

# COMPARISON OF EARLY INTRAVENOUS TO ORAL SWITCH AMOXICILLIN/CLAVULANATE WITH PARENTERAL CEFTRIAZONE IN TREATMENT OF HOSPITALIZED PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA

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## ABSTRACT

**Objective:** To compare the clinical efficacy and cost effectiveness of early intravenous to oral switch Amoxicillin/Clavulanate and parenteral Ceftriazone in treatment of hospitalized patients with community acquired pneumonia (CAP).

**Design:** Open, randomized, parallel group comparative study.

**Setting:** Department of Medicine at Services Hospital, Lahore

**Patients and Methods:** Fifty patients with community acquired pneumonia requiring intravenous antibiotics on admission to the hospital and fulfilling study criteria were enrolled and randomly assigned to receive therapy either with Amoxicillin/Clavulanate or Ceftriazone. Patients in Amoxicillin/Clavulanate group were switched from IV to oral antibiotics based upon switch criteria whereas those in Ceftriazone group completed the therapy parenterally.

**Main Outcome Measures:** The two groups were compared to each other on the basis of clinical and bacteriological outcome at the end of treatment and follow up. Treatment costs were calculated for the two study groups.

**Results:** The two study groups had equal clinical efficacy, both at the end of treatment and follow up. Mean duration of treatment was equal for both groups (8 days); however mean hospitalization stay was significantly shorter (4.1 day) for Amoxicillin/Clavulanate group as compared to Ceftriazone group (8.2 days). The cumulative savings for intravenous to oral switch Amoxicillin/Clavulanate was Rs. 1,70,137 or Rs. 7,397 saved per patient.

**Conclusion:** Early intravenous to oral switch Amoxicillin/Clavulanate had comparable clinical efficacy to parenteral Ceftriazone and resulted in reduced hospitalization stay and decreased treatment costs and is a more cost effective treatment of community- acquired pneumonia patients requiring intravenous antibiotics on admission.

**KEYWORDS:** Community acquired pneumonia, switch therapy, antibiotics.

**Abbreviations:** CAP= community acquired pneumonia, IV= intravenous, SD= Standard Deviation, COPD= chronic obstructive pulmonary disease

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## INTRODUCTION

Community acquired pneumonia continues to be a major health problem despite the availability of potent antimicrobial agents. The medical and economic impact of pneumonia on society is great and is increasing, so the hospitals and physicians are challenged to provide a high standard of care in a cost-effective manner. As the pressure of cost containment has increased, decisions concerning the appropriate duration of intravenous antibiotics, length of hospital stay and the economics of antibiotic therapy have come under scrutiny.

Early intravenous to oral switch has received much attention recently mainly because of the economic benefits resulting from the treatment costs, fewer complications and earlier discharge from hospital. A number of studies carried out in Europe and United States to evaluate the intravenous to oral switch therapy have supported its application and have documented favorable effects on the cost-effectiveness of treatment of pneumonia.

There has been no major study carried out locally in Pakistan to study and evaluate the application of switch therapy and its cost benefits. This study has been carried out to compare the clinical efficacy of early intravenous to oral switch Amoxicillin/Clavulanate with parenteral Ceftriaxone in the treatment of hospitalized patients with community acquired pneumonia and to find out whether the early switch from intravenous to oral Amoxicillin/Clavulanate results in decreased hospital stay and hence reduction in the costs involved in treating such patients.

## PATIENTS AND METHODS

It was an open, randomized group comparative study carried out at Department of Medicine, Services Hospital Lahore from May 1998 to February 2000.

Fifty adult patients with community acquired pneumonia (CAP) requiring intravenous antibiotic therapy on admission to hospital and fulfilling the study criteria were enrolled in the study after obtaining written informed consent. The diagnosis was clinical but had to be confirmed with a chest x-ray showing new infiltrates. Patients were excluded from the study if they were suspected to have atypical pneumonia or pulmonary Tuberculosis, had previous allergic reactions to the study medications, were immunocompromised with WBC  $<1000/\text{mm}^3$  or receiving long term steroids or immunosuppressive medications, were pregnant or breast feeding or were receiving concomitant antibiotic therapy.

Patients were randomized to two groups, each with twenty-five patients assigned either to Amoxicillin/Clavulanate or Ceftriaxone re-

spectively. Randomization was on simple numerical basis with first patient being assigned to the Amoxicillin/Clavulanate group, followed by 3<sup>rd</sup>, 5<sup>th</sup> and every following odd number till the 49<sup>th</sup> patient was enrolled. Similarly the second patient and every following even number were included in the Ceftriaxone group till the 50<sup>th</sup> patient was enrolled.

Patients in the Amoxicillin/Clavulanate group were treated with the intravenous (IV) Amoxicillin/Clavulanate, 1.2 grams every 8 hours followed by oral Amoxicillin/Clavulanate 625mg three times a day. Patients in the Ceftriaxone group received intravenous Ceftriaxone 1 to 2 grams once a day. Patients were treated for a minimum of 7 days or more depending upon the clinical response.

Ceftriaxone dose ranges between 1-2 grams a day for a wide variety of bacterial infections. It is generally accepted that 1 gram of IV is used in treating most of the infections, whereas 2 grams of IV is used to treat more severe infections. There has been no consensus among infectious disease experts regarding one dose<sup>1</sup> and this is the reason, that leading pharmacology texts like Physician Desk Reference (PDR) and Epocrates Rx recommends dose ranging from 1-2 grams daily instead of committing to one dose. It has been shown that impacts of small dose dependent changes in the pharmacokinetics of Ceftriaxone is of negligible clinical significance.<sup>2</sup>

Because of the above mentioned reasons we did not fix the dose of Ceftriaxone but instead left it at the discretion of examining physician at the time of patient enrollment to initiate the specific dose based upon patients clinical condition. Fourteen patients were treated with 1 gram Ceftriaxone daily and 8 patients received 2 grams of Ceftriaxone daily.

All patients had their blood cultured and sputum collected for gram stain and cultures. Full blood count with differential, blood urea nitrogen, serum creatinine, glucose, electrolytes and serum transaminases were estimated at the inclusion and later if needed. Patients were clinically evaluated daily during their hospitalization.

Patients randomized to Amoxicillin/Clavulanate group were switched from IV to oral therapy if they were improving symptomatically, were afebrile for at least 8 hours and there was no indication of abnormal gastrointestinal absorption like diarrhea or vomiting. Patients remained admitted for one day after switch to ascertain that they were clinically stable and tolerating oral medicine. Patients in Ceftriaxone group were discharged after completion of seven days of parenteral therapy.

Patients were clinically evaluated daily during their hospitalization. Patients in both groups were assessed clinically with special emphasis on signs and symptoms of pneumonia and their vital signs including temperature, respiratory rate, blood pressure and pulse. They were also evaluated specifically about any adverse effects related to study medications in both groups. Full blood counts with differential, blood urea, serum creatinine, blood glucose, serum electrolytes and serum transaminases were obtained at the inclusion and during the course of hospitalization if considered clinically necessary by the examining physician.

Patients who were showing insufficient clinical response at any time during the study were withdrawn and treated empirically.

All patients had follow up visits 3 to 4 weeks after the end of treatment and evaluated for clinical status and symptom recurrence. A chest x-ray was taken. All patients were evaluated periodically for any adverse event during treatment. Patients were classified into the categories of 'clinical cure' when there was resolution of signs and symptoms, 'clinical failure' when there was incomplete resolution of signs and symptoms and 'indeterminate' when either they could not complete treatment or they did not attend the follow up visit.

Bacteriological end points were proven eradication with documented elimination of pathogens by culture, presumptive eradication when clinical outcome was cure and subsequent culture was not available, persistence of initial pathogen, recurrence of the organism at follow up after earlier eradication and indeter-

minate when bacteriological evaluation could not be made.

Savings related to reduced length of hospitalization were calculated based on the average daily cost of hospitalization to a private hospital. Net savings in drug costs were calculated based upon the costs of injectible forms of Augmentin (SmithKline and Beecham) and injectible Rocephin (Roche) and oral form of Augmentin at the retail prices available at the time of study. The cost of drug administration was calculated from pharmacy preparation and nursing times and based on average salaries of nurses and pharmacists at the time of study.

All results were expressed as Mean (X) and Standard Deviation (SD) of the mean. The two patient groups were compared with each other at the end of treatment and follow up, applying the Z test of significance to test the alternative hypothesis that clinical efficacy of the two study groups is not equal. After rejecting the alternative hypothesis, the total costs involved and net savings were calculated.

## RESULTS

Patients were aged between 20 and 86 years. Mean age was 54.1 years in Amoxicillin/Clavulanate group and 53.6 years in Ceftriaxone group. 14 (56%) patients in Amoxicillin/Clavulanate group and 15 (60%) patients in Ceftriaxone group were men. 5 patients (20%) in Amoxicillin/Clavulanate and 6 (24%) in Ceftriaxone group were smokers whereas 13 patients (52%) in Amoxicillin/Clavulanate group and 12(48%) in Ceftriaxone group had COPD. Four patients (16%) in Amoxicillin/Clavulanate group and 5 (20%) in Ceftriaxone group were diabetics.

The common clinical and laboratory observations in the study patients are presented in Table-I.

Initial sputum culture was positive in 10 patients (40%) in Amoxicillin/Clavulanate group and 8 patients (32%) in Ceftriaxone group. Twentyfive patients (50%) did not grow any pathogen in their sputum and in 7 patients

(14%) initial sputum sample was not available for bacteriological determination. The relative distribution of organisms in bacteriologically positive sputum culture is provided in Table-II.

Mean duration of therapy was 8.1 days (SD=1.2) for Amoxicillin/Clavulanate group and 8.2 days (SD=1.1) for Ceftriaxone group. Mean hospitalization stay was 4.1 days (SD=0.92) for Amoxicillin/Clavulanate group as compared to 8.2 days (SD=1.1) for Ceftriaxone group. Patients were switched from IV to oral Amoxicillin/Clavulanate on average of 3<sup>rd</sup> admission day (1 patient on day one, 6 on day two, 10 on day three, 3 on day four and 3 on day five with a mean of 3.1 days and a SD of 1.1 days).

Twenty-three (92%) of the 25 patients in Amoxicillin/Clavulanate group were clinically cured at the end of treatment as compared to 22 (88%) of patients in the Ceftriaxone group. Both of the clinical failures at the end of treatment in the Amoxicillin/Clavulanate group were due to lack of adequate clinical response, where another antibiotic had to be used. Two of the three clinical failures at the end of treatment in Ceftriaxone group were due to lack of adequate clinical response necessitating the use of additional antibiotic whereas one patient

had serious adverse effect. Application of Z test of significance on the proportion of patients clinically cured at the end of treatment yielded a value of  $Z = 0.47$  which was statistically insignificant at  $p < 0.05$ .

In the Amoxicillin/Clavulanate group, out of 23 patients that were clinically cured at the end of treatment, 22 were asymptomatic at follow up with one patient being lost to follow up. Hence the overall efficacy in patients in Amoxicillin/Clavulanate group was 88%.

In the Ceftriaxone group, out of 22 patients that were clinically cured at the end of treatment, 20 were asymptomatic at follow up with one patient having recurrence of symptoms requiring readmission and one patient being lost to follow up. Hence the overall clinical efficacy in patients in Ceftriaxone group was 80%. Application of Z test of significance on the proportion of patients clinically cured at the follow up in the two study groups yielded a value of  $Z = 0.73$  which was statistically insignificant at  $p < 0.05$  hence rejecting the alternative hypothesis that clinical efficacy of the two study group is not equal. This documented that the two study groups had equal clinical efficacy both at the end of treatment and at the follow up and cost calculations and net savings could be calculated for the intravenous to oral switch Amoxicillin/Clavulanate group.

Out of 10 patients with positive serum culture in the Amoxicillin/Clavulanate group, there was proven eradication in 5 patients, and presumptive eradication in 3 patients. Two patients had persistence of Streptococcus pneumoniae that was resistant to Amoxicillin/Clavulanate. Out of 8 patients with positive

Table-I: Clinical and laboratory manifestations in patients

<b>Clinical Manifestations</b>	
Cough	48 (95%)
Sputum Production	43 (86%)
Tachypnea	42 (84%)
Fever	35 (70%)
Tachycardia	32 (65%)
Chills	21 (42%)
Chest Pain	20 (40%)
<b>Laboratory Features</b>	
Leukocytosis	40 (80%)
Infiltrates on chest x-ray	
Single lobe	40(80%)
Multiple lobes	10 (20%)
Blood Cultures	
Bacteremic	4 (8%)
Non Bacteremic	46 (92%)

Table-II: Relative distribution of organisms in bacteriologically positive sputum cultures

<i>Organisms</i>	<i>Number of positive cultures (%)</i>
Streptococcus Pneumoniae	8 (44%)
Haemophilus influenza	7 (38%)
Moraxella catarrhalis	1 (6%)
Escherichia coli	1 (6%)
Klebsiella Pneumoniae	1 (6%)

sputum culture in the Ceftriaxone group, 3 had proven eradication, two had presumptive eradication, 2 patients had bacteriological persistence (one with resistant *Escherichia coli* and other with resistant *Haemophilus influenzae*). One patient had recurrence with *Streptococcus pneumoniae* in the follow up period.

Three patients in the Amoxicillin/Clavulanate group had non-serious adverse events including diarrhea in two and rash in one, both which were transient and settled without discontinuing the drug. Three patients in the Ceftriaxone group had non-serious adverse effects including transient rash in one, and reversible increase in transaminases in two patients that settled without discontinuation of study medication. There was one serious adverse event, death, in one patient in Ceftriaxone that was not related to study medication.

The average length of hospital stay in Amoxicillin/Clavulanate group was 4 days as compared to 8 days for patients treated with parenteral Ceftriaxone. A total of 92 days were thus saved for the clinically evaluable 23 patients in Amoxicillin/Clavulanate therapy (2 had clinical failures and thus not included in cost evaluation). This multiplied by an average daily cost of hospitalization in a private hospital of around Rs. 800 per day gives a sum of Rs. 73,600 saved in patients, who were treated with intravenous to oral switch Amoxicillin/Clavulanate therapy resulting in reduced hospital stay.

Patients in Amoxicillin/Clavulanate group received parenteral therapy for an average of 3 days as compared to 8 days for patient in the Ceftriaxone group. Cost of 1G injection of Rocephin was Rs.530 at the time of study and 14 patients required 1G per day while 8 patients required 2G per day of Ceftriaxone. The total treatment cost of Ceftriaxone group was Rs.129,480 or Rs.5885 per patient. Cost of 1.2G injection of Augmentin was Rs.130 and one 625mg tablet of Augmentin was Rs.14.8 resulting in a total cost of Rs. 34,024 or Rs. 1,479 per patient. Administration of a single dose of intravenous antibiotic required approximately 15

minutes of nursing time. This amounted to a saving of Rs.811 in the Amoxicillin/Clavulanate group when calculated from average salary of nurses of approximately Rs. 166 per 8-hour day. Similarly 782 minutes of pharmacist working time was saved, assuming an intravenous prescription taking an average of 5 minutes of pharmacist working time. This when applied to average pharmacist salary of Rs. 160 per 8-hour day amounted to Rs. 270 saved.

The cumulative total savings calculated for intravenous to oral switch Amoxicillin/Clavulanate compared with parenteral Ceftriaxone in 23 patients treated in Amoxicillin/Clavulanate group was Rs. 73,600 + Rs. 95,456 +Rs 811+ Rs. 270 amounting to Rs. 1,70,137 or Rs. 7,397 saved per patient. Total savings are summarized in Table-III.

Table-III: Savings related to patients treated with intravenous to oral switch Amoxicillin/Clavulanate

<i>Type of Savings</i>	<i>Estimated Savings</i>
Savings related to decreased length of hospital stay	Rs. 73,600
Savings related to decreased drug cost	Rs. 95,456
Savings related to nursing/pharmacist charges	Rs. 1,081
Savings per patient	Rs. 7,397
Total hospital savings	Rs.170, 137

## DISCUSSION

This study was carried out to evaluate the impact of one of the measures to decrease the period of hospitalization i.e. early intravenous to oral switch therapy with Amoxicillin/Clavulanate, on the costs involved in the treatment of CAP as compared to parenteral Ceftriaxone in patients requiring hospitalization.

The cost associated with CAP are staggering. In a recent population based study carried out in Spain, the mean direct cost of pneumonia treated in the hospital setting was 1,553

Euros as compared to 196 Euros for outpatient treatment<sup>3</sup>.

As the pressure for cost containment has increased, the hospitals and physicians are challenged to provide a high standard of care in a cost effective manner and decisions concerning the appropriate duration of intravenous therapy, length of hospital stay and economics of antibiotic therapy have come under scrutiny<sup>4</sup>.

The treatment of hospitalized patients with CAP has traditionally been with intravenous antibiotics. Replacing intravenous antibiotics with oral antibiotics in the treatment of serious infection is known as Switch Therapy. With the development of new oral antibiotics that require less frequent dosing and provide excellent oral absorption, switch therapy has become an important option for treatment of CAP<sup>5</sup>.

In addition, switch therapy may have psychological and clinical benefits for the patient. Among these are decreased incidence of nosocomial infection (urinary tract and catheter-related infections), decreased complications of intravenous therapy (thrombophlebitis and line sepsis) and shorter length of hospital stay. It also results in lower drug acquisition costs, reduction in pharmacy drug preparation, no need for IV delivery systems to administer antibacterials and decreased nursing time<sup>6</sup>.

Our study deals with practical implication of lower cost antibiotic i.e. Amoxicillin/Clavulanate as compared to more costly Ceftriaxone, and the switch therapy resulting in decreased hospital stay, on the clinical outcome of patients with CAP and its impact on the cost involved. Our study demonstrated that average length of hospital stay in patients where intravenous to oral switch therapy was used much shorter as compared to the group where parenteral therapy was maintained (4.1 days in Amoxicillin/Clavulanate group versus 8.1 days in Ceftriaxone group). Since the clinical end points were comparable in both groups, it can be inferred that decreasing the length of hospital stay has no adverse impact on the clinical outcome provided the patients do not fall

under the category of severe CAP and have no markers of poor prognosis. This finding was consistent with the observations made by McCormick and colleagues<sup>7</sup> who prospectively studied 1,188 patients with CAP and concluded that the patient with the shorter stay of hospitalization had medical outcomes not different from those who had longer stay in the hospital.

Several investigations have shown that the institution of switch therapy may be safe and may have economic benefits as well. In their 12 month prospective study of CAP patients Laing and colleagues<sup>8</sup> found that an early switch from IV to oral antibiotic therapy resulted in significant reduction in length of hospital stay without compromising patient outcomes. Similar observations were made by Van Der Eerden et al<sup>9</sup>, Fernandez et al<sup>10</sup> and Castro-Guardiola et al<sup>11</sup> in their respective studies.

In this study significant cost savings were made by the use of Amoxicillin/Clavulanate, which is a cheaper antibiotic as compared to Ceftriaxone. Since the clinical efficacy obtained in the Amoxicillin/Clavulanate group was comparable to the Ceftriaxone group, it emphasizes the point that lower cost antibiotics should be used where possible in place of expensive antibiotics. This finding is consistent with the earlier observation made by Gilbert and colleagues<sup>12</sup> who analyzed the records of 927 inpatient and 1328 outpatients with and reported that patients treated at hospitals with lower antimicrobial costs do not demonstrate worse medical outcomes as compared to centers where costly antimicrobials were used.

The cost reductions in the treatment of CAP patients treated with switch therapy in our study are consistent with various studies carried out in United States and United Kingdom over past few years. Hendrickson and North<sup>13</sup> studied the economic benefits obtained by switching patients from intravenous Ceftriaxone to oral Cefpodoxime and demonstrated cost savings of \$46.05 per patient for antibacterial therapy as well as one-day reduction in hospital stay resulting in further saving of \$827 per patient. Ramirez and Ahkee<sup>14</sup>

studied the cost benefits associated with switching the patients of CAP from IV Ceftriaxone to oral Cefixime and reported net savings of \$1512 per patient.

One of the main objectives of our study was to evaluate the application of intravenous to oral switch therapy and its cost benefits. Whereas the concept of intravenous to oral switch therapy has been firmly established and recognized for its cost benefits all over Europe, United States, Australia and in certain Asian countries<sup>15</sup>, no studies have been done in Pakistan, to date, according to our knowledge, to evaluate its usefulness locally.

It may be argued that the patients in the Ceftriaxone group remained hospitalized for full seven days, although they improved similarly to the Amoxi-clavulanate group. The answer to this question is that the study was designed primarily to evaluate the cost benefits associated to intravenous to oral switch. It was not designed to prove the supremacy of one antibiotic over the other. Both, Ceftriaxone and Amoxi-clavulanate, are established efficacious medications with proven clinical efficacy. By proving that patients in both study groups had equivalent and comparable clinical improvement, we wanted to highlight the enormous economical benefits that the intravenous to oral switch therapy has to offer. Unfortunately this concept is not fully appreciated by healthcare providers in Pakistan and we frequently observe many patients that remain hospitalized on intravenous antibiotics, although they could be safely and in fact more efficiently managed as outpatients on oral therapy.

Some might feel that ceftriaxone could be given as intravenous in the outpatient department, but the concept of OPAT (Outpatient Parenteral Antibiotic Therapy) while gaining growing acceptance in certain European countries like Italy, is still not widely accepted elsewhere in the world.<sup>16</sup> In Pakistan, we do not have adequate resources and means to establish a meaningful OPAT program. Even if we had carried out intravenous Ceftriaxone injections as outpatient under study conditions, the results of the study would have not been ap-

plicable to a predominant majority of hospitals in Pakistan where OPAT facilities are virtually nonexistent. It can also be very dangerous to leave intravenous catheter left in place in patients with potential hazards of thrombophlebitis and line related sepsis.<sup>17</sup> Even in developed countries like United States there are continued questions about safety and effectiveness of OPAT programs. The value of OPAT is in doubt because of the lack of published information concerning outcomes and its impacts on patient care.<sup>18</sup> Efforts are being made in United States to develop outcome based OPAT registry to supervise such programs. It is obvious that in the absence of above mentioned monitoring facilities it will be hazardous to promote or encourage such OPAT options in Pakistan.

We agree that if we had carried out administration of intravenous Ceftriaxone injections as outpatient, costs benefits that were obtained in the Amoxi-clavulanate intravenous to oral switch group would have decreased but then we have to consider the costs involved in administration of OPAT program and outpatient facilities where patients could have their intravenous medications infused (Ceftriaxone injection is infused over 15 to 30 minutes). This would translate into provision of outpatient beds and intravenous infusion stands and other required miscellaneous facilities. All of this would contribute towards final cost.<sup>19</sup>

This study was not designed to evaluate the OPAT option but to address the application of intravenous to oral switch antibiotic regimes for community acquired pneumonia and to highlight the cost benefits associated with this. We believe that in a developing country like Pakistan widespread application of this concept of switch therapy would result in substantial cost benefits.

## CONCLUSION

Early intravenous to oral switch Amoxicillin/Clavulanate has comparable clinical efficacy to parenteral Ceftriaxone and resulted in reduced hospitalization stay and

decreased treatment costs and is a more cost effective treatment of community- acquired patients requiring intravenous antibiotics on admission.

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