A retrospective study to evaluate the efficacy of a new antibiotic adjuvant entity (β-lactam/β-lactamase inhibitor/adjuvant disodium edetate combination) for management of sepsis

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Abstract

Aim and objective: The management of patients with sepsis and septic shock requires an integrated approach of accurate diagnosis along with rapid initiation of appropriate antimicrobial therapy. Here we present a retrospective analysis of a new therapy opted and outcome of the patients suffering from gram negative bacterial sepsis.

Materials and methods: A retrospective study was conducted to evaluate efficacy of new antibiotic adjuvant entity (Ceftriaxone+sulbactam+adjuvant disodium edetate) in 45 patients (showing sensitivity to AAE) with gram negative bacterial sepsis, treated at tertiary-care hospital between March 2013 to December 2014. AAE therapy was initiated empirically and continued based on the results of the in-vitro microbiological susceptibility testing and clinical outcome.

Results: Out of 45 patients, 37 (82.22%) patients were diagnosed with bacterial infections, which are susceptible to AAE, where as the 8 (17.18%) bacteria showed intermediate susceptibility towards AAE. Out of 37 patients treated with AAE, successful clinical response was observed in 25 (67.56%) patients with AAE alone, while in remaining 12 patients clinical cure was achieved with AAE and Colistin combination therapy. 08 patients with bacteria showing intermediate susceptibility towards AAE were successfully cured with AAE and colistin combination therapy.

Conclusion: AAE with its adjuvant and beta lactam/beta lactamase inhibitor combinations has the potential to be considered as a safe and efficient treatment option against gram negative bacterial sepsis. It provided clinical and microbiological cure both in mono and combination therapy used against gram negative bacterial sepsis.

Keywords: Ceftriaxone/sulbactam-disodium edetate, gram negative bacterial infections, sepsis, retrospective study

Introduction

Nosocomial or health care-associated gram negative infections account for a high morbidity and mortality rate among hospitalized patients [1]. It is estimated that in 2002, a total of 1.7 million hospital-acquired infections occurred (4.5 per 100 admissions) and almost 99,000 deaths resulted from or were associated with a hospital-acquired infection [2], making hospital-acquired infections the sixth leading cause of death in the United States [3]. The situation is even more alarming in developing countries like India. Bacterial Sepsis is a systemic inflammatory response syndrome (SIRS) occurring in presence of suspected or proven infection [4]. It is the second most common cause of death in non- coronary intensive care units (ICU) and the tenth overall cause of death in high income countries [5,6]. The incidence of sepsis in the past two decades has annually increased by 9%, to reach 240 per 100 000 people in the USA by 2013 [7,8]. Some of the most frequently isolated gram negative bacteria in sepsis are Klebsiella spp., Escherichia coli (E. coli), and Pseudomonas aeruginosa (P. aeruginosa) [9]. Endotoxin (LPS) is a major component of the outer membrane of gram
negative bacteria and a critical factor in the pathogenesis of
gram negative bacterial sepsis [10]. Sepsis is a serious medical
condition which require immediate medical attention. The
probable etiology is immunological response of human body
towards different infections in the lungs, urinary tract, skin,
abdomen or other part of the body with or without invasive
medical procedures like the insertion of catheter/ stent etc.
These infections can introduce bacteria into the bloodstream
which ultimately adversely affects all body organs functioning
and can result in multi organ complication/ failure and death.

Gram negative pathogens are highly efficient at up-regulating
or acquiring genes that code for mechanisms of antibiotic
drug resistance, especially in the presence of antibiotic selec-
tion pressure [11]. Multi drug-resistant Gram-negative bacteria
have emerged as a major threat to hospitalized patients and
have been reported to be associated with mortality rates
ranging from 30 to 70% [12-18]. Decade ago, cephalosporins
along with other antibiotics were the drug of choice for sepsis
management which later shifted to carbapenems due to
emergence of resistant stains [19,20]. This is mainly because

carbapenems are not inactivated by these enzymes in vitro
and have been demonstrated to have adequate effectiveness for
the treatment of serious Gram-negative bacterial infections
at various body sites till date [20,21]. However in past few years,
carbapenem resistance among gram negative bacteria has
been reported increasingly throughout the world and India
[22-27]. This carbapenem resistance is mainly attributed to
the ability of the bacteria to produce MBL enzymes (carbap-
emases) and due to efflux of penems by smart bacteria. In
India, the prevalence of MBLs range from 8% to 79% [28-31].

Use of adjuvants along with beta lactam and beta lactamase
inhibitor combinations is a new approach to treat these multi
drug resistant bacterial infections [32]. Fixed dose combination
of Ceftriaxone+ sulbactam+ adjuvantedisodium edetate is one
such novel antibiotic adjuvant entity (AAE) approved by the
Drug Controller General of India (DCGI) and increasingly used
in Indian hospitals. Thus in view of all growing resistance to
standard of care for sepsis management, rising therapy
failures, newer therapies were evaluated for their safety and
efficacy in sepsis. Present study is a retrospective analysis of
the clinical and microbiological efficacy of AAE mono-therapy
and AAE plus colistin combination therapy in management of
gram negative sepsis.

Materials and methods
Patients and antibiotic therapy
Study was conducted at 200 bedded tertiary care hospital. We
retrospectively reviewed data of clinically cured patients in
whom AAE was used empirically for management of sepsis.

Data of 50 patients (Figure 1) suffering from Gram negative
bacterial sepsis like abdominal, respiratory and urosepsis, who
were treated between March 2013 to December 2014 were
evaluated. These patients were administered with a novel
antibiotic adjuvant entity AAE, (Ceftriaxone+ sulbactam+EDTA)

BID empirically, herein after termed as AAE. Among evaluated
50 patients, 45 clinically cured patients, showing sensitivity to-
wards AAE were considered in the study, while the rest 05 (AAE
resistant) patients were excluded from the study. Characters
like gender, age, infection type, source of infection, causative
pathogen, dosage and regime of antibiotic therapy for these
patients were recorded. AAE was initially started empirically
based on the clinical presentation and treating physician’s
decision and was continued or shifted based on the in-vitro
microbiological susceptibility report and clinical response.
A dose of 3.0 g/12 hours of AAE was used and in cases were
patients were more critical or failed to respond to AAE alone,
colistin therapy with a loading dose of 9 MIU followed by BD
doses of 4.5 MIU were used along with previous antibiotic.

On retrospective evaluation based on microbial suscepti-
bility patients were divided in two groups. Patients showing
susceptibility to AAE 37 (82.22%) were kept in Group G-1,
where as the remaining 08 (17.77%) cultures showing inter-
mediate susceptibility were kept in Group G-2. On day 03 of

treatment, along with bacteriological evaluations, the progress
of the therapy (measured in terms of the improvement in
the clinical signs and symptoms) was also recorded. Patients
showing improvement in clinical signs and symptoms (like
stabilization of vital signs and lab parameters) AAE empiric
therapy was continued. Patients which failed to respond to
AAE mono-therapy clinically (showing no/less improvement)
despite microbial sensitivity, were switched to AAE and colistin
combination therapy. Group G2 patients, showing interme-
diate susceptibility towards AAE were treated with colistin
along with the empiric AAE after 3rd day till end of therapy.

In-vitro microbial antibiotic susceptibility testing
Antimicrobial susceptibility testing of the pathogens isolated
from the patients was done by Kirby–Bauer disk diffusion
method as recommended by the Clinical Laboratory Standards
Institute (CLSI) guidelines (2012) [33]. Meropenem disk (10

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Clinical analysis of patients
Patient’s clinical status was evaluated based on the clinical signs and symptoms associated with Gram negative bacterial sepsis like fever, chills, decreased urination, hypo tension, rapid pulse rate, increased heart beat, nausea, vomiting diarrhoea, difficulty in breathing, deranged laboratory parameters like low hemoglobin, platelet count, increased/decreased total leukocyte count, deranged LFT and RFT depending upon the type of original infection (origin of sepsis: respiratory, abdominal or urosepsis). The signs symptoms and laboratory parameters of base line visit, after 3 days of AAE empirical antibiotic therapy and also the end of therapy were evaluated. BAL, ET secretions, urine or blood samples from the patients were tested for the diagnosis of causative pathogens. Clinical response of the therapy evaluated at the end of the treatment was recorded and classified as cured (complete remission of local and systemic signs and symptoms), improved (improvement of local and systemic signs and symptoms but without complete resolution) or failure (no improvement or deterioration of signs and symptoms).

Results
Patients and demographic characteristics
45 clinically cured patients out of 50 patients taken retrospectively, in the considered study period at a tertiary care hospital were diagnosed with infections with AAE sensitive pathogens. The demographic and baseline characteristics of these 45 patients whose data were analysed in this study are given in Table 1. Respiratory sepsis was the most predominant infection diagnosed, contributing a share of 46.66% (21) among the 45 treated patients. Respiratory sepsis was followed by urosepsis observed in 17 (37.77%) patients. However abdominal sepsis was in 07 (15.55%) patients which is comparatively low than other two sepsis types (Table 1). Among the 45 single pathogen cultures were showing intermediate susceptibility towards AAE and the remaining 5 were resistant to it. Among these 45 pathogens, 37 (82.22%) were susceptible to AAE and 08 (17.18%) showed intermediate susceptibility. Among the isolated pathogens highest susceptibility towards AAE was observed in E coli (88.23%) and Pseudomonas sp. (85.71%) closely followed by Acinetobacter sp. (77.77%) and Klebsiella sp. (75%). Ertapenem and Meropenem were equally susceptible against E coli with 88.23% and 77.47% susceptibility respectively. However, the remaining pathogens showed less susceptible to penems indicating either prevalence of metallo betalactamases or efflux type resistance usually observed in penems. Doripenem, although a newer penem was found to be the least susceptible drug (Table 2). However all the tested pathogens showed low non significant (<10%) susceptibilities towards the other tested antibiotics (data not shown).

Efficacy of antibiotic therapy
All the 45 patients considered for the study were given AAE empirically. Among these, 37 patients of group 1 which were identified with AAE susceptible bacterial infections with signs of clinical improvement, were continued with the same treatment. Successful clinical response was observed in 25/37 patients at the end of mono therapy. The mean treatment duration among these 25 patients cured with AAE therapy was (9.6 days±1.44 (SD)). 12 Patients, which failed to respond to AAE clinically (showing less improvement clinically) after 3 days, were switched to AAE and colistin combination therapy. The mean treatment duration among these 12 patients cured with AAE and colistin combination therapy was (11.33 days±2.26 (SD)) (Table 3). All the patients of group 2 (8 patients) whose cultures were showing intermediate susceptibility towards AAE and shifted to AAE plus colistin combination therapy, were cured. The mean treatment duration among these 08 patients cured with AAE and colistin combination therapy was (12.87 days±2.53 (SD)) (Table 4). Overall it was found that 55.55% cases were cured with AAE monotherapy and 44.55% cases with AAE and colistin combo therapy.

### Table 2. Demographics characteristics of the patients treated during the study period.

| Characteristic         | Value |
|------------------------|-------|
| Evaluable patients     | 45    |
| Age, mean year SD      | 56.88±13.77 |
| No. male:female        | 29:21 (58%;42%) |
| **Type of infection (%)** |
| Abdominal sepsis       | 07 (15.55%) |
| Respiratory sepsis     | 21 (46.66%) |
| Urosepsis              | 17 (37.77%) |
| Sepsis due to *E coli* | 17 (37.77%) |
| Sepsis due to *Klebsiella sp.* | 12 (26.66%) |
| Sepsis due to *Pseudomonas sp.* | 09 (20.00%) |
| Sepsis due to *Acinetobacter sp.* | 07 (15.55%) |

### Table 1. In-vitro microbial antibiotic susceptibility testing

The results of *In-vitro* microbial antibiotic susceptibility testing carried out for isolated pathogens against AAE and different antibiotics are depicted in Table 2. Among the 50 patients evaluated, cultures isolated from 45 patients showed sensitivity towards AAE and the remaining 5 were resistant to it. Among these 45 pathogens, 37 (82.22%) were susceptible to AAE and 08 (17.18%) showed intermediate susceptibility. Among the isolated pathogens highest susceptibility towards AAE was observed in *E coli* (88.23%) and *Pseudomonas sp.* (85.71%) closely followed by *Acinetobacter sp.* (77.77%) and *Klebsiella sp.* (75%). Ertapenem and Meropenem were equally susceptible against *E coli* with 88.23% and 77.47% susceptibility respectively. However, the remaining pathogens showed less susceptible to penems indicating either prevalence of metallo betalactamases or efflux type resistance usually observed in penems. Doripenem, although a newer penem was found to be the least susceptible drug (Table 2). However all the tested pathogens showed low non significant (<10%) susceptibilities towards the other tested antibiotics (data not shown).
Table 2. *In-vitro* antibiotic susceptibility testing for isolated bacteria.

| S. No | Isolated pathogens | Number of individual isolates | Susceptibility/resistance % |
|-------|--------------------|-------------------------------|-----------------------------|
|       |                    |                               | AAE | Meropenem | Doripenem | Ertapenem |
|       |                    |                               | S  | I    | S  | I    | S  | I    |
| 1     | *E. coli*          | 17                            | 88.23 | 11.77 | 76.47 | 23.53 | 58.82 | 41.18 | 88.23 | 11.77 |
| 2     | *Klebsiella sp.*   | 12                            | 75 | 25     | 41.66 | 58.33 | 50 | 50     | 58.33 | 41.67 |
| 3     | *Acinetobacter sp.* | 09                          | 77.77 | 22.23 | 44.44 | 55.55 | 55.55 | 44.45 | 44.44 | 55.55 |
| 4     | *Pseudomonas sp.* | 07                           | 85.71 | 14.28 | 57.14 | 42.86 | 14.28 | 85.72 | 28.57 | 71.42 |

S: Susceptibility; I: Intermediate susceptibility

Table 3. Summary of antibiotic therapy for the patients with cultures susceptible to AAE.

| S. No | Age | Organism       | AAE dose (g) | Duration (days) | Clinical response | Therapy shifted to AAE+Colistin (MICU loading and 4.5 MIU BID) | Duration (days) | Clinical response |
|-------|-----|----------------|--------------|-----------------|-------------------|---------------------------------------------------------------|----------------|-------------------|
| 1     | 44  | *Pseudomonas sp.* | 3.0          | 9               | Cured             | NA                                                            | NA             | NA                |
| 2     | 81  | *E. coli*       | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 6              | Cured             |
| 3     | 59  | *Klebsiella sp.* | 3.0          | 9               | Cured             | NA                                                            | NA             | NA                |
| 4     | 78  | *Klebsiella sp.* | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 9              | Cured             |
| 5     | 52  | *Klebsiella sp.* | 3.0          | 8               | Cured             | NA                                                            | NA             | NA                |
| 6     | 55  | *Acinetobacter sp.* | 3.0          | 11              | Cured             | NA                                                            | NA             | NA                |
| 7     | 74  | *Acinetobacter sp.* | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 11             | Cured             |
| 8     | 71  | *E. coli*       | 3.0          | 9               | Cured             | NA                                                            | NA             | NA                |
| 9     | 69  | *Klebsiella sp.* | 3.0          | 12              | Cured             | NA                                                            | NA             | NA                |
| 10    | 39  | *E. coli*       | 3.0          | 9               | Cured             | NA                                                            | NA             | NA                |
| 11    | 45  | *Klebsiella sp.* | 3.0          | 10              | Cured             | NA                                                            | NA             | NA                |
| 12    | 61  | *Klebsiella sp.* | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 7              | Cured             |
| 13    | 52  | *Klebsiella sp.* | 3.0          | 8               | Cured             | NA                                                            | NA             | NA                |
| 14    | 59  | *Pseudomonas sp.* | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 12             | Cured             |
| 15    | 62  | *Acinetobacter sp.* | 3.0          | 9               | Cured             | NA                                                            | NA             | NA                |
| 16    | 48  | *Acinetobacter sp.* | 3.0          | 11              | Cured             | NA                                                            | NA             | NA                |
| 17    | 81  | *Klebsiella sp.* | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 10             | Cured             |
| 18    | 57  | *E. coli*       | 3.0          | 9               | Cured             | NA                                                            | NA             | NA                |
| 19    | 64  | *E. coli*       | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 6              | Cured             |
| 20    | 41  | *Pseudomonas sp.* | 3.0          | 12              | Cured             | NA                                                            | NA             | NA                |
| 21    | 37  | *E. coli*       | 3.0          | 10              | Cured             | NA                                                            | NA             | NA                |
| 22    | 56  | *E. coli*       | 3.0          | 9               | Cured             | NA                                                            | NA             | NA                |
| 23    | 35  | *Pseudomonas sp.* | 3.0          | 8               | Cured             | NA                                                            | NA             | NA                |
| 24    | 44  | *E. coli*       | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 5              | Cured             |
| 25    | 78  | *E. coli*       | 3.0          | 8               | Cured             | NA                                                            | NA             | NA                |
| 26    | 46  | *E. coli*       | 3.0          | 13              | Cured             | NA                                                            | NA             | NA                |
| 27    | 58  | *Pseudomonas sp.* | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 9              | Cured             |
| 28    | 58  | *E. coli*       | 3.0          | 3               | Failure           | 3.0 g AAE+colistin                                            | 9              | Cured             |
| 29    | 49  | *Acinetobacter sp.* | 3.0          | 10              | Cured             | NA                                                            | NA             | NA                |
| 30    | 63  | *E. coli*       | 3.0          | 8               | Cured             | NA                                                            | NA             | NA                |
Continuation of Table 3.

| S. No | Age | Organism         | AAE dose | Duration (days) | Clinical response | Therapy shifted to AAE+Colistin Duration (days) | Clinical response |
|-------|-----|------------------|----------|-----------------|-------------------|-----------------------------------------------|-------------------|
| 31    | 70  | Acinetobacter sp.| 3.0 g    | 3               | Failure           | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 10                | Cured             |
| 32    | 41  | E coli           | 3.0 g    | 11              | Cured             | NA                                            | NA                | NA                |
| 33    | 54  | Klebsiella sp.   | 3.0 g    | 9               | Cured             | NA                                            | NA                | NA                |
| 34    | 66  | E coli           | 3.0 g    | 9               | Cured             | NA                                            | NA                | NA                |
| 35    | 30  | Pseudomonas sp.  | 3.0 g    | 3               | Failure           | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 6                 | Cured             |
| 36    | 59  | E coli           | 3.0 g    | 11              | Cured             | NA                                            | NA                | NA                |
| 37    | 32  | Pseudomonas sp.  | 3.0 g    | 8               | Cured             | NA                                            | NA                | NA                |

Table 4. Summary of antibiotic therapy for the patients with cultures intermediate susceptible to AAE.

| S. No | Age | Organism         | AAE dose | Duration (days) | Therapy shifted to AAE+Colistin Duration (days) | Clinical response |
|-------|-----|------------------|----------|-----------------|-----------------------------------------------|-------------------|
| 1     | 49  | Klebsiella sp.   | 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 8                 | Cured             |
| 2     | 86  | Pseudomonas sp.  | 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 8                 | Cured             |
| 3     | 77  | Klebsiella sp.   | 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 13                | Cured             |
| 4     | 63  | Klebsiella sp.   | 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 6                 | Cured             |
| 5     | 58  | Pseudomonas sp.  | 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 9                 | Cured             |
| 6     | 55  | E coli           | 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 11                | Cured             |
| 7     | 49  | Acinetobacter sp.| 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 13                | Cured             |
| 8     | 55  | E coli           | 3.0 g    | 3               | 3.0 g AAE+colistin (9 MIU loading and 4.5 MIU BID) | 11                | Cured             |

Discussion

Gram negative bacteria have often been implicated in the pathogenesis of sepsis and septic shock [34]. Sepsis is the number one cause of deaths in the intensive care unit accounting for some 200,000 fatalities in the US annually. Sepsis incidences continues to rise in US [35] and worldwide [36], perhaps due to increased invasive procedures, immunosuppression, and drug resistance. Mortality associated with sepsis, unfortunately, has essentially remained unchanged at about 45% [37], despite tremendous strides in antimicrobial chemotherapy, pointing to the absence of therapeutic strategies aimed specifically at the pathophysiology of sepsis. The current data represents the retrospective study of 45 gram negative sepsis patients who were treated with novel AAE either as mono or combination therapy right from the diagnosis.

In-vitro microbial antibiotic susceptibility testing of the bacteria isolated from the 45 patients yielded 2 group of bacteria; G1—the bacteria which are susceptible to AAE and G2—the bacteria showing intermediate susceptibility towards AAE. Out of 37 patients, 25 (67.56%) patients of group G1, which were treated with AAE achieved clinical success. These results advocate the consistency of in vitro and in vivo results. A higher percentage of the clinical cure rates justifies the selection of AAE for the empirical therapy, because delayed appropriate antibiotic therapy is known to be strongly associated with increased mortality in patients with septic shock [38]. Thus the appropriate empirical therapy is required to reduce the mortality rates in sepsis infections. In 12 (32.43%) patients, who failed respond to the AAE empirical therapy, clinical success was achieved when colistin was given along with AAE as a combination therapy. Similar results with complete clinical success was achieved, in the patients with AAE intermediate susceptible bacterial infection, when AAE and colistin combination therapy was used. The efficiency of AAE and colistin combination therapy might be because of the synergy between the two drugs. The mechanisms of synergy are often not fully understood, however it is believed that, colistin, increases the permeability of other antibiotic through the bacterial outer membrane by a detergent mechanism [39]. This mechanism can counteract acquired resistance mediated by decreased antibiotic permeability (e.g., porin loss), and will also enable antibiotics which fail to act in case of severe
bacterial infections like sepsis [40]. The clinical success results obtained with the AAE and colistin combination therapy are justifiable by the support of the previous reports. Combination therapy for suspected sepsis and severe gram-negative infections typically includes a broad-spectrum beta-lactam and colistin [41-45].

Conclusion
The present retrospective study generated a representative status of the susceptibility among gram negative pathogens isolated from sepsis infections and its effective management using cabapenem sparing therapy of novel AAE with or without colistin. The major aspects emerged from the present study are, the rise of the carbapenem resistance incidences among the pathogens isolated from sepsis, proved efficacy of new AAE (both in mono as well as in combination with colistin) to treat the infections caused by gram negative bacteria. The present study advocates the high efficacy of beta lactam and beta lactamase inhibitor combinations with an adjuvant in both mono and combination therapies.

Competing interests
The author declares that he has no competing interests.

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