Using criteria for clinical stability to define clinical response in hospitalized patients with community-acquired pneumonia (CAP)

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ABSTRACT

Introduction: The FDA recommends that hospitalized patients with CAP should be evaluated for early outcomes. These early outcomes are defined as clinical response or clinical failure within 72 hours after initiation of treatment. Criteria for clinical stability can be used to define early clinical response (≤3 days) and late clinical response (4-7 days). Data evaluating the number of CAP patients that will reach early clinical stability using the recommended FDA outcome timing are limited.
The objective of this study was to define the percentage of hospitalized patients with CAP who reach FDA endpoints of clinical response at different time periods.
Methods: This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. Using criteria for clinical stability as well as clinical failure, patients were categorized as early versus late clinical improvement or clinical failure and non-resolving pneumonia.
Results: A total of 2724 patients were included in the analysis. Early clinical response was present in 1029 (38%), late clinical response in 781 (29%), early clinical failure in 201 (7%), late clinical failure in 104 (4%) and non-resolving pneumonia in 609 (22%) patients.
Conclusions: This study indicates that clinical response occurs in approximately 2/3 of hospitalized patients with CAP, with the majority of patients reaching FDA timing for early clinical improvement. These data suggest that the FDA recommendation of evaluating clinical response to therapy within the first 72 hours of hospitalization is applicable to a significant number of patients.

INTRODUCTION

Community-acquired pneumonia (CAP) is the eighth leading cause of death along with influenza in the USA and the sixth leading cause of death of those 65 years and older, as well as the number one cause of death from infectious diseases[1] . The reported mortality of CAP varies with the population being evaluated, ranging from less than 5% among outpatients, to approximately 12% among all hospitalized CAP patients, but rising to over 30% among those admitted to the intensive care unit (ICU). Short-term mortality and 1-year mortality may be as high as 40% in patients who have been admitted to the hospital with CAP.[2] In the United States, patients with CAP are primarily managed out of the hospital, but those admitted to the hospital consume the greatest proportion of economic resources.
Patients typically have subjective improvement within three to five days of treatment.
The FDA recommends that hospitalized patients with CAP should be evaluated for early outcomes.[3] These early outcomes are defined as clinical response or clinical failure within 72 hours after initiation of treatment. Criteria for clinical stability can be used to define early clinical response (≤3 days) and late clinical response (4-7 days). Data evaluating the number of CAP patients that will reach early clinical stability using the recommended FDA outcome timing are limited.
The objective of this study was to define the percentage of hospitalized patients with CAP who reach FDA endpoints of clinical response at different time periods.
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MATERIALS AND METHODS

This was a secondary data analysis of the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study database. Data was collected between 2001 and 2015. In each participating center, non-consecutive medical records of hospitalized patients with the diagnosis of CAP were reviewed. A sample of the data collection form is available at the study website (www.caposite.com). Validation of data quality was performed at the study center before the case was entered in to the CAPO database. Institutional Review Board approval was obtained by each participating center.

STUDY DEFINITIONS-

Community Acquired Pneumonia:

Diagnosis of CAP required the presence of criterion A, B, and C:

A. New pulmonary infiltrate on imaging (CT scan or chest x-ray) at the time of admission to the hospital.
B. Signs and Symptoms of CAP (at least one of the following)
   1. New or increased cough (per the patient)
   2. Fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F).
   3. Changes in WBC (leukocytosis >11,000 cells/mm^3, left shift > 10% band forms/microliter, or leukopenia < 4,000 cells/mm^3
C. Working diagnosis of CAP at the time of hospital admission with antimicrobial therapy given within 24 hours of admission.

Time to clinical stability (TCS):

A patient was defined as clinically stable the day that the following four criteria were met:

- Improved cough and shortness of breath
- Lack of fever for at least 8 hours
- Improving leukocytosis (decreased at least 10% from the previous day), and
- Tolerating oral intake with adequate gastrointestinal absorption.

Patients were evaluated daily within the first 7 days of hospitalization to determine the day when clinical stability was reached.
Using criteria for clinical stability as well as clinical failure, patients were categorized as early versus late clinical improvement or clinical failure and non-resolving pneumonia.

Early Clinical improvement-
If the patient is clinically improved within 72 hours of admission, it is termed as early clinical improvement.

Late Clinical Improvement-
If the patient is clinically improved in 4-7 days of admission, it is termed as late clinical improvement.

Early Clinical Deterioration-
If the patient deteriorates within 72 hours of admission, It is termed as early clinical deterioration.

Late Clinical Deterioration-
If the patient deteriorates in 4-7 days of admission, It is termed as late clinical deterioration.

Non-Resolving pneumonia-
If the patient does not reach clinical stability or clinical failure within the first week of admission, the patient is defined as a non-resolving pneumonia

RESULTS

- A total of 2,724 patients were included in the analysis.
- Patient characteristics are depicted in Table 1.
- The clinical response for all the population is depicted in Figure 1.

Table 1-Patients' characteristics are shown in the following table-

Variables	Column1
Demographics	
Age, Median(IQR)	68 (31)
Males, n(%)	2525 (59.4)
Nursing Home, n(%)	184 (4.3)
Comorbidities	
Cardiac Arrhythmia, n(%)	179 (4.2)
Diabetes Mellitus , n(%)	765 (18)
CHF, n(%)	668 (15.7)
Acute Myocardial Infarction, n(%)	53 (1.2)
Long-term Arrhythmia, n(%)	66 (1.6)
CVA, n(%)	11 (0.3)
Cardiovascular Meds, n(%)	575 (13.5)
HIV, n(%)	317 (7.5)
Liver Disease, n(%)	280 (6.6)
Cancer, n(%)	454 (10.7)
COPD, n(%)	960 (22.6)
Cardio-pulmonary Edema, n(%)	115 (2.7)
Pulmonary Embolism, n(%)	23 (0.5)
Renal Disease, n(%)	383 (9)
Physical Examination	
Temperature, Median(IQR)	37.8 (1.6)
Respiratory Rate, Median(IQR)	22 (10)
Systolic Blood Pressure, Median(IQR)	125 (30)
Altered Mental Status, n(%)	530 (12.5)
Labs / Radiography	
Glucose, Median(IQR)	120 (49)
Sodium , Median(IQR)	136 (6)
PAO2 (ABG), Median(IQR)	62.5 (19.8)
Ph (ABG), Median(IQR)	7.5 (0.1)
Hematocrit, Median(IQR)	38 (8)
Pleural Effusion, n(%)	103 (2.4)
BUN, Median(IQR)	31 (31.4)
Severity of Disease	
Pneumonia Severity Index, Median(IQR)	112 (49)
Admitted to ICU, n(%)	562 (13.2)

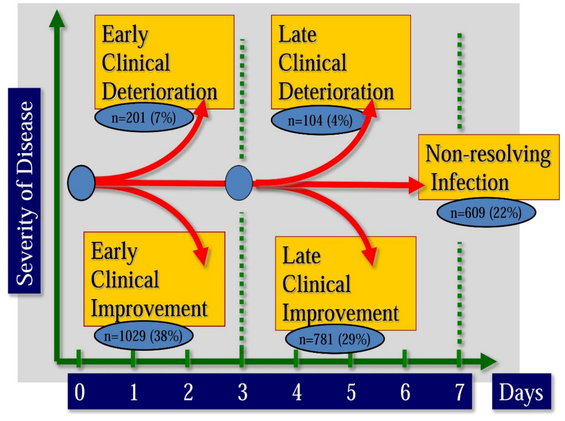

Figure:1-Clinical Response in the hospitalized patients with CAP

CONCLUSIONS

- This study indicates that clinical response occurs in approximately 2/3 of hospitalized patients with CAP, with the majority of patients reaching FDA timing for early clinical improvement.
- These data suggest that the FDA recommendation of evaluating clinical response to therapy within the first 72 hours of hospitalization is applicable to a significant number of patients.
- Patients who reached clinical improvement and are able to tolerate oral medications can be switched to oral antibiotics, thus decreasing the number of days that intravenous access may be needed.
- Clinical failures can be seen in the patients with inappropriate antimicrobial therapy, misdiagnoses of community acquired pneumonia, superimposed nosocomial infections, medical complications or metastatic infection.
- The challenge for future research is to:
  1. Define the substantial causes of non-resolving pneumonia
  2. To improve patient outcomes.
  3. To define most cost-effective antimicrobial therapy.

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