. Subsequently, experts from academia, industry, clinical research, and clinical practice facilitated a series of articles that deal with specific guidance and operational issues. These articles further testify to the scientific validity and value of PROs and are published as a supplement to the journal *Value in Health*[12, 13].

**Time to clinical event.** Time to clinical event (also referred to as time to clinical stability) is attractive as an end point for several reasons. End points such as fever resolution and normalization of the WBC count are part of standard practice. Instead of an arbitrary duration of therapy, duration could be individualized according to the time to normalization of temperature, WBC count, or both. Another benefit is the potential for clinical efficacy with less drug, which hopefully translates into better compliance with treatment, fewer adverse effects, less drug resistance, and less expense.

To date, the use of time-to-event end points has focused on hospitalized patients with CAP [14–17]. The number of potential end points is greater for hospitalized patients. In addition to time to normalization of temperature and WBC count, time to clinical stability of pulse, respiratory rate, and oxygen saturation could potentially be measured.

Creativity is needed for measurements of time to end point for outpatients with CAP. It would be necessary to validate the accuracy and reproducibility of patient-recorded temperature measurements. Other than normalization of a WBC count that was abnormal at baseline, no other time-to-event measures are evident.

There is interest in other laboratory measurements that reflect the host inflammatory response. Sequential quantitative procalcitonin levels are an example. The current status of procalcitonin levels is reviewed elsewhere in this supplement [18]. In addition, the use of surrogates such as procalcitonin can have significant implications for the design and interpretation of clinical trials.

**SUMMARY**

Since the introduction of antibacterials into clinical practice, infectious disease investigators have been leaders in the establishment of accurate, valid, and reproducible end points in clinical trials. For outpatients with mild CAP who are enrolled in clinical trials to assess the comparative safety and efficacy of antibacterials, it appears that currently the best end-point tools are validated PRO questionnaires and careful quantitation of time to relevant event (i.e., time to clinical stability). Creativity is needed to develop and validate additional outcome markers for CAP in outpatients.

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