Antibiotic Timing in Community-Acquired Pneumonia Patients

Introduction

The time to first antibiotic dose (TFAD) is a critical question that needs to be carefully evaluated. It is considered as an important performance indicator in community-acquired pneumonia (CAP). The European guidelines recommend initiation of antibiotics within the first two hours of hospitalization, whereas the current Infectious Disease Society of America/ American Thoracic Society consensus guidelines advise the initiation of the first antibiotic dose in the emergency department.1,2

Clinical Evidences Disputing the 4-Hour Rule

Several subsequent studies questioned the policy of initiation of antibiotics within the first four hours. A prospective observational study conducted by Silber et al. reported that there was no reduction in the time to clinical stability with the administration of antibiotics within 4 hours in adult patients with moderate-to-severe CAP.3

Bruns et al. conducted a study to evaluate the effect of minimizing the TFAD on the early clinical outcome in patients with moderate-to-severe CAP. Proportion of patients with clinical instability, admission to the intensive care unit (ICU) or mortality on day 3, were expressed as early clinical failure. It was found that Pneumonia Severity Index, confusion, Staphylococcus aureus infection and multi-lobar pneumonia were independently associated with early clinical failure.

Time to first antibiotic dose was however, not associated with early clinical failure. Hence, it is not advisable to consider TFAD as a performance indicator in patients with moderate-to-severe CAP.4

Metersky et al. determined the frequency of medicare patients who are discharged with a diagnosis of pneumonia with atypical presentation. This could lead to diagnostic uncertainty and a resultant appropriate delay in antibiotic administration. It was found that about 22% of patients presented in a manner that had the potential to result in delayed antibiotic treatment due to diagnostic uncertainty. This study demonstrated that many patients of pneumonia can present with atypical symptoms. If antibiotic treatment is given within 4 hours for all patients, it would necessitate the treatment of many patients before a firm diagnosis can be made.5

Waterer et al. conducted a prospective cohort study to investigate the factors that predict a prolonged TFAD and their association with mortality in patients with CAP. It was found that in CAP patients with an altered mental state or minimal signs of sepsis, antibiotic administration was often delayed. The time to first antibiotic dose was considered to be a marker of comorbidities responsible for both an atypical presentation and mortality rates rather than having a direct role in the outcomes.6

A finding from a retrospective study of 548 patients by Welker et al. reported that there was a reduction in the accuracy of the initial diagnosis of CAP when the required TFAD was changed from 8 hours to 4 hours. Hence, it was suggested that there was no reduction in actual TFAD achieved in these patients.7

Synopsis from the Guidelines

- The USA National Pneumonia Medicare Quality Improvement project and the National Quality Forum recommends administration of antibiotics within 6 hours instead of 4 hours in the management of pneumonia, because of the unintended overuse of antibiotics before 4-hour window.8
- After the diagnosis of CAP, antibiotics are to be administered at the earliest. However, no specific timeframe is recommended according to the treatment guidelines of Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) 2007 guidelines.1
- Guidelines for the management of adult patients with CAP by the Infectious Diseases Society of America / American Thoracic Society has advised that patients receive antibiotics in the emergency department, rather than specifying a number of hours for the TFAD.1,7

Concerns with the Administration of Antibiotics within 4 Hours

Overdiagnosis/misdiagnosis of CAP, inappropriate utilization of antibiotics, no association to mortality, length of hospital stay, time to clinical stability and pressure on clinicians to start the first dose of antibiotic despite diagnostic uncertainty, were the concerns with the administration of antibiotics within 4 hours.7

Ideal Time to Switch from Intravenous to Oral Antibiotics

The choice and timing of switch from intravenous (I.V.) to oral route of antibiotic administration depends of several factors.1,2 They are as follows:
- Absence of any contraindications to oral administration
- Availability of microbiological information pinpointing etiology of the pathogen
- Clear evidence that the patient is responding well to initial therapy

Literature Review

Several large, well-designed studies have touched upon the timing of switching from intravenous to oral route. A meta-analysis by Rhew et al. investigated the effectiveness of early switch and early discharge strategies in CAP patients.9 Ten prospective, interventional, CAP-specific studies that evaluated length of stay were included in the study. Of these, nine studies applied an early switch from parenteral to oral antibiotic criteria using six different criteria for switching. Five of the studies that applied early switch criteria also applied separate criteria for early discharge. There was no reduction observed with the mean change in length of the stay with studies/ of early switch and early discharge.9

It was concluded that there was a considerable variation in early switch from parenteral to oral antibiotic criteria in patients with CAP. Early switch and early discharge strategies may significantly and safely reduce the mean length of stay (LOS) when the recommended LOS is shorter than the actual length of stay.9
Athanaessa et al. conducted a meta-analysis which evaluated early switch to oral treatment in hospitalized patients with moderate-to-severe CAP. Relevant randomized controlled trials with the same total duration of antibacterial treatment in the compared groups (early switch from intravenous to oral and conventional intravenous treatment for the whole duration of therapy) were included in the analysis. There was no difference in the treatment success, mortality and recurrence of CAP between early switch to oral treatment and intravenous-only treatment groups. Shorter duration of hospitalization was observed in the early switch group. It was concluded that early switch to oral antibiotics can be as effective as continuous intravenous treatment in patients with moderate-to-severe CAP. Further, it was also suggested that early switch also reduces the duration of hospitalization.

Ramirez and Bordon conducted a study to evaluate the clinical outcomes while switching from intravenous to oral therapy in hospitalized patients with CAP. The medical records of 400 patients were reviewed. There were four criteria which were used to define clinical stability of the patient and to select the candidate for switch therapy:

- Improvement of cough and shortness of breath
- Patient being afebrile for a minimum of 8 hours
- White blood cell count reaching normal levels
- Adequate oral intake and gastrointestinal tract absorption

About 36 patients were bacteremic. Clinical failure was not seen in 18 patients who reached clinical stability and were switched to oral therapy, and in 7 patients who reached clinical stability and were on continuous intravenous therapy. It was concluded that it was safe to switch from intravenous to oral therapy in hospitalized patients with CAP after the patient was clinically stable.

Mertz et al. conducted a study to assess outcomes following implementation of a checklist with criteria for switching from intravenous to oral antibiotics on unslected patients in two general medical wards. A printed checklist of criteria for switching on the third day of intravenous treatment was placed in the medical charts. The decision to switch was at the attending physician’s discretion. The 4-month period before intervention (control phase) was compared with the equivalent 4-month period during the intervention phase. Outcomes measured were duration of intravenous therapy, safety, adherence to the checklist, reasons against switching patients and antibiotic cost. About 61.4% of the patients were switched to oral treatment. There was a 19% reduction in the number of days of intravenous treatment. There was no increase in the complications. Persisting fever and absence of clinical improvement were the contributing factors for switching. It was concluded that switch from intravenous to oral treatment can reduce the duration of intravenous therapy without any negative effect on clinical outcome.

Nathan et al. conducted a study to assess the clinical benefit of in hospital observation after the switch from intravenous to oral antibiotics. A retrospective examination of the United States Medicare National Pneumonia Project database was performed. Patients were divided into ‘not observed’ cohort (patients discharged the same day of switching) and an ‘observed for 1 day’ cohort (patients remained hospitalized for 1 day after switching). There was no difference in 14-day hospital readmission and 30-day mortality rate in both the groups. It was concluded that routine practice of in-hospital observation after the switch from intravenous to oral antibiotics for patients with CAP who have reached clinical stability can be avoided.

### Community-Acquired Pneumonia and Sepsis

Rivers et al. conducted a randomized study to assess the efficacy of early goal-directed therapy before admission to the intensive care unit. Patients with severe sepsis or septic shock were included in the study. They were randomized to receive either 6 hours of early goal-directed therapy or standard therapy. In-hospital mortality was the primary outcome measure of the study. Other outcome measures were resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores (72 hours). It was found that in-hospital mortality was about 30.5% and 46.5% in early goal-directed therapy group and standard therapy group, respectively (p=0.009). There was significantly higher mean central venous oxygen saturation (70.4% vs. 65.3%), lower lactate concentration (3.0 vs. 3.9 mmol/L), lower base deficit (2.0 vs. 5.1 mmol per liter) and higher pH (7.40 vs. 7.36) in patients assigned to early goal-directed therapy compared to the other group. Significantly lower mean APACHE II scores (13.0 vs. 15.9, p<0.001) were found in patients assigned to early goal-directed therapy. Significant benefits with respect to outcome was reported with early goal-directed therapy in patients with severe sepsis and septic shock.

Clermont et al. conducted a retrospective analysis of a prospective observational outcome study from the pneumonia patient outcomes research team (PORT). The objectives of the study were to describe the onset and timing of severe sepsis during the hospital course for patients hospitalized with CAP and to determine the ability of the systemic inflammatory response syndrome (SIRS) and other proposed risk stratification scores measured at emergency department (ED) presentation to predict progression to severe sepsis, septic shock or death. About 82% of patients had SIRS. This condition (SIRS) was not associated with the progression of CAP to severe sepsis, or septic shock, whereas pneumonia severity index was found to be associated.

In hospitalized CAP patients, severe sepsis is very common, but SIRS is not a significant predictor of the same.

These are some of the important findings on sepsis associated with hospitalized CAP.

- The presence of SIRS does not predict the later development of severe sepsis.
- Organ dysfunction in severe sepsis is due to generation of endogenous proinflammatory cytokines.
- There has been improvement in mortality with appropriate goal-directed therapy of CAP within first 48 hours of admission.
- Sepsis also occurs in CAP patients outside the ICU; however, the data within this group of patients is less.
- SIRS was thought to be the main cause of severe sepsis.

### Intravenous drug | Oral replacement
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Amoxicillin+Clavulanic acid | Amoxicillin+Clavulanic acid
Ceftriaxone or cefotaxime | Amoxicillin+Clavulanic acid
Levofoxacin | Levofoxacin
Clarithromycin | Clarithromycin
Piperacillin+tazobactam or cefoperazone+sulbactam | Amoxicillin+Clavulanic acid
Ertapenem | Amoxicillin+Clavulanic acid
It is been reported that organ dysfunction in CAP cannot be predicted by SIRS criteria. 

Low mortality (<5%) is seen in adequately treated CAP patients in the outpatient setting. About 10% of CAP patients require ICU admission.

Mortality ranges from 22% to 55% in CAP patients over 65 years of age and requiring mechanical ventilation.

About 30–50% of mortality is reported with severe sepsis and the mortality rate has remained stable over the years.

**Indian Scenario: Special Challenges in the Treatment of Patients with Severe CAP**

Community-acquired pneumonia is found to be associated with a significant morbidity and mortality, even though better and more potent antibiotic drugs are available coupled with improved supportive care. The main factor seems to be discrepancy in the management and poor adherence to the existing management guidelines. Community-acquired pneumonia is commonly misdiagnosed followed by undertreatment or overtreatment. Currently, the major concern is increasing infection with multidrug-resistant (MDR) organisms due to antibiotic misuse and also increased contact with health services. The prevalence of specific organisms at any given point of time should also be considered.

**Community-Acquired Pneumonia and Hypotension**

Septic shock is defined as hypotension resistant to fluid resuscitation in sepsis. The mortality from CAP due to *Streptococcus pneumoniae* and other organisms increases in the septic shock. Mortality rate is high with vasopressor agents or mechanical ventilation.

- Intensive care unit admission is indicated in patients with CAP and hypotension, where vasopressors are used.
- Sepsis and septic shock in the setting of CAP should be managed on similar lines to that in the setting of an extrapulmonary infection.

**Community-Acquired Pneumonia and Respiratory Failure**

- High level of support is required in patients with respiratory failure.
- Trial of noninvasive ventilation is required in patients in respiratory distress or those with moderate hypoxemia (PF ratio >150).
- The need for intubation and intermediate-term mortality is decreased with noninvasive ventilation in patients with respiratory distress or those with moderate hypoxemia.
- Intubation and ventilation are advised in patients with failure of a noninvasive ventilation trial, non-improvement in respiratory rate and respiratory acidosis.
- Intubation is advised in patients with acute respiratory distress syndrome or severe respiratory failure (PF <150) without non-invasive ventilation trial.
- It is difficult to distinguish acute respiratory distress syndrome from an underlying primary cause (e.g. viral pneumonia) radiologically. Low tidal volume strategy (6 cm/kg ideal body weight) offers survival advantage in mechanically ventilated patients.
- One of the minor criteria for the diagnosis of severe CAP is respiratory failure (PaO2/FIO2 ratio of <250). Respiratory failure is associated with high mortality.

**Recommendations**

- The timing of antibiotic therapy depends on the severity of the CAP at the time of hospital admission. Severe cases of CAP require immediate institution of therapy, which must be adjusted after confirming microbiological etiology.
- Switch from intravenous antibiotics to oral treatment is recommended in case of observed improvement in symptoms, improved respiratory rate and oxygen saturations, patient being afebrile for >24 hours, hemodynamic stability, reduction in white blood cell count (if elevated earlier) and absence of nausea/ vomiting.
- Appropriate oral medications should be used without compromising on the spectrum of cover of the bacterial flora by the antibiotic.
- In the absence of a culture/sensitivity report identifying an organism and an appropriate oral antibiotic, following oral replacements are suggested.
- Special care and intensive management is required in some special population of patients like those with severe CAP, sepsis, hypotension and respiratory failure.

**References**

11. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-


