Research Article

# A Study on Clinical Pharmacist Interventions in the Management of Sepsis in a Tertiary Care Hospital

**U. Aravind Krishnan[1], Rony Mathew[1], Ivy Jesse[1], Siby Joseph*[2a,b], Shyam Sundar P[3]**

[1]Pharm. D Interns, Dept of Pharmacy Practice, Amrita School of Pharmacy, AIMS Health Sciences Campus, Kochi, Kerala, India.

[2a]Asst. Professor, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.

[2b]Research Scholar, JJT University, Rajasthan, India.

[3]Clinical Additional Professor, Dept of Anaesthesiology, Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala, India.

***Corresponding author's E-mail:** sibymadappallil@gmail.com

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**ABSTRACT**

Sepsis is a disorder categorized by systemic response to infection that can swiftly lead to death. Drug Related Problems (DRPs) have been shown to be happening in hospitalized patients. In sepsis patients this may worsen prognosis. We aimed to analyse impact of clinical pharmacist's interventions on sepsis patients with objectives of identifying and resolving drug related problems (DRPs) if any. An interventional study was conducted and retrospective data of previous one year was taken as control group. Patients clinically diagnosed as sepsis with age ≥ 18 years and admitted in selected ICUs, were included but Patients who got discharged against medical advice were excluded. The selected medical record numbers by convenient sampling were randomized using graph pad software to get 100 samples in control group. Prospective cases that met study criteria and admitted every third day were recruited. In addition to documented evidence about each patient, direct interaction with patients and Health care providers (HCPs) were carried out during prospective data collection. An aggregate of 57 and 92 DRPs were identified from retrospective (100) and prospective populace (100) respectively. About 77.04% of problems could be totally resolved in consultation with HCPs. High acceptance rate of our interventions highlights the importance of clinical pharmacists working in tandem with other health care providers in critical care areas for better patient outcome. So a fulltime clinical pharmacist in intensive care units can provide a consistent level of pharmaceutical care with minimum drug related problems in life threatening conditions like sepsis.

**Keywords:** Drug related Problems, sepsis, intervention.

## INTRODUCTION

Sepsis is a clinical condition with a variety of increasingly severe manifestations. The term sepsis is the body's response to an infection that has moved beyond the local tissue to turn out to besystemic inflammatory response syndrome (SIRS) which swiftly lead to death.[1]

Severe sepsis or septic shock is a life-threatening, dysregulated physiologic and exaggerated inflammatory response to infection that carries a high risk of death. Management of severe sepsis is expensive; often including a number of modalities.[2] There is evidence that early detection and treatment of severe sepsis including delivery of antibiotics within one hour is associated with improved outcomes. The prompt administration of appropriate (pathogen susceptible) antibiotic is regarded as one of the most vital steps to care for these patients. It is also important to execute de-escalation strategies in the course of treatment.

Mortality is believed to increase by 7.6 percent for every hour delay in antibiotic administration. However, in a country like India, time to appropriate antibiotic administration remains very problematic.

The complexity of these patients, and a high health provider to patient ratio, as well as institutional delays in obtaining medication from the pharmacy department and administering the medication, often results in time to antibiotic administration of greater than one hour[3]. Also, most inpatient nursing units are not organized to deliver sepsis care in a one hour time frame. Administering a fitting empirical antimicrobial treatment within the first hour of diagnosis is aneconomical intervention with reduced mortality. Strategies have to be set up for the reduction of preventable ADRs. Such approaches include ensuring all the health professionals have good pharmacological knowledge, engaging adequate number of clinical pharmacists and computerising the whole prescription process.[4] Much of the progressive reduction in mortality rates for septic shock is related in part to prevention of iatrogenic complications.[5] Pharmacists are thus optimally placed to interact with a variety of health care professionals and they have manifold roles in management of patients with sepsis, severe sepsis or septic shock.[6]

Our study included patients who were clinically diagnosed for sepsis with age ≥ 18years and patients admitted in Gastrointestinal surgical ICU, Orthopedics-Neurosurgery ICU and medical ICUs. Patients who got discharged against medical advice and patient and/or their caregivers who are not willing to participate in the study were excluded.

Our main objectives were to assess the severity of sepsis using APACHE-II scoring system, to determine the predisposing factors and pathogens causing sepsis, to assess the therapeutic modalities in faring with sepsis, to

compare between early empirical antibiotic treatment and its accuracy with the culture sensitivity report, to identify the differences in outcome with and without de-escalation of antibiotics in sepsis measure the outcome by assessing the 28 day mortality after sepsis and to identify and resolve drug related problems (DRPs) if any.

### Methodology

We conducted an interventional study using retrospective data as control group. The patients were randomly selected based on inclusion and exclusion criteria. The clinical condition, microbiological culture sensitivity reports and other laboratory parameters were correlated to draw inferences. DRPs were analyzed and were classified according to the PCNE (Pharmaceutical Care Network Europe) Classification scheme for DRPs V6.2 which is the latest version. To analyse the severity of sepsis, a scoring system named as "APACHE-II scoring system" was employed. The APACHE II was measured using ClinCalc.com-an online evidence-based clinical decision support tools and calculators for medical professionals. Finally, the computed score was converted its respective percent mortality.

The impact of clinical pharmacists (CP) interventions in sepsis management with regards pharmacotherapy, interpretation of microbial culture sensitivity results, managing adverse drug events with associated drug related problems were reviewed.

## RESULTS

A total of 200 cases were selected as study sample based on convenient sampling with equal number of retrospective and prospective patients. Majority of patients were in the age group of 58 – 67 in both the population.

The male to female ratio corresponds to 8:2 in retrospective and 6:4 in prospective group. The statistical analysis for the age group didn't reveal any statistical significance (p=0.06) which means both the groups are comparable.

The comorbidities in study population, source of sepsis and the staging were assessed and the results are depicted in Table 1.

The bugs from the blood samples were identified and spotted out that when a slight drop in isolates of E. Coli were observed in prospective populace (9 in retrospective and 4 in prospective) an alarming trudge in *Klebsiellapneumoniae* (7 in retrospective and 12 in prospective) and *Pseudomonas aeruginosa* (3 in retrospective and 4 in prospective) has been perceived. Other single isolates of 20 microbes indorsed to sepsis in prospective group whereas only 4 in retrospective.

Gram negatives isolates were more attributed to sepsis than gram positive microbes (66 and 12 in retrospective and 78 and 22 in prospective).

**Table 1:** Demographic Characteristics of Subjects Included in the Study

| Characteristics | Number of Patients | |
|---|---|---|
| | Retrospective (n=100) | Prospective (n=100) |
| Female sex | 23 | 41 |
| Male sex | 77 | 59 |
| **Co-morbidities** | | |
| Cerebrospinal | 4 | 8 |
| Metabolic | 7 | 10 |
| Gastrointestinal | 28 | 21 |
| Oncologic | 17 | 15 |
| Renal | 30 | 28 |
| Respiratory | 14 | 18 |
| **Source of sepsis** | | |
| Ascitic fluid | 2 | 0 |
| BAL | 4 | 29 |
| Bile | 1 | 2 |
| Unknown source | 27 | 10 |
| Drain fluid | 1 | 2 |
| Peritonelfuid | 6 | 5 |
| Pleural fluid | 10 | 2 |
| Pus | 1 | 7 |
| Sputum | 12 | 4 |
| Skin and soft tissue | 10 | 6 |
| Urinary catheter/UTI | 26 | 33 |
| **Staging of sepsis** | | |
| Sepsis | 24 | 32 |
| Severe sepsis | 16 | 29 |
| Septic shock | 60 | 39 |

**Table 2:** PCNE Classification V 6.2 (implying on CAUSE) of DRPs

| Classification of DRPs | Retrospective | Prospective |
|---|---|---|
| Drug Selection | | |
| **C 1** | 22 | 42 |
| Drug Form | | |
| **C 2** | 4 | 6 |
| Dose Selection | | |
| **C 3** | 25 | 28 |
| Treatment Duration | | |
| **C 4** | 2 | 3 |
| Drug Use/Administration Process | | |
| **C 5** | 3 | 7 |
| Logistics | | |
| **C 6** | 1 | 1 |
| Patient | | |
| **C 7** | 0 | 2 |
| Other | | |
| **C 8** | 0 | 3 |
| Total | 57 | 92 |

**Table 3:** PCNE Classification V 6.2 (Implying on Interventions) of DRPs

| Classification of Interventions | Interventions that could have been done in Retrospective group | Interventions that were carried out in Prospective group |
|---|---|---|
| I 3.1 (Drug changed to) | 9 | 8 |
| I 3.2 (Dosage changed to) | 26 | 28 |
| I 3.3 (Formulation changed to) | 3 | 4 |
| I 3.4 (Instruction for use changed to) | 7 | 12 |
| I 3.5 (Drug stopped) | 5 | 20 |
| I 3.6 (New drug started) | 7 | 20 |
| **Total** | **57** | **92** |

**Pattern of Antibiotic Usage in Managing Sepsis**

Piperacillin/tazobactam was the mostly used (37 each in retrospective and prospective) empirical antibiotic in sepsis management followed by meropenem (14 in retrospective and 31 in prospective), cefoperazone/sulbactam 26 in retrospective and 17 in prospective), clindamycin (13 in retrospective and 12 in prospective) and ceftriaxone (10 in retrospective and 12 in prospective).

The empirical versus definitive antibiotic therapy in managing sepsis was also discerned. Only 69% of the cultures were positive in retrospective and 82% were positive in prospective populace. It was observed that empirical antibiotic selection in the prospective cohort was more identical to definitive therapy (56.5%) than in the retrospective group (43.5%).

A total of 57 and 92 DRPs were identified from retrospective and prospective populace respectively. Table 2.summarizes the DRPs observed which were categorised as per PCNE guidelines.

The major cause of DRPs was on drug selection followed by dose selection, drug use/administration process, and drug form and treatment duration. Besides these, patient related and other (miscellaneous) causes for DRPs were also identified in prospective group.

Table 2 refers the DRPs in retrospective and prospective populace. Deterioration/improvement of disease state requiring dose adjustment (C 3.7) remained as a

prominent problem. Inappropriate drugs, dose and duration of drugs in targeting pharmacotherapy of sepsis were also a notable issue.

The retrospective data were perused to identify the possible DRPs encountered and the methodologies were so designed to counter those setbacks by the practice of CPs interventions.

Table 3 encapsulates the CPs recommendations with the number of interventions accepted, rejected, modified and accepted, accepted but not changed. The most intervention done is the 'change in dosage' (I3.2) followed by 'new drug started' (I3.6) and 'drug stopped' (I3.5). Interventions under 'instruction for use changed to' (I3.4) could be identified more while prospective sampling and appropriate suggestions were made.

The outcomes of the interventions were also tabulated based on PCNE guidelines. About 77.04% of the problems could be totally solved but the remaining couldn't be solved due to multiple factors and/or reasons (Eg: rejection of an intervention by physician, impact of socio-economic factors).

Analysis of statistical significance using a chi-square test reported as there is a significant difference (p=<0.001) between DRPs in both the population.

The interventions by CPs on dosage adjustment (30.43% of acceptance, n=28) was made on status of subjects kidney (with Cockroft-Gault equation) and liver function tests (with Child Pugh class) and also based on standard dosing recommendation guidelines.

Interventions on new drug started and drug stopped accounts for 21.73% (n=20) each, followed by 10.86% (n=10) in changing the instructions for usage of drugs and 8.69% (n= 8) in the drug selection.

The ADRs were scored on basis of Naranjo scale and out of 7 in retrospective, 2 were possible and 5 were probable and out of 12 in prospective, 9 were probable and 3 were possible.

Drug induced blood dyscrasias was the major ADR observed with a frequency of 2.5% trailed by antibiotic induced diarrhea as well as steroid induced hyperglycemia (2%), followed by drug induced electrolyte disturbances, acute kidney injury and seizures (≤1.5%).

**APACHE II Score**

Only 182 cases had all the necessary variables for APACHE II score calculation. The results revealed that 77 out of the 182 patients were alive whereas 105 patients died. The mean APACHE II score was 23.30 ± 7.91 (estimated mortality 47.35% ± 0.23%) in retrospective and 19.94 ± 7.16 (estimated mortality 37.77% ± 0.21%) in prospective group.

The actual mortality rate was also correlated with APACHE II score and it was ascertained that as the score increased, the actual mortality rates were also increased. The results are as presented in the Figure 1.

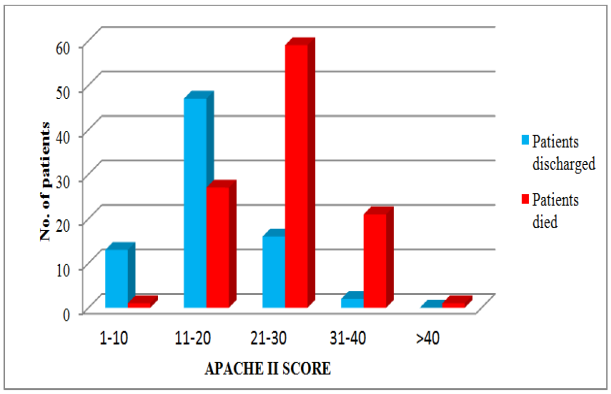


**Figure 1:** Relationship of APACHE II Score with the Outcome of Patients (n=182)

**Table 4:** Relation between APACHE Scores and DRPs

| APACHE SCORES (No of Patients) | Total No of DRPs |
|---|---|
| 1 to 10 (14) | 121.42% |
| 11 to 20 (74) | 64.00% |
| 21to 30 (75) | 74.32% |
| 31to 40 (23) | 56.52% |

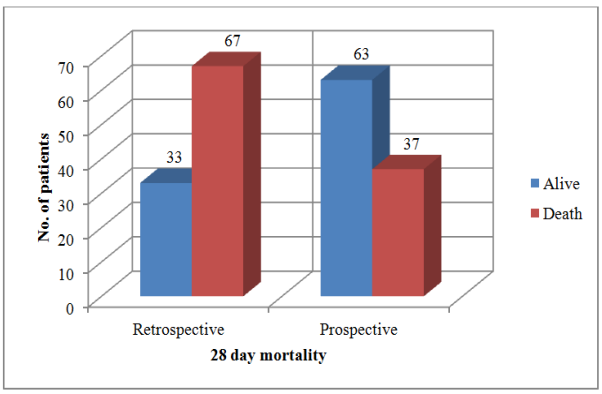


**Figure 2:** Comparison of 28 day Mortality among the Study Groups.

When analysed, it was found that there is slight increase in rate of DRPs with increase in the APACHE scores in the 11 to 20 and 21 to 30 score ranges. DRPs were not comparable to obtain accurate results in the 1 to10 and 31 to 40 score ranges due to less number of cases in them. Results are shown in Table 4.

The analysis of 28 day mortality among the study sample suggests that a 30% reduction in mortality within 28 days in prospective populace. The overall survival also hiked from 32% to 57% in the test group.

**De-escalation of Antibiotics**

As soon as the culture results were available, the spectrum of antibiotics was narrowed and de-escalation was assessed. When 5 such de-escalation was done in

retrospective group, 9 were done in prospective group by active interventions of clinical pharmacist.

## DISCUSSION

Sepsis has been around since the dawn of time, having been described for more than 2000 years, although clinical definitions are recent.[7] Severe sepsis as well as septic shock represents one of the oldest and most pressing problems in medicine. To determine the prognostic value of pre-existing comorbidities in the outcome of septicaemia in critically ill patients, Pittet[8] did a five year retrospective study in the ICUs of a tertiary care centre in Switzerland. Their observation was that prognostic factors associated with mortality from septicaemia were older age, higher admission APACHE II score, gastrointestinal surgery, rapidly fatal diseases and the number of co-morbidities. It was concluded that APACHE II and co-morbidities were identified as the two independent predictors of mortality. In our study, it was perceived that the conditions related to renal problems (29%) like acute and chronic renal failure, pyelonephritis and renal cell carcinomas were predominant in both the groups in sepsis population. This is followed by gastrointestinal ailments (24.5%) such as chronic liver disease, hepatitis and biliary issues; respiratory diseases (16%) oncologic disorders (16%). Metabolic disorders (8.5%) embraced diabetes mellitus, was found to be a common comorbidity. Cumulative comorbidities were associated with greater acute organ dysfunction and mortality.

Vincent JL[9] in a multiple-centre study assessed the common sites of infection in sepsis. They identified lung as the most common site of infection (68%). Even though our study was single centered and only cases of selected ICUs were analyzed, consonant results indicative of the leading primary sites of infections that led to sepsis were chest-related infections representing the respiratory source (35.10% in retrospective and 36% in prospective). Pneumonia, asthma, severe immunodeficiency diseases contributed towards respiratory source. Patients with sepsis and more organ dysfunction had a higher mortality rate (75.2%) than patients with simple sepsis (15.05%). In patients with sepsis, age, positive fluid balance, septic shock, cancer and immuno suppressed conditions were the important prognostic variables for intensive care unit mortality.

On perceiving antibiotic utilizations, it was detected that Piperacillin/tazobactam was the mostly used (37 each in retrospective and prospective) empirical antibiotic in sepsis management followed by meropenem (14 and 31), cefoperazone/sulbactam (26 and 17), clindamycin (13 and 12) and ceftriaxone (10 and 12). The empirical versus definitive antibiotic therapy in managing sepsis was also discerned and observed the empirical antibiotic selection in the prospective cohort were more identical to definitive therapy (56.5%) than in the retrospective group (43.5%). This probably is due to the administration of suitable loading doses, dose optimization and selection of antibiotic combinations. This substantiates the presence of a clinical pharmacist can aid the physicians in selecting the right antibiotic in managing condition like sepsis.

The acceptance and/or response of HCPs towards CPs interventions were weighed. Lucca JM[10] performed an interventional study in a tertiary care hospital in India to assess the impact of clinical pharmacists (CPs) intervention on DRPs in 895 patients over a 7 month period in a medical and surgical ICUs and most of the problems were regarding inappropriate drug dosing (25%). They received a fairly good rate of acceptance of 85% and they concluded the study by stressing the need for a CP's have greater potential in preventing and/or minimizing the DRPs. On similar grounds, in our study HCPs response to CPs interventions displayed a reasonable percentage of acceptance of 77.04%. The interventions by CPs on dosage adjustment (30.43% of acceptance, n=28), which topped the list, was made on status of subjects kidney (with Cockroft Gault equation) and liver function tests (with Child Pugh class) and also based on standard dosing recommendation guidelines. Interventions on new drug started and drug stopped accounts for 21.73% (n=20) each, followed by 10.86% (n=10) in changing the instructions for usage of drugs and 8.69% (n= 8) in the drug selection.

The DRPs were evaluated and classified in accordance to the PCNE system and this was employed for further analysis. Deterioration/improvement of disease state requiring dose adjustment (C 3.7) remained as a prominent problem (10 in prospective and 8 in retrospective). Majority of them were being failure to give loading doses of antibiotics or incorrect dosing such as for Teicoplanin, Tigecycline, Meropenem and Colistin; inaccurate dosage adjustment in renal and hepatic impairment, cases especially for antibiotics. Inappropriate drugs, dose and duration of drugs in targeting pharmacotherapy of sepsis were also a notable issue. Inappropriate antibiotic dosing even in susceptible microbes leads to the phenomena of antimicrobial resistance which is already a global issue.

## CONCLUSION

Our study detected a significant number of DRPs where, the major causes of DRPs were on drug selection followed by dose selection, drug use/administration process, drug form and treatment duration. The high acceptance rate of our intervention highlights the importance of clinical pharmacists working in tandem with other health care providers for better patient outcome. So if a fulltime clinical pharmacist is appointed in the intensive care units a consistent level of pharmaceutical care can be ensured with minimum drug related problems.

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