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Elores Publications
Mann Ki Baat: Prime Minister Highlights Problem of Antibiotics in India

In his radio address “Mann Ki Baat” on 26 July 2016 Sunday, Prime Minister Narendra Modi spoke about the menace of antibiotic resistance (ABR) and the urgent need to tackle it.

During the programme, the PM said that unnecessary consumption of antibiotics was adding on to the problem of ABR. Explaining how overuse and underuse of antibiotics on a regular basis makes microbes stronger, Modi urged people not to resort to antibiotics for quick relief without prescriptions.

Prime Minister Narendra Modi used his Mann ki Baat radio address to warn against faulty and unnecessary intake of antibiotics, which is pertinent for a country where, annually, around 58,000 neonatal deaths—as per a PLOS Medicine study—can be attributed to sepsis resistant to first-generation antibiotics. For some diseases, resistance has galloped — fluoroquinolone resistance in *Salmonella typhii*, the bacteria that causes typhoid rose from 8% in 2008 to 24% in 2014 while carbapenem resistance in *Klebsiella pneumoniae*, the pathogen behind one of the most common hospital-acquired infections, increased from 2% to 52% between 2002 and 2009. Meanwhile, the same PLOS study finds that Indians remain one of the largest consumer of antibiotics across the world.
Storm Signals: Rising Carbapenem Resistance

Resistance to a wide variety of common antimicrobials made the proliferation of Extended Spectrum β-Lactamase (ESBL) producing strains a serious global health concern that complicated treatment strategies. High prevalence of ESBL producing pathogens has been reported in the last decade. 60-70% *E.coli* and 40-60% *Klebsiella spp.* are found to be ESBL producers in studies published in 2010. Carbapenems were the drug of choice to counter these resistant pathogens. However, rise in carbapenem consumption has lead to a steady rise in incidence of the infamous carbapenem resistant New Delhi Metallo-β-lactamase (NDM).

The rapidity with which new types of antibiotic resistance can disseminate globally following their initial emergence or recognition is exemplified by the NDM. The first documented case of infection caused by bacteria producing NDM occurred in 2008. Since its first description, NDM carbapenemase has been reported from 40 countries worldwide, encompassing all continents except South America and Antarctica. The spread of NDM has a complex epidemiology involving the spread of a variety of species of NDM-positive bacteria and the inter-strain, inter-species and inter-genus transmission of diverse plasmids containing bla NDM, with the latter mechanism having played a more prominent role. Already the prevalence of carbapenem resistance in India varies from 12–60% as per recent studies. Very few options remain for the treatment of these virulent pathogens. At this pace, untreatable infections could emerge on a large scale and the world may experience in some cases dramatic situations of the pre-antibiotic era. Already, clinicians in endemic areas routinely encounter patients with infections that do not respond to available treatments and laboratories often report MDR or even PDR bacteria. In the USA alone, 2 million people acquire serious infections due to antibiotic-resistant bacteria each year and according to the Centers for Disease Control and Prevention (CDC), 23,000 of them die as a result. If this is the scenario in a highly developed nation like the USA, in a developing nation such as India with an enormously large population, one can only wonder how situation will unfold which is brewing underneath over the last few years.

 Particularly, it has been known that with the continued excessive usage of carbapenems, carbapenem-resistant gram-negative nosocomial pathogens will continue to evolve accumulating more carbapenem-resistance mechanisms, or more than one carbapenemase-encoding gene. This will lead in many cases to increased carbapenem MICs further, ruling out the current best-to-date therapeutic choice against carbapenemase producers. In addition, the role of combination therapy, including carbapenem containing regimens remains to be defined. There are several important concerns regarding all of these treatment options such as limited efficacy, increasing reports of resistance, and specific toxicities. Data from retrospective studies favor combination therapy over single-agent therapy for the treatment of carbapenem resistant bloodstream infections. More importantly, new antibiotics are greatly needed.

In view of the increasing failure rate of carbapenems and dearth of newer class of antibiotics even in research pipeline, a new antibiotic/combination of antibiotics which can work more efficiently against ESBL and MBL producing enterobacteriaceae and work as carbapenem sparer is the need of the hour. Use of adjuvants along with beta lactam and beta lactamase inhibitor combinations is a new approach to treat these multi drug resistant bacterial infections.
Elores an Antibiotic Adjuvant Entity (AAE)

Elores an antibiotic adjuvant entity (AAE) of Ceftriaxone + sulbactam + adjuvant disodium edetate is one such novel composition increasingly used in Indian hospitals with substantial amount of success against MDR infections. The current booklet is a collection of abstracts from different in-vitro and in-vivo studies, starting from pre-clinical and animal studies published in various journals across the world exploring and establishing the efficacy of Elores against MDR gram negative pathogens along with a favorable safety profile. Initial pre clinical and animal studies were conducted at our in-house research facility Venus Medicine Research Centre (VMRC), which were later corroborated by another set of in-vitro sensitivity studies and phase-III studies for getting marketing approval clearance from Central Drugs Standard Control Organization (Indian FDA). Further, after the requisite approval from DCGI also Elores was made available at a very limited number of tertiary care centers with a purpose to prevent its overuse and possible misuse. Later, the promise exhibited by this new antibiotic adjuvant entity against multi drug resistant gram negative bacteria further led to multiple microbiologists and clinicians driven studies exploring its effects in clinical settings, independently or in combination with different class antibiotics such as Colistin.
Background:
Fixed Dose Combinations (FDCs) refer to products containing two or more active ingredients used for a particular indication(s). The development of FDCs is becoming increasingly high either to improve compliance or to benefit from the added effects of the two or more active drugs given together. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of chronic conditions. FDCs should always be based on convincing therapeutic justification. Each fixed dose combination should be carefully justified and clinically relevant (e.g. in cases when each component of the FDC has several possible dosages, that have shown benefit on clinical outcomes may be preferable). Appendix VI of Schedule Y (Drugs & Cosmetics Rules 1945) specifies the requirements for approval for marketing of various types of FDCs.

Important Consideration:
A clear justification with a valid therapeutic rationale of the particular combination of active substances proposed will be the basis of approval. It is not always necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality. In case of FDC where all the active ingredients are approved individually, if a Clinical Trial (CT) is required, confirmatory studies to prove efficacy, preferably by parallel group comparisons in which the FDC is compared to its individual substances may be considered. When feasible, a placebo arm may be incorporated. Comparative CTs of the FDC with reference treatment may be necessary, especially when the therapeutic justification talks more on the FDCs superiority over a reference treatment.

An application for a marketing authorization may comprise:
• Entirely original data (From studies/ Clinical Trials).
• Entirely data from the literature.
• Both original data and data from the literature (“hybrid”).

For FDCs, it is likely that hybrid submissions will be the most common type.

Chemical and pharmaceutical data should be always totally original, unless there is sufficient justification with literature when partial data can be in-original.

Contribution of a novel solution for a global unmet medical need from Indian soil has always been the most cherished dream for every Indian scientist. It’s a moment of pride for us to present Elores as a solution for multi drug resistant gram negative pathogens and thus offering a carbapenem sparing option to the clinicians. On special occasion of publishing of this journal focused on sharing the insights on Elores research, I would like to particularly acknowledge the efforts of my team of scientists and technicians at VMRC, who tirelessly worked in order to explore different mechanisms of this Antibiotic Adjuvant Entity at the same time simultaneously analyzing its safety aspects, particularly after it scored above other tested choices and exhibited promise during our initial exploratory experiments on multiple other similar entities. I would also thank the experts from 47 countries for recognizing novel benefits of this unique solution for the global concern of Antimicrobial Resistance and granting patents to this AAE for their respective country. I am grateful to all the review committee members of DST Lockheed Martin India Innovation Growth Program for identifying the potential of this product and adjudging it with a gold medal.

It is heartening to see the acknowledgement of our efforts by multitudes of medical experts clinicians and microbiologists who chose to document their experiences with Elores in medical journals and thus further worked towards enhancing the confidence of other fraternity members on its therapeutic possibilities, I am really thankful to all those experts. Our journey so far with the discovery of this unique Indian innovation to tackle global concern of antimicrobial resistance has been quite overwhelming, particularly with the observation that, already with in such a short span of time of its market introduction Elores has already been instrumental in providing cover against gram negative infections for more than 150000 patient days in leading tertiary care centers of the country. Finally, I would like to thank the medical fraternity, clinicians and microbiologists who have been using Elores for the benefit of patients. I welcome all to join hands with us in fighting the menace of growing Antimicrobial Resistance and move forward as a less antibiotic resistant India.

Dr. Manu Chaudhary
Joint Managing Director & Head of Research
Venus Remedies Ltd.
The India Innovation Growth Programme is a joint initiative of the Department of Science and Technology, Govt. of India; Lockheed Martin Corporation; Indo-US Science and Technology Forum, Federation of Indian Chambers of Commerce and Industry; Stanford Graduate School of Business and the IC² Institute at the University of Texas. The aim of this programme is to accelerate innovative Indian technologies into the global markets. The India Innovation Growth Program is the only program of its kind, because of its focus on teaching using world-class commercialization strategies and the business development assistance provided.

The India Innovation Growth Programme, launched in March 2007, was started with the objective of enhancing the growth and development of India’s entrepreneurial economy. The aim of this programme is to accelerate innovative new Indian technologies into markets in the United States and around the world.

During the first phase of the programme, the project team comprising of subject matter experts from FICCI selects 100 innovative technologies from a wide range of sectors such as aeronautics, agriculture, biotechnology, chemistry, communications, computing, defense, electronics, environment, healthcare, information technology, manufacturing, materials, life sciences, nanotechnology, petrochemical, semiconductors and transportation.

FICCI approved applications and technologies are then evaluated and ranked by a joint team comprising all programme partners. Predefined parameters (such as development status, patent status, funding required to technology development, etc.) are used to select the most appropriate technology companies to go forward in the programme. The assessments are done in two
Venus Medicine Research Centre
Baddi, Himachal Pradesh
phases. During the first phase, evaluators review and offer constructive feedback on the technical and commercialization potential of the application submissions. In the second phase refined applications are scored based on predefined parameters and evaluator feedback to select the top 50.

During the second phase of the program, the selected 50 innovators are given week long advanced training in basic principles of product commercialization, readiness for market, business models, IP rights, competitive positioning, and mechanisms for revenue by experienced faculty members from the Stanford Graduate School of Business. The entrepreneurship workshop is organized to provide training to the innovators and also prepare them to participate in an Innovator’s competition.

The top 50 innovators then present their innovations to a panel of judges comprising renowned technologists and commercialization experts from India and the United States. At the end of the competition, 30 best innovations are finally awarded.

Thereafter, the top 50 innovators receive professional business development assistance from FICCI and top 8 both by FICCI and the IC² Institute, University of Texas. The business development managers at FICCI and IC² Institute work towards assisting the winners in commercializing their technological innovations and finding them suitable business partners in India as well as global markets.
Abstracts from In-vivo Studies, Case Studies and In-vitro Studies by External Authors

Abstracts from Phase-III and PK-PD Studies on Elores

Abstracts from In-vitro studies on Elores Sensitivity by External Authors and VMRC

Abstracts from Pre-clinical and Animal Studies on Elores
Abstracts from *in-vivo* Studies, Case Studies and *in-vitro* Studies by External Authors

The ever dynamic discipline of medical sciences keeps updating itself over the time, new researches and discoveries are scrutinized, recognized and embraced in practice based on respective merit, this way old and less efficient approaches are replaced by newer more effective solutions. The idea of evidence-based medicine has existed for over 100 years, but with advent of technology its need and usage has increased tremendously in the last two decades. Medical practitioners now-a-days intend to optimize decision-making by emphasizing the use of evidence from well designed and conducted research. Although all medicine based on science already has some degree of empirical support.

Any research to get published in a peer reviewed medical journal needs to cross multiple barriers or quality bench marks. Primarily a research papers should contain previously unpublished results of original research, which must be presented in sufficient detail to ensure the reproducibility of the described experiments and should present new experimental studies in elaborate form that constitute a significant contribution to current knowledge.

A rigorous peer-review and editing process is used by most of the medical journals to evaluate manuscripts for scientific accuracy, novelty, and importance. These publication processes are the major reason for the reputation for particular journal among others.

Thousands of submissions are received by these journals each year and majorities of these research submissions are rejected at primary scrutiny levels due to various reasons, on an average about 5% to 50% percent are eventually able to see publications depending on the respective journal’s editorial parameters.

The peer-review process is supposed to work in improving research reports while preventing overstated results from reaching physicians and the public. Each manuscript which is created after careful long hours of observations, only gets published after going through additional hundreds of hours of work by editors, statistical experts, illustrators, manuscript editors, proofreaders, etc, who need to work in ensuring that each published paper meets expected quality standards.

All manuscripts submitted to the journal are immediately sent for peer-review to the reviewers. After receiving the reviewers report, the respective queries are communicated to the authors for additional information or possible reorganization of the article. Authors are expected to submit revised manuscript with additional details or modifications following the recommendations of the concerned editorial team within a specific time limit. After the submission of revised manuscript, it is sent for re-review to the reviewers, this process is repeated multiple times in most cases and only after the article comes up as per parameters suggested by reviewers the approvals are provided, once approved intimation is sent to the author which is followed by the publication of article in respective/ upcoming issues.

Only a novel entity which offers a unique solution to a global unmet medical need can afford to garner these kind of efforts from a multitude of experts from different geographical locations. That is exactly what Elores presents, a unique solution to global concern of Antimicrobial Resistance and quite definitely it was this reason that attracted multiple research efforts on highlighting special attributes of this antibiotic adjuvant entity, finally leading to a plethora of publications. Perhaps, Elores is the among the very few novel entities across the globe to have attracted publication of more than 60 articles in peer reviewed journals in a short span of its discovery of last ten years. These articles provide insights into the discoveries of 60 different facets of Elores being explored and highlighted by the experts from various clinical and research backgrounds, a discovery which still continues...

Current chapter carries 33 abstracts from studies on Elores published by external authors.
1. Alternative Empiric Therapy to Carbapenems in Management of Drug Resistant Gram Negative Pathogens: A New Way to Spare Carbapenems

A New Antibiotic Adjuvant Entity (Ceftriaxone + Sulbactam+ Disodium Edetate): An Alternative to Carbapenems for the Management of Intensive Care Unit Infection

Author: Sachin Verma

Abstract

Aim: Carbapenem resistant bacterial infections have limited treatment options and are associated with high mortality. Here we present a retrospective analysis of treatment and outcome for ICU patients suffering from moderate to severe urinary tract infection (UTI), lower respiratory tract infection (LRTI) and intra-abdominal infections (IAI) to assess the efficacy of novel antibiotic adjuvant entity (AAE); ceftriaxone + sulbactam + disodium edetate, as an effective alternative for carbapenems in critically ill patients.

Materials and Methods: A retrospective study was conducted to evaluate efficacy of AAE in 84 patients showing sensitivity to AAE with UTI, LRTI and IAI treated at IVY hospital, Mohali, India between January 2013 to November 2014. The antibiotic therapy was initiated empirically and continued based on the results of the microbiological susceptibility testing and clinical outcome.

Results: 64 (76.19%), patients were diagnosed with single-organism infections, among which, 14 (16.16%) bacteria were resistant to meropenem and all the bacteria were susceptible to AAE. Empirical meropenem treatment was given to 25 patients, of which 18 (72%) patients achieved clinical success. 24 (75%) patients of 32 patients treated with AAE, achieved clinical success and the remaining 8 patients were cured when colistin was given with AAE. 20 (23.80%), patients were diagnosed with polymicrobial infections. Among 20 polymicrobial infectious patients, bacterial samples of 12 patients showed sensitivity towards AAE and meropenem, where as the remaining 8 (40%) samples showed intermediate susceptibility towards both cabapenem and AAE. 9 (45%) patients were cured with AAE, while the remaining 11 patients were cured with AAE and colistin combination therapy.

Conclusion: From the above study, it can be concluded that patients experience similar rates of clinical response in carbapenem susceptible cases and in some cases where patients failed to respond to carbapenem therapy but responded to AAE treatment. Hence, AAE can be used as an alternative to carbapenems in the treatment of moderate and severe infections caused by gram negative organisms.

Keywords: Ceftriaxone/sulbactam-EDTA; intra-abdominal infections; lower respiratory tract infections; retrospective study; urinary tract infections.
2. **In-vitro Antimicrobial Susceptibility of Ceftriaxone/Sulbactam / Ethylene Diamine Tetra Acetic Acid and Comparison to other Beta-Lactam/Beta-Lactamase Inhibitors, Carbapenems and Colistin against Gram Negative Bacteria**

**Abstract**

**Background:** Drug resistance against Gram Negative Bacteria (GNB) is increasing. Incidence of ESBL producing bacteria is around 70-80%. Carbapenem resistance has also been reached 40-90% for the GNB. We are also obtaining Colistin resistant isolates. Resistance against Beta-lactam (BL)/beta-lactamase inhibitor (BLI) combinations is already very high. No new antibiotic or antibiotic group is in pipeline, at-least for the next 5-10 years. With this background, the objective of this study is to compare in vitro susceptibility of new BL/BLI combination Ceftriaxone/Sulbactam/Ethylene diamine tetra acetic Acid (CSE) to Piperacillin/Tazobactam, Cefoperazone/Sulbactam, Cefepime/Tazobactam, Meropenem, Imipenem and Colistin.

**Methods & Materials:** Study was conducted on all clinical samples received from all critical care units between January 2014 and June 2015. Identification and susceptibility was done by Vitek 2 compact system. Susceptibilities of Ceftriaxone/Sulbactam/Ethylene diamine tetra acetic Acid and Cefepime/Tazobactam were done by disc diffusion method on the bases of CLSI guidelines. *Escherichia coli, Klebsiella sp., Pseudomonas sp.* and *Acinetobacter sp.* isolates were included in the study.

**Results:** *Escherichia coli* (324, 25%) was the most common bacteria isolated followed by *Klebsiella sp.* (309, 24%), *Pseudomonas sp.* (217, 17%) and *Acinetobacter sp.* (214, 17%) from all clinical samples. % Susceptibilities were as given in table below.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of Isolates</th>
<th>CSE</th>
<th>Cefepime/Tazobactam</th>
<th>Piperacillin/Tazobactam</th>
<th>Cefoperazone/Sulbactam</th>
<th>Meropenem</th>
<th>Imipenem</th>
<th>Colistin</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli</td>
<td>324</td>
<td>67.4</td>
<td>77.3</td>
<td>46.5</td>
<td>57.9</td>
<td>73.1</td>
<td>72.7</td>
<td>99.5</td>
</tr>
<tr>
<td>Klebsiella sp.</td>
<td>309</td>
<td>28.3</td>
<td>37.6</td>
<td>18.6</td>
<td>26.2</td>
<td>32</td>
<td>32</td>
<td>70.9</td>
</tr>
<tr>
<td>Pseudomonas sp.</td>
<td>217</td>
<td>43.1</td>
<td>64.1</td>
<td>40.6</td>
<td>46.9</td>
<td>52.4</td>
<td>50.3</td>
<td>93.8</td>
</tr>
<tr>
<td>Acinetobacter sp.</td>
<td>214</td>
<td>24.3</td>
<td>13.9</td>
<td>11.3</td>
<td>23.6</td>
<td>12.5</td>
<td>11.8</td>
<td>95.8</td>
</tr>
</tbody>
</table>

**Conclusion:** Colistin was the most sensitive antimicrobial for all GNB. Carbapenem resistance was around 27% - 89%. CSE susceptibility was better than Piperacillin/Tazobactam and Cefoperazone/Sulbactam and comparable to Meropenem and Imipenem. Although the number of isolates included in this study were less in number, a larger study needs to be conducted. This is an in vitro susceptibility data hence study has to be conducted for clinical efficiency of CSE.
3. **Antibiotic Adjuvant Therapy for Multi-Drug Resistant Carbapenemases Producing *Klebsiella pneumoniae* Associated Sepsis: A Case Study**

Author: Gupta R  

**Abstract**

Rising resistance and spread of *K. pneumoniae* strains, create great concerns in treating sepsis patients due to high incidence of mortality and morbidity. The current study is a case of a 20-year-old male with sepsis and bilateral lung lesions infected with Multi-Drug Resistant (MDR) carbapenemase producing *K. pneumoniae* (KPC) showing resistance to carbapenem and polymyxin. Based on sensitivity report, patient was put on antibiotic adjuvant: Elores (ceftriaxone, sulbactam, disodium edetate) along with fluconazole for 10 days. Elores was instituted with remarkable recovery and patient was discharged.

**Keywords:** ESBL; Elores; Enterobacteriaceae; MBL
4. Antibiotic Adjuvant Therapy in Diabetic Patients with Cellulitis Induced Pan Drug Resistance Infection in Lower-Limb Amputation Patient: A Case Study

Authors: Hemant Kumar Pande, Gyanendra Neekhra

Abstract
Rising complications in diabetic patient suffering with cellulitis is a serious concern. Diabetic patients with cellulitis have an increased chance of bacterial infection and are associated with high incidence of amputation. Diabetic patient flora gives an ideal environment to gram positive and gram negative bacterial growth. Increased morbidity and mortality is noted in antimicrobial resistant gram-negative bacterial infections, especially in diabetic patients who have undergone amputation. Here we discuss a case of cellulitis with pan drug resistant infection in post lower-limb amputation treated successfully with newer antibiotic adjuvant entity: Elores (ceftriaxone+sulbactam+adjuvant disodium edetate).
5. **Antibiotic Sensitivity Pattern of Bacterial Pathogens in Rajeev Gandhi Cancer Hospital, Delhi**

Author: Neelam Sachdeva  

**Abstract**  
We performed a retrospective, comparative study to evaluate efficacy outcomes of empiric Elores (ceftriaxone/sulbactam/EDTA) therapy compared with the meropenem, imipenem and piperacillin/tazobactam in patients suspected of bacterial infections. Among the isolates which showed the presence of bacteria, around 36.0 % samples were of urine followed by sputum and blood which contributed to 15.7 % and 11.5 % respectively. Among the isolates, *Escherichia coli* (51.7%) was found to be the most dominant pathogen followed by *Klebsiella pneumoniae* (29.5%), *Pseudomonas aeruginosa* (15.0%), *Acinetobacter baumannii* (2.3%), and *Proteus mirabilis* (1.5%). Higher susceptibility rates were achieved with Elores in comparison with piperacillin/tazobactam and meropenem. Susceptibility pattern for imipenem was almost same as that for Elores. Piperacillin/tazobactam resistance was high in all the tested pathogens ranging from 54.0 % (least in *P. aeruginosa*) to 100.0 % (highest in *Proteus spp.*) when compared to Elores to which low resistance was observed ranging from 19.0 % (least in *P. aeruginosa*) to 33.3 % (highest in *A. baumannii*) was observed. Overall, the results of the present study strongly advocate the superiority of Elores over piperacillin/tazobactam and meropenem and an equivalence to imipenem. Elores can be a very effective alternative to treat against the deadly multi drug resistant gram negative bacteria, sparing penems as reserve drugs.
Abstract
Rising challenge in treating nearly a million burn patients in India, with high mortality and morbidity attributed to nosocomial infections, is a serious concern. With cascades of reactions taking place in serious burn patients, there is a massive release of humoral factors, such as cytokines, prostaglandins, vasoactive prostanoids, and leukotrienes, along with multiple defects of cellular and humoral components of defense system. This immunocompromised state favors increased chances of nosocomial infections such as pneumonia and blood stream infections. The present case discusses a novel treatment approach with Elores (ceftriaxone, sulbactam, and adjuvant disodium edetate) in effectively treating burn patient with bacteremia and ventilator-associated pneumonia.

Keywords: Bacteremia, Elores, electric burns, ventilator-associated pneumonia.
7. Use of CSE-1034 (Elores™) in Management of Complicated Urinary Tract Infection due to Multi Drug Resistant *Klebsiella Pneumoniae*

Author: Sanjiv Bansal  

**Abstract**  
*Klebsiella pneumoniae* is one of the causative agents for various diseases, including urinary tract infection (UTI), pneumonia and septicemia. In the present case report, a case of 35 year old male suffering from urinary tract infection with multi drug resistant *Klebsiella pneumoniae* has been discussed. This patient was successfully treated with Elores™ (Ceftriaxone/Sulbactam/Disodium-Edetate).
8. Use of Elores™ in Guiding Successful Treatment of Ventilator Associated Pneumonia Due to Multi Drug Resistant Acinetobacter baumannii and Klebsiella pneumoniae

Author: Ashish Gupta and Sunny Rupal
Journal: British Journal of Medicine & Medical Research 17(9) : 1-6, 2016, Article no. BJMMR.28546

Abstract
Introduction: Increased antimicrobial resistance of Acinetobacter baumannii (A. baumannii) and Klebsiella pneumoniae (K. pneumoniae), is of great concern worldwide. Management of ventilator associated pneumonia (VAP) due to MDR poses a challenge for clinicians.

Case Presentation: Here we are discussing a case of 47 year old male patient diagnosed with VAP due to A. baumannii and K. pneumoniae. Use of Elores™ (Ceftriaxone/Sulbactam/Disodium-edetate) as antibiotic for the treatment of VAP due to MDR pathogen K. pneumoniae and A. baumannii resulted in clinical cure of infection.

Conclusion: Elores™ can be considered as a safe and efficacious antibiotic to treat MDR gram negative pathogen in VAP.

Keywords: Ceftriaxone/Sulbactam/Disodium-edetate; antibiotic resistance; Acinetobacter baumannii; Klebsiella pneumoniae; CSE1034; ventilator associated pneumonia (VAP).
9. Comparative Pharmacoeconomics and Efficacy Analysis of a new Antibiotic Adjuvant Entity and Piperacillin-Tazobactam for the Management of Intra-abdominal Infections: A Retrospective Study

Authors: Sandip Jhadav, Nitin Sawant

Abstract

Objective: To analyze the comparative efficacy of piperacillin-tazobactam (PIP-TAZ) and ceftriaxone-sulbactam with adjuvant (CSA) in the treatment of intra-abdominal infections (IAIs) and to assess the costs associated with respective therapies.

Methods: The present study analyzed the data collected from 94 IAI patients treated at a tertiary-care hospital. Patient characteristics, infection types, surgical procedures, antibiotic therapies, treatment durations were recorded and overall cost involved in the infections management was estimated in Indian rupee.

Results: In total, 46 patients received PIP-TAZ and 48 patients received CSA. The clinical cure was seen in 39.13% patients of PIP-TAZ group and 62.50% patients of CSA group. The patients diagnosed with mixed culture (gram-positive and negative) infections, needed additional cover of clindamycin to achieve clinical success. The failure patients from PIP-TAZ group were shifted to meropenem therapy. For the patients where meropenem and CSA therapy failed, colistin was given as an additional cover. Comparative cost expenditure analysis of the two drug treatment groups revealed that, the overall treatment cost for patients cured with empirical PIP-TAZ group was 51.79% more than that of CSA therapy. The strongest predictor of the increase in treatment costs was clinical failure. Similar trends were maintained for the patients cured with clindamycin additional therapy and change of therapy, with PIP-TAZ group accounting 36.11% and 39.99% more expenditure than CSA group.

Conclusions: This study demonstrates that CSA has comparatively higher efficacy as compared to PIP-TAZ when used along with metronidazole in patients with different types of IAIs. Pharmacoeconomic analysis clearly shows that starting appropriate empirical antibiotic therapy has a large impact on the cost of treatment in management of IAIs and selection of CSA, can significantly reduce the cost involved in the treatment.
10. **A Retrospective Comparative Study to Evaluate the Use of a New Beta-lactam + Beta-lactamase Inhibitor (Ceftriaxone + Sulbactam + Disodium Edetate) in Comparison to Meropenem in the Management of Gram-negative Bacterial Sepsis**

Authors: Vijay Kumar Agrawal, Abhishek Bansal, Meenu Pujani, Mamta Jawa, Parul Mahajan, Anil Jain
Journal: Tropical Journal of Medical Research | Vol 19 • Issue 1 • Jan-Jun 2016

**Abstract**

**Introduction and Objective:** Gram-negative bacterial sepsis and anti-microbial resistance are global health concerns. The present study is a comparative retrospective analysis of the outcome of two antibacterial therapies (Ceftriaxone + Sulbactam + Adjuvant Disodium edetate [FDC] and Meropenem) used for management of patients suffering from gram-negative bacterial sepsis.

**Materials and Methods:** Both the therapies (FDC or Meropenem) were initiated empirically on the basis of clinical presentation of the patients and treating physician's decision and continued based on the results of the *in vitro* microbiological susceptibility testing pattern and clinical outcome.

**Results:** 70 patients with known gram-negative bacterial infections showing sensitivity to FDC and Meropenem were included in the study. Fifty-seven (81.42%) out of 70 cultures isolated from the patients showed susceptibility towards FDC, whereas the isolates showed comparatively lower susceptibility (45 [64.28%]) towards Meropenem. Twenty (54.05%) out of 37 patients treated with FDC were cured, while the remaining patients achieved clinical success with FDC + Colistin combination therapy. On the other hand, only 11 (33.33%) out of 33 patients to whom Meropenem was given empirically were cured, and the remaining 22 patients required Meropenem and Colistin combination therapy to achieve clinical cure.

**Conclusion:** This new FDC exhibits better antimicrobial susceptibility than Meropenem and a better efficacy in gram-negative sepsis management. This new FDC in combination with Colistin can be used to treat severe sepsis patients, which often fails to respond to monotherapy. This new FDC and Colistin can be an effective alternate therapy to Meropenem and Colistin.

**Keywords:** Antibiotic adjuvant entity, carbapenems, colistin, drug resistance
11. A Case Report of Community Acquired Pneumonia due to Multi-drug Resistance *Pseudomonas aeruginosa* Treated with Elores

Author: Danish Memon  

**Abstract**  
Community-acquired pneumonia (CAP) is a common and potentially serious illness associated with considerable morbidity and mortality, particularly in patients infected with multidrug resistance (MDR) gram-negative bacilli. After *S. pneumoniae*, *Pseudomonas aeruginosa* is the second most common pneumonia causing pathogen followed by *K. pneumoniae* and *S. aureus* in India. An alarming rise in the incidence of bacteria resistant even to last resort of antibiotics in recent years, forced clinicians to change antibiotic treatment options in pneumonia. Here we discuss a case of CAP infected with MDR *Pseudomonas aeruginosa* which is resistant to carbapenems and successfully treated with a new antibiotic adjuvant entity (AAE); ELORES (Ceftriaxone + Sulbactam with Adjuvant Disodium Edetate).

**Keywords:** CAP; MDR; *Pseudomonas aeruginosa*; AAE; Elores.
12. A Case of Poly-Infection with cUTI and Grade III Bed Sores in Type II Diabetes Treated with New Antibiotic Adjuvant Entity: A Case Report

Author: Suneet Kumar Verma

Abstract
Critically ill patients with diabetes are commonly associated with urinary tract infection and high-risk of bed sores or pressure ulcers. We report a case of 72 year old male patient, a known case of meningoencephalitis, treated 1 month back. He arrived to our emergency department, with chief complaints of fever and increased drowsiness since 10-12 days. Based on the initial examination, the patient was empirically managed with intravenous meropenem 1 g every 8 hrs. However, due to patient’s poor clinical response antibiotic therapy was switched to Elores 1.5 g B.D dose with 90 minutes infusion. The patient received Elores therapy for 7 days, based on lab reports and general condition, he was put on oral antibiotics and shifted to ward. On the 5th day of post ward transfer, the patient developed mild pleural effusion with mild hypokinesis, he was again shifted to medical intensive care unit. Cardiology consultation was sought and was managed. In view of suspected hospital-acquired pneumonia, prophylactic treatment of Elores 1.5 g bd was continued for 5 days. The patient responded to the treatment well, was stable and discharged with follow-up advice.

Keywords: Antibiotic adjuvant entity, complicated urinary tract infections, Elores, poly-infection.
13. Effective Management of Critical HAP Patient Infected with MDR *Acinetobacter baumannii* with Multiple Co-morbidities

Author: Deepak Bhasin

**Abstract:**

Emergence of multi drug resistance (MDR) strains of *Acinetobacter baumannii* (*A. baumannii*), resistant to most of the available antibacterial drugs is of great concern globally. Management of the infections caused by these MDR strains especially pneumonia is a great challenge for physicians and clinical microbiologists. In the present study, we discuss a case of a 71 year old male patient diagnosed with MDR *A. baumannii* pneumoniae with known co-morbidities of CKD, hypertension, diabetis mellitus and coronary artery disease (CAD) treated with a newer antibiotic adjuvant entity: Elores (ceftriaxone+sulbactam+disodium edetate) and recovered well.
14. Efficacy of Ceftriaxone-Sulbactam-EDTA Combination in Immuno Compromised Patients in a Tertiary Care Cancer Centre

Authors: Sanjay Biswas, Vivek Bhatt and Rohini Kelkar
Journal: Journal of drug Metabolism and Toxicology 2015, 6:4

Abstract

Introduction: The resistance to the antimicrobials has been increasing over the years and is varying from country to country. Among the causes of β-lactam antibiotic resistance, the production of ESBLs appeared to be most common. ESBLs are plasmid mediated and can be easily transmitted among members of enterobacteriaceae, thus facilitating the dissemination of resistance, not only to β-lactam, but to other commonly used antibiotics including aminoglycosides and quinolone. To overcome ESBLs resistance, carbapenem drugs have been introduced in clinical settings, although carbapenems resistance has been reported increasingly worldwide. Resistance in bacteria to carbapenems is due to the production of carbapenem hydrolyzing enzymes called carbapenemases, which is encoded by KPC, VIM and IMP genes. The aim of the present study was to compare the susceptibility pattern of ceftriaxone-sulbactam-EDTA (CSE) combination with other routinely used antibiotics in immunocompromised patients.

Materials and Methods: A total of 33930 clinical samples were received in the Dept. of Microbiology in 2014. All the samples were processed as per standard microbiological methods. Antimicrobial susceptibility testing of cefoperazone-sulbactam, ceftriaxone-sulbactam-EDTA, imipenem and meropenem of 195 gram negative isolates, included in this study, were carried out by disc diffusion method as per CLSI guidelines. ATCC strains were used as standards. Interpretative criteria of Ceftriaxone were used for interpretation of CSE.

Results: Of the 33930 samples received, only 195 Gram negative isolates, from different clinical samples, were included in this study. Blood was the most common isolate followed by broncho-alveolar lavages, wound swabs and drain fluids. Escherichia coli was the commonest isolate followed by Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter spp. Carbapenems were the most sensitive antimicrobial followed by cefoperazone-sulbactam, ceftriaxone-sulbactam-EDTA and piperacillin-tazobactam.

Conclusions: Results obtained in the current study clearly demonstrates the good in-vitro activity of ceftriaxone plus sulbactam plus EDTA as compared to other beta-lactam beta-lactamase inhibitor combinations. The enhanced susceptibility of ceftriaxone+EDTA+sulbactam against different clinical isolates is likely to be associated with synergistic activity of ceftriaxone+sulbactam+EDTA. EDTA chelates the divalent ions, thus enhancing the susceptibility of ceftriaxone plus EDTA plus sulbactam towards different microorganisms. EDTA also enhances the susceptibility by altering the outer membrane permeability, which in turn increased penetration of drugs inside the bacterial cells.
15. Dominant Polycystic Kidney Disease with Acute Pyelonephritis due to Multi-Drug Resistant *Staphylococcus* D Group and *Candida albicans*

Author: Mahendra Kumar Atlani  
Journal: IJSS Case Reports & Reviews | December 2015 | Vol 2 | Issue 7

Abstract
Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary kidney disease caused due to a mutation in PKD1 gene and the PKD2 gene located at chromosome level 16 and chromosome 4. ADPKD often leads to progressive kidney (renal) failure, primarily due to continued enlargement of the cysts and replacement of normal kidney tissue. The present case is of a 70-year-old male diabetic patient with ADPKD along with acute pyelonephritis caused by multi-drug resistant *Staphylococcus* D group and *Candida albicans*, treated with a new antibiotic adjuvant entity ceftriaxone/sulbactam/disodium edetate, and fluconazole recovered completely.

**Keywords:** Autosomal dominant polycystic kidney disease, Elores, Multi-drug resistant, PKD1 gene, PKD2 gene, Pyelonephritis.

Authors: Iqbal Aziz, Mohd Amin Mir

Abstract

Aims: To study the comparative efficacy of Piperacillin/Tazobactam (PIP-TAZ) and new fixed dose combination (FDC) of ceftriaxone + sulbactam + ethylene diamine tetra acetic acid (EDTA) in treatment of intra-abdominal infections (IAIs) and to analyze the cost expenditures with these therapies.

Methods: Case sheets of patients treated for IAI with either of PIP-TAZ or FDC were analyzed. Demographic characteristics, surgical procedure, antibiotic therapy and length of hospital stay were recorded and the cost of total hospital care was analyzed. Efficacy was measured in terms of microbiological and clinical successes.

Results: Out of 120 patients identified as culture positive, empirical PIP-TAZ was given in 58 patients, of whom 39 (67.24%) patients achieved clinical success. The remaining achieved success with either meropenem or meropenem + colistin combination. Out of 62 FDC treated patients, 54 (87.09%) achieved clinical success and the remaining patients were cured with FDC + colistin combination therapy. The clinical success rates in culture negative patients treated with FDC and PIP-TAZ were 87.5% and 21.42% respectively. Comparative cost expenditure analysis of the two treatment groups revealed that the overall treatment cost for successful patients treated with FDC was 36.72% lesser than that of PIP-TAZ treated groups. Similarly, the failed patient group also resulted in 35.44% higher expenditure in PIP-TAZ group than in FDC group.

Conclusion: The study reveals the superior efficacy of FDC over PIP-TAZ treatment in IAI which has a direct impact on the cost of treatment. The comparative pharmacoeconomic analysis shows that the selection of FDC over PIP-TAZ reduces up to 35% costs involved in IAI treatments.

Keywords: Intra-abdominal infections, Piperacillin/Tazobactam, Fixed dose combination, Pharmacoeconomic analysis
Abstract

Background: In the visage of multidrug resistance among gram negative bacilli, we look forward to carbapenem group of drugs as empiric choice in seriously ill patients. However increasing resistance to carbapenems, the last resort, is of growing concern for all. It's high time to look beyond carbapenems and emphasize on carbapenem sparsers.

Objective: This study is to find the susceptibility pattern of the novel adjuvant antimicrobial CSE 1034 a combination of ceftriaxone+sulbactam+disodium edetate for the current ESBL and MBL isolates in a tertiary care centre.

Materials and Methods: A total of 823 gram negative bacterial isolates were obtained from different clinical specimens during the period of March, 2013 to October, 2013. The overall prevalence of metallo betalactamase producing gram negative organisms was 11% (n=91). We included a total of 141 clinical isolates for this study.

Results: Among 141 clinical isolates, 50 isolates (35%) were ESBL producers and 91 (65%) were MBL producers. Maximum numbers of ESBL producers were identified in Escherichia coli followed by Klebsiella pneumoniae, Acinetobacter baumannii and Proteus spp. Maximum numbers of MBL producers were identified in Klebsiella pneumoniae followed by Pseudomonas aeruginosa. CSE 1034 (Ceftriaxone+sulbactam+disodium edetate) showed fairly good in-vitro susceptibility for these ESBL and MBL producing isolates. It exhibited 64 % to 100% susceptibility and 18% to 22% intermediate sensitivity to ESBL producing isolates and 42 % to 89 % susceptible and 10 % to 51 % intermediate response to MBL producing isolates.

Conclusion: With increasing resistance to the commonly prescribed drugs used to treat infections caused by variety of gram negative organisms, Ceftriaxone+sulbactam+disodium edetate, a novel Antibiotic Adjuvant Entity (AAE) may be a promising option.
18. A Patient with Primary Laryngeal Aspergillosis and Secondary Lung Infection of Multi Drug Resistant *E. coli*: A Rare Case Report

Author: Reshma Basu, MD.
Journal: Research 2014;1:669

Abstract
Pulmonary polymicrobial infection of *Aspergillus fumigatus* and *Escherichia coli* is a rare disorder in an immunocompetent host. We report a case of primary laryngeal aspergillosis with secondary bacterial infection in a 35 year-old immunocompetent Indian female patient. She complained of fever, hoarseness of voice, dysphagia, stridor and respiratory obstruction. Culture of sputum and pleural effusate revealed infection of *A. fumigatus* and multidrug resistant (MDR) ESBL producing-*E. coli* respectively. To the best of our knowledge this is the first case of polymicrobial infection associated with primary laryngeal aspergillosis and secondary bacterial lung infection. Treatment with Voriconazole and an antibiotic adjuvant entity (AAE) of Ceftriaxone, Sulbactam and Disodium edetate (Elores™) successfully resolved the patient.
19. A Combination Strategy of Ceftriaxone, Sulbactam and Disodium Edetate for the Treatment of Multi-Drug Resistant (MDR) Septicaemia: A Retrospective, Observational Study in Indian Tertiary Care Hospital

Authors: Umakant Nagashetty Patil and Kiran Lakkol Jambulingappa

Abstract

Introduction: Previous studies have suggested the use of rational combination therapy for the treatment of multi-drug resistant (MDR) infections. An antibiotic adjuvant entity (AAE) of ceftriaxone, sulbactam and disodium edetate (Elores) was approved for multi-drug resistant infections in India.

Aim: This study was designed to investigate the efficacy and safety of this AAE in patients with sepsis due to extended spectrum beta lactamase (ESBL) and metallo-beta lactamase (MBL) producing pathogens.

Materials and Methods: A retrospective observational study was conducted in patients admitted in intensive care unit (ICU) at tertiary health care site in India, with enrollment from 24 March, 2012 to 7 Aug, 2012. Patients eligible for enrollment had clear infection of bacterial septicaemia, were aged 12-65 years, and were considered for treatment with cephalosporins class of antibiotics.

Results: Total 18 patients were included in the study and all assigned to combination of ceftriaxone, sulbactam and disodium edetate. Complete clinical cure in terms of relief and no-disease symptoms had observed in 15 (83.3%) subjects, however 3 (16.6%) showed treatment failure (TF). Similarly for bacteriological eradication response, 15 (83.3%) patients displayed complete bacteriological eradication response and 03 (16.6%) subjects showed TF. No serious side effect was observed during the study.

Conclusion: This study recommends the use of combination of ceftriaxone, sulbactam and disodium edetate (EDTA) for the treatment of MDR septicaemia associated with ESBL and MBL producing microbes.

Keywords: Antibiotic Adjuvant Entity, bacterial septicaemia, combination therapy
20. Comparative Antimicrobial Efficacy Evaluation of a New Product Elores against Meropenem on Gram Negative Isolates

Authors: Manoj Kumar, Shikha Chaudhary2, Diljot Kumar Makkar, Neeru Garg, Sanjeevkumar Chugh

Abstract
Background and Objective: Increased resistance of Gram-negative bacteria towards most of the available antibiotics, especially beta-lactam antibiotics is a prime difficulty for the treatment of infections caused by these pathogens. In view of the fact that there is a continuous increase in the antibiotic resistance and the limited available therapeutic options, we aimed the present work to evaluate the antibiotic susceptibility pattern of 847 isolates towards meropenem and Elores (ceftriaxone + sulbactam + adjuvant ethylene diamine tetra acetic acid).

Methods: A total of 1180 clinical samples were collected from patients suspected of bacterial infection between January 2014 to June 2014. These samples were subjected for bacterial identification. Antibiotic susceptibility testing were carried out according to the recommendations of Clinical Laboratory Standards Institute (CLSI) guidelines.

Results: Among the samples which showed the presence of bacteria, around 29.04% samples were of sputum followed by urine and blood which contributed to 21.95% and 12.51%, respectively. *Escherichia coli* (39.55%) was found to be the most dominant pathogen, followed by *Pseudomonas aeruginosa* (19.12%), *Klebsiella pneumoniae* (12.39%), *Proteus mirabilis* (8.50%), *Klebsiella oxytoca* (8.26%), *Acinetobacter baumannii* (5.31%), *Morganella morganii* (3.77%), *Serratia marcescens* (2.24%). The susceptibility of Elores was comparable with meropenem in some of the organisms, but Elores displayed higher susceptibility in *E. coli*, *A. baumannii*, *K. pneumoniae*, *P. mirabilis*, *K. oxytoca*, *M. morganii* and *S. marcescens* which might be due to presence of metallo-beta lactamases in these isolates.

Conclusion: Overall, the results of this study strongly advocate the equivalence of Elores with meropenem and can be of very effective alternative to treat against the deadly multi drug resistant gram-negative bacteria.

Author: M K Singh


Abstract

Neurogenic bladder leads to urological complications like urinary incontinence, vesicourethral reflux and recurrent urinary tract infections (UTIs). High prevalence of resistant Gram negative pathogen induced catheter-associated bacteriuria with increased morbidity and mortality are reported in patients of neurogenic bladder caused by spinal cord injury. Predominant reason for rising resistance is prolonged or repeated exposure to antimicrobial agents causing selection pressure. The common multi drug resistant (MDR) Gram negative pathogens are *E. coli*, *Pseudomonas spp.*, *A. baumannii*, *K. pneumoniae* and *Enterococcus*. Here we are discussing a case of MDR *Klebsiella pneumoniae* induced cUTI in a patient with neurogenic bladder successfully treated with Elores (ceftriaxone+sulbactam+disodium edetate) an Antibiotic Adjuvant Entity.
22. Prevalence and Susceptibility Analysis of Gram Negative Pathogens

Authors: Dr Diljot Kaur Makkar, Manoj Kumar, Shikha Chaudhary, Suresh Goyal, Palak Aggarwal, Neeru Garg

Abstract:
Antimicrobial resistance is a growing threat worldwide. Predominant mechanism for resistance to the β-lactam antibiotics in Gram negative bacilli is the production of β-lactamases. The present work was aimed to evaluate the antibiotic susceptibility pattern of 368 isolates, isolated from more than 563 clinical samples towards Piperacillin/tazobactam, Imipenem/cilastatin, Amoxacillin/Clavulanic acid and compared its efficacy with a new antibiotic adjuvant entity Elores (ceftriaxone+sulbactam with adjuvant ethylene diamine tetra acetic acid/EDTA). Among the samples which showed the presence of pathogens, around 47.3% samples were of urine followed by blood, pus and sputum samples which contributed to 36.0%, 8.7% and 5.2% respectively. Among the isolates, E. coli (61.4%) was found to be the most dominant pathogen. Klebsiella species (22.0%), and P. aeruginosa (14.4%), also contributed significantly to the isolated pool of pathogens followed by A. baumannii (1.1%), and P. mirabilis (1.1%). Higher susceptibility rates were achieved by Elores in comparison with Piperacillin/tazobactam and Amoxacillin/clavulanic acid. Imipenem/cilastatin resistance was high in A. baumannii (75%) whereas Proteus spp. showed (100%) susceptibility. Predominant pathogens when compared to Elores to which low resistance ranged from (12.0%) (least in Proteus spp.) to (22.0%) (highest in Klebsiella spp.) was observed. Overall, the results of the present study strongly advocate the superiority of Elores over Piperacillin/tazobactam, Imipenem, Amoxacillin/Clavulanic acid and can be of very effective alternative to treat against the deadly multi drug resistant gram negative bacteria.
23. **Trend in Susceptibility Pattern to Commonly Used Antibacterial Agents and Role of Ceftriaxone+Sulbactam+Disodium Edetate Combination against Extended Spectrum Beta-Lactamase and Carbapenemase Producing Gram Negative Isolates**

Authors: K Prasanthi, K Nagamani, PR Anuradha and DS Murty


**Abstract**

In the present study, we attempted to find the resistance pattern to antibacterial agents among extended spectrum beta-lactamases (ESBL) and carbapenemase positive isolates, obtained from different clinical specimens at Gandhi Medical College Hospital, Hyderabad, India. A total of 299 isolates consisting of 250 ESBL and 49 carbapenemase producing isolates were recovered from various samples collected from intensive care units (ICU) and wards. Antibiotic susceptibility study was done by the disc diffusion method according to the Clinical Laboratory Standards Institute guidelines. Out of 299 isolates, 281 (93.9%) were of enterobacteriaceae family and 18 (6.0%) were from non-enterobacteriaceae. Of enterobacteriaceae family, 184 (65.5%) were *E. coli* and 97 (34.5%) were *K. pneumoniae*. Among non-enterobacteriaceae, 9 of each were *Acinetobacter* spp and *P. aeruginosa*. The most prevalent pathogen was *E. coli* followed by *K. pneumoniae*, and equal prevalence of *Acinetobacter* spp and *P. aeruginosa*. Ceftriaxone+sulbactam+disodium edetate (Elores) was the most effective drug showing 100% susceptibility to *P. aeruginosa* followed by *E. coli* (88.4%), *K. pneumoniae* (78.0%), *Acinetobacter* spp (66.6%). The comparator drugs showed low sensitivity up to 55.0%. Carbapenemase producers, showed 100% resistance to Meropenem. However, Elores showed sensitivity ranging from 50.0% to 58% in carbapenemases producing *E.coli, K. pneumoniae* and *P. aeruginosa*. This study provides important data for clinicians to plan the appropriate treatment regimen. As Elores showed better activity against both enterobacteriaceae and non-enterobacteriaceae family pathogens, it may be a useful option to treat the infections caused by these organisms.
Abstract
Background: Increasing prevalence of carbapenem resistance in gram negative bacteria due to excessive and indiscriminate use of carbapenems has forced the medical fraternity to find out ways to spare carbapenems. This retrospective study was aimed to explore a new fixed dose combination (FDC) of ceftriaxone+ sulbactam with adjuvant disodium edetate as a carbapenem sparing drug in the management of moderate to severe bacterial infections of lower respiratory tract infections (LRTIs), urinary tract infections (UTIs) and intra-abdominal infections (IAIs).

Methods: A retrospective analysis involves those patients in whom FDC or meropenem was used empirically for the management of these infections caused by multidrug resistant pathogens.

Results: The average age of evaluated patients was 58.17±13.98 years. Out of 107 patients, 95 patients selected for the evaluations in which LRTIs, UTIs and IAIs were diagnosed in 43 (45.26%), 32 (33.68%) and 20 (21.05%) patients, respectively. The most common pathogen was Escherichia coli (38.94%), followed by Klebsiella species (26.31%), Pseudomonas species (18.94%) and Acinetobacter species (15.78%). According to the susceptibility results, FDC appeared as the most active antibacterial agent against E. coli (94.54%) followed by Acinetobacter species (93.33%), Pseudomonas species (88.88%) and Klebsiella species (84%). On the other hand, meropenem susceptibility to E. coli was 86.47% followed by Acinetobacter species (78.57%), Pseudomonas species (66.66%) and Klebsiella species (64%). Further our results revealed that FDC has >75% clinical success compared to meropenem (~61% clinical success).

Conclusion: These results depict non-inferiority of new FDC in the treatment of moderate to severe gram negative bacterial infections caused by carbapenem resistant organisms and therefore, it should be considered as an alternative to carbapenem for treating LRTIs, UTIs and IAIs.
25. Alarmingly Rising β-Lactamase-Mediated Meropenem Resistance in Nosocomial Infections in Indian Hospitals

Author: Shikha Chaudhary, Manoj Kumar, Rahul Gupta, Esha Walia and Anshika Gangal

Abstract:
Growing insensitivity to multiple antibiotic groups particularly beta-lactams has been a concern for past decade. The concerns of antibiotic resistance, lack of new antibiotics and limited therapeutic options led us to compare the susceptibility of a new antibiotic adjuvant entity Elores (ceftriaxone + sulbactam + ethylene diamine tetra acetic acid, EDTA) with meropenem among gram negative organisms isolated from >1100 clinical samples obtained from various hospitals of India during past six months. Out of total samples analyzed 923 samples showed the presence of infection and 281 samples were sterile. E. coli (44.2%) was found to be the most dominant pathogen followed by P. aeruginosa (18.2%), K. pneumoniae (10.9%), A. baumannii (9.0%), M. morganii (4.9%), P. mirabilis (4.8%), S. marcescens (3.0%), K. oxytoca (3.8%) and E. cloacae (1.2%). Higher success rates have been achieved with Ceftriaxone + sulbactam + EDTA in comparison to meropenem. Use of meropenem in the light of alarmingly rising resistance (9 to 62 %) warrants restricted use and re-evaluation of the therapies where penems are used in high doses and to evaluate ceftriaxone+sulbactam+EDTA as alternative. Results of meropenem was comparable to ceftriaxone+sulbactam+EDTA against M. morgannii, P. aeruginosa, and S. mercescens but in enterobacters ceftriaxone+sulbactam+EDTA exhibited around 3% to 33% higher susceptibility. We conclude that ceftriaxone+sulbactam+EDTA is much more effective against most of the multidrug resistant (MDR) pathogens and can be of a better option to treat against these pathogens.
Abstract
In this study we report a case of 63-year-old woman with symptoms of pyrexia, malaise, shortness of breath, cough with expectoration and anorexia who was admitted to our hospital, showing a homogenous opacity in the left lower mid zone along the peripheral upper zone on a chest radiography and was diagnosed with lung abscess of the left side (destroyed lung). Culture reports of bronchoscopically obtained lung parenchyma, bronchoalveolar lavage (BAL) and endotracheal aspirates revealed pulmonary abscess caused by multidrug resistant (MDR) *Pseudomonas aeruginosa*. The current management of acute lung abscess is difficult. Based on culture and sensitivity report patient was put on intravenous Elores (Ceftriaxone/Sulbactam/Disodium edetate—a non-antibiotic adjuvant) and injection amikacin, with support of intravenous (IV) anti-pyretics, IV fluids, nebulization, physiotherapy for postural drainage and other supportive measures, who recovered well.
27. A Retrospective Study to Evaluate the Efficacy of a New Antibiotic Adjuvant Entity (ß-lactam/ß-lactamase Inhibitor/Adjuvant Disodium Edetate Combination) for Management of Sepsis

Author: Sachin Verma
Journal: Research Journal of Infectious Diseases, 2015, Vol, 3; article 3

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. 8 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
28. Comparative Assessment of Antibiotic Susceptibility Pattern of Gram Negative Pathogens Isolated from Intensive Care Unit Patients in Pune

Authors: S. Arora and N. Munshi
Journal: British Microbiology Research Journal10(2): 1-9, 2015, Article no.BMRJ.18199

Abstract

Introduction and Aim: Extended spectrum β-lactamases (ESBLs) and metallo-β-lactamases (MBLs) production is one of the main means of the resistance developed by gram negative bacteria against β-lactam antibiotics. The present study was carried out to evaluate the incidences of ESBL and MBL producers in gram negative bacteria isolated from Ruby Hall Clinic, Pune, Maharashtra, India and to evaluate the efficacy of drugs against these bacteria.

Methodology: 254 different samples collected from various sources were screened for the presence of bacterial pathogens. The pathogens were identified using selective media technique. The ESBL and MBL producer’s screening and the antimicrobial susceptibility testing (AST) of pathogens towards a new drug; Elores (ceftriaxone + sulbactam with adjuvant ethylene diamine tetra acetic acid, EDTA) in comparison with commonly used antibiotics like meropenem, imipenem, piperacillin-tazobactam and cefoperazone-sulbactam was carried out according to CLSI guidelines.

Results: Among 254 samples collected, 200 samples showed the presence of bacterial infections with Klebsiella spp. (39%) as the most predominant pathogens followed by, E. coli (32%) and Pseudomonas spp. (16.5%), Acinetobacter spp. (12.5%). Of the identified pathogens, 61% (122/200) were found to be ESBL producers and 4.5% (9/200) were MBL producers. Nearly, 3.5% (7/200) pathogens were both ESBL and MBL producers. However another significant number (66 isolates) of pathogens were identified as non-ESBL/ non-MBL producers. Further, our data showed that, Elores was highly susceptible (87 to 100%) followed by imipenem-cilastatin (30 to 67%), meropenem (33 to 68%), cefoperazone-sulbactam (24 to 70%) and piperacillin-tazobactam (4 to 81%) against gram negative bacteria.

Conclusion: The results of the present study concludes, that Elores is an useful option to treat the infections caused by carbapenemase producing multi-drug resistance gram negative bacteria.
29. **A Case Study: Viral Pneumonia induced Acute Respiratory Distress Syndrome with super infection of ESBL producing Klebsiella pneumoniae treated with Antibiotic Adjuvant Entity: Elores**

Author: Dr. Neeraj Gupta  

**Abstract**

Viral pneumonia is a rising concern worldwide, especially in children and young adults. Viral pneumonia can rapidly progress to Acute Respiratory Distress Syndrome (ARDS) which is a syndrome of acute respiratory failure with symptoms of dyspnea, tachypnea and progressive arterial hypoxia requiring mechanical ventilation. Gram-negative super-infection with *E. coli, Klebsiella* spp., and *P. aeruginosa* are common in mechanical ventilated patients, leading to increased hospital stay, cost of treatment, morbidity and mortality in children. Here we discuss a case of viral pneumonia induced ARDS with nosocomial infection (super-infection) of ESBL producing *K. pneumoniae*, in a patient hypersensitive to Meropenem and Colistin, treated successfully with newer antibiotic adjuvant entity: Elores.
30. **Retrospective Analysis of Antibiotic Susceptibility and Resistance Patterns Against Nosocomial Gram Negative Pathogens in Fortis Memorial Research Institute, Gurgaon**

*Author: Ruchika Bagga*


**Abstract**

Antibiotic resistance is an alarming problem globally, especially in developing nations like India. This study was aimed to study the susceptibility pattern of nosocomial gram negative microbes towards meropenem, piperacillin+tazobactam, amikacin and ceftriaxone+sulbactam+EDTA (Elores) in Fortis Hospital, Gurgaon, India. A total of 129 clinical isolates from various clinical specimens were collected. All the samples were processed under strict quality control measures and identified as per standard microbiological methods. Susceptibility study was done by the disc diffusion method according to the procedure of Clinical Laboratory Standard Institute guidelines. Among 129 samples tested, 85 samples showed the presence of infection and 44 were sterile. Among the isolates, *E. coli* (43.52%) was found to be the most dominant pathogen followed by *K. pneumoniae* (20%), *A. baumannii* (9.41%), *P. aeruginosa* (9.41%). However, other Gram negative bacteria accounted for a cumulative share of 17.64%. Among the tested antibiotics, Elores was the most effective against all the tested pathogens with 87 to 100 % susceptibility. Results of meropenem susceptibility were comparable to Elores against *P. aeruginosa* (100% susceptibility), and other gram negative bacteria (93.35), except *K. pneumoniae*, *E. coli* and *A. baumannii*. The susceptibilities of meropenem against *A. baumannii*, *E. coli* and *K. pneumoniae* were 62.5, 37.8 and 35.3%. respectively. The susceptibilities of piperacillin+tazobactam and amikacin varied 29 to 64% and 47 to 83 %, respectively. Susceptibility to pathogens isolated from blood, sputum, urine, endotracheal secretion and broncho alveolar lavage showed poor response to all drugs studied except Elores. On the basis of our results we conclude that Elores is more effective than other tested antibiotics routinely used to treat gram negative bacterial infections.
31. Management of Pneumonia with Multiloculated Left Pleural Effusion caused by Extended Spectrum Beta-Lactamases Producing *Klebsiella pneumoniae*

Authors: Suresh Goyal

**Abstract**
Increase in the mortality and morbidity in pleural infection is a concern worldwide due to increasing resistant gram negative pathogens like *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella* species. Rise of pneumonia due to *K. pneumoniae*, is more likely observed in alcoholics, diabetics, hospitalized and patients receiving mechanical ventilation. In the present study, we discuss a case of a 59 year old male patient with pulmonary effusion infected with extended spectrum beta-lactamases (ESBL) producing *K. pneumoniae* with co-morbidities of uncontrolled Type II diabetes mellitus (DM), hypertension and coronary artery disease (CAD), treated with a newer antibiotic adjuvant entity: Elores (ceftriaxone/sulbactam/disodium edetate) and recovered well.

**Keywords:** Gram negative pathogens, beta-lactamases, Elores.
32. Elores Treatment in Patient with Urinary Tract Infection due to Multi Drug Resistant *Escherichia coli* and Secondary Thrombocytopenia: A Rare Case Study

**Abstract**
We are reporting an unusual case of urinary tract infection caused by MDR ESBL producing *E. coli* and secondary thrombocytopenia. It is a rare case of infection successfully treated with Elores (Ceftriaxone + Sulbactam + Disodium Edetate).

**Keywords:** UTI, thrombocytopenia, *Escherichia coli*, Elores

Author: Dr. M K Singh
Abstract
Aim/Objective: Increase in incidences of pneumonia due to multi-drug resistant methicillin resistant Staphylococcus aureus (MRSA) in both community and health care settings is of great concern globally. Present study aims to retrospectively analyze the efficacy of new fixed dose combination with antibiotic adjuvant entity (FDC) in comparison with vancomycin to treat patients with multi-drug resistant MRSA pneumonia.

Materials and Methods: During this retrospective study, case sheets of patients who were treated for MRSA pneumonia with vancomycin or fixed dose combination of vancomycin + ceftriaxone + adjuvant (FDC) between 20 March 2010 to 20 October 2014 at tertiary care center, were analyzed. Various demographic features, antibiotic therapy, length of treatment duration and the resulting efficacy were evaluated. Microbiological success was measured in terms of bacterial eradication, while clinical success was monitored in terms of complete omission of systemic signs and symptoms.

Results: Among 136 patients analyzed, 113 cases were having positive culture for MRSA, and hence were further analyzed. Out of these 113 patients, empirical treatment with vancomycin was given in 59 patients and 54 patients were treated with FDC empirically. After initial culture reports, 22 patients showing resistance to vancomycin were shifted to FDC. Amidst all the patients, 24 (64.86%) of 37 from vancomycin group and 62 (81.57%) of 76 from FDC group achieved clinical success. 9 patients out of these failure cases were cured with FDC + colistin combination therapy. Failure rates in FDC treated patients were significantly low (6.57%) as compared to vancomycin group (13.51%).

Conclusion: For the treatment of different types of multi-drug resistant MRSA pneumonia, the empirical intravenous FDC therapy was safe and well tolerated with higher efficacy than vancomycin. Most of the vancomycin failure cases responded to FDC therapy and were cured. This retrospective study also concludes that an alternative option of FDC + colistin is safe and effective to treat the patients which fail to respond to FDC monotherapy.

Keywords: Pneumonia, MRSA, Multi-drug resistant bacteria, Fixed dose combination, Retrospective study
Abstracts from Phase-III and PK-PD Studies on Elores

Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'standard' treatment. Because of their size and comparatively long duration, Phase III trials are expensive, time-consuming and difficult trials to design and run. This can also be called the "pre-marketing phase" because it actually is supposed to measure the patient response to the drug in larger numbers, at multiple centers, in a regulated manner, and is a mandatory requirement for getting approval from regulatory authorities.

Other reasons for performing trials at this stage include attempts by the innovator(sponsor) at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as "Phase IIIb studies". On an average globally, about 50% of drug candidates either fail during the Phase III trial or are rejected by the respective national regulatory agencies. However, Elores successfully completed the Phase-III study and which was later published in two separate articles in a peer reviewed journal.

PK/PD strategies are implemented in early research phases of drug discovery projects to enable successful transition of drug development. In case of Elores the PK/PD study was conducted in 2012 at Hyderabad with the purpose of understanding the PK/PD correlation of all its components. Effective PK/PD study design, analysis, and interpretation can help scientists elucidate the relationship between PK and PD for all the components of the drug, understand the mechanism of drug action, and identify PK properties for further improvement and optimal compound design. Additionally, PK/PD modeling can help increase the translation of in-vitro compound potency to the in-vivo setting, thus to reduce the number of in-vivo animal studies, and also to improve translation of findings from preclinical species into the clinical setting. Characterizing the relationship between the pharmacokinetics (PK, concentration vs. time) and pharmacodynamics (PD, effect vs. time) is an important tool in the discovery and development of new drugs in the pharmaceutical industry.
PK / PD
Indices for antibiotics key:

- $T > MIC$, time for which the plasma concentration of the drug exceeds the MIC
- $fT_{MIC}$, time that the unbound or ‘free’ concentration of the drug exceeds the MIC
- $C_{\text{MIC}}$, ratio of maximum antibiotic concentration ($C_{\text{MIC}}$) to the MIC
- $AUC_{MIC}$, ratio of the area under the concentration-time curve during a 24-hour time period ($AUC_{MIC}$) to the MIC.

**Antibiotic**

**Host**

**Pathogen**

**Infection treatment » Clinical Cure**
1. A Randomized, Open-Label, Prospective, Multicenter Phase-III Clinical Trial of Elores in Lower Respiratory Tract and Urinary Tract Infections

Authors: Manu Chaudhary and Anurag Payasi

Abstract

Background: Lower respiratory tract infections (LRTIs) and urinary tract infections (UTIs) are the leading causes of death worldwide. Treatment of these infections require the use of antibiotics with enhanced activity against a broad spectrum of respiratory and urinary pathogens. This study was designed to study clinical and bacteriological efficacy as well as tolerability of ceftiaxone + disodium edetate + sulbactam (the novel Antibiotic Adjuvant Entity; Elores) in adult patients in the treatment of lower respiratory tract infections (LRTIs) and urinary tract infections (UTIs).

Methods: A randomized, open-label, multicenter study was conducted on 297 patients which included 204 in UTIs and 93 in LRTIs. A total of 148 patients were there in Elores group with 102 cases of UTIs and 46 LRTIs; 149 in ceftriaxone group with 102 cases of UTIs and 47 LRTIs. The patients received 3–10 days of treatment with Elores 3.0 g twice daily and ceftriaxone 2.0 g twice daily in two divided doses.

Results and Discussion: Clinical cure rates in ITT (Intend to treat) populations of Elores were 83.33% (85/102), 91.30% (42/46) in the UTIs and LRTIs, respectively, and 34.31% (35/102), 31.91% (15/47) in the ceftriaxone group for UTIs and LRTIs, respectively. The corresponding bacterial eradication rates were 95% (57/60) and 97.05% (33/34) for Elores in the UTIs and LRTIs, respectively and 80.64% (50/62) and 71.42% (10/14) for ceftriaxone in the UTIs and LRTIs, respectively. Adverse reaction were observed in 20.59% (21/102) and 15.22% (7/46) in Elores groups of UTIs and LRTIs, respectively and 36.27% (37/102) and 31.91% (14/47) in ceftriaxone groups of UTIs and LRTIs, respectively.

Conclusions: Results obtained in the present study, together with microbiological evaluation data suggest that Elores is more effective and safe antibacterial agent for the treatment of LRTIs and UTIs infections.
2. Clinical, Microbial Efficacy and Tolerability of Elores, a Novel Antibiotic Adjuvant Entity in ESBL Producing Pathogens: Prospective Randomized Controlled Clinical Trial

Authors: Manu Chaudhary and Anurag Payasi
Journal: Journal of Pharmacy Research 7(4):275–280 · April 201

Abstract
Objective: To compare clinical and bacteriological efficacy as well as tolerability of ceftriaxone-sulbactam with adjuvant disodium edetate (the novel antibiotic adjuvant entity; Elores) in the treatment of skin and skin structure infections (SSSIs) and bone and joint infections (BJIs).

Methods: Patients were randomized into group A (ceftriaxone; n = 26 for SSSIs; n = 35 for BJIs) group B (Elores; n = 30 for SSSIs; n = 35 for BJIs). The patients were administered with Elores 3.0 g twice daily and ceftriaxone 2.0 g twice daily in two divided doses for 3–10 days.

Results: Out of the total population, percentage of clinically cured patients was 80.33% in Elores group and 30.77% in ceftriaxone group. However, 53.33% patients failed to respond to ceftriaxone in comparison to no clinical failure in Elores group at the end of therapy. There was 23.08% cumulative bacterial eradication in both indications BJIs and SSSIs of group A whereas a significantly higher 85.25% cumulative bacterial eradications was noted with group B in both indications. However, 58.46% cases failed to respond to ceftriaxone bacteriologically.

Conclusion: Results of this study indicates that Elores is more safe and effective regimen in treating ESBL producing gram-negative and gram-positive pathogens in comparison to plain ceftriaxone.
3. Pharmacokinetics and Pharmacodynamics of Elores in Complicated Urinary Tract Infections caused by Extended Spectrum Beta-Lactamase Strains

Authors: V. S. Suresh Attili and Manu Chaudhary

Abstract
The pharmacokinetic/pharmacodynamic indices generally predict the efficacy of antibiotics when used alone. The information related to these indices for the combination products and that too in cases of resistant bacterial infections is limited. The present study involved treatment of 12 subjects with severe complicated urinary tract infections caused by resistant extended spectrum beta lactamase bacterial strains with Elores; ceftriaxone and sulbactam combination with non-antibiotic adjuvant ethylene diamine tetra acetate. In this study Elores 3g bd dose was administered and the pharmacokinetic/pharmacodynamic indices were evaluated. To see the impact of lower Elores dose on these indices, 3g od data was simulated using pharmacokinetic parameters from 3g bd dose. The pharmacokinetic/pharmacodynamic indices suggest that Elores 3g od can treat mild to moderate infection wherein minimum inhibitory concentration requirement is <16µg/mL; however for severe complicated urinary tract infections with resistant strains wherein the requirement is 16-32µg/mL, Elores 3g bd should be the choice.
Abstracts from *In-vitro* Studies on Elores Sensitivity by External Authors and VMRC

Microbiology data provide important information to guide clinical development of an investigational new drug. Microbiology data guide clinicians on the use of an antibacterial drug for its intended indications. Therefore, evaluation of the activity of an antibacterial drug, including its active components and major metabolites becomes important. The performance of antimicrobial susceptibility testing is important to confirm susceptibility to chosen empirical antimicrobial agents, or to detect its resistance in individual bacterial isolates.

Since its conception as a possible solution for the problem of carbapenem resistance, Elores has undergone numerous *in-vitro* sensitivity studies before the final conclusions on its efficacy against MDR gram negative pathogens were drawn. In this chapter, published articles on 27 such sensitivity studies of Elores vis-a-vis other antibiotics evaluating the *in vitro* antimicrobial susceptibility are presented in abstract forms. The goals of testing were to detect possible drug resistance in common pathogens involved in hospital acquired infections and to evaluate comparative susceptibility of drugs of choice against those pathogens. In general, the most widely used testing methods include broth microdilution or rapid automated instrument methods that are used widely in tertiary care centers. Manual methods that provide flexibility include the disk diffusion and gradient diffusion methods. Each method has strengths and weaknesses, including organisms that may be accurately tested by the specific method. Current testing method used most frequently for Elores is disc diffusion method, it provides fairly accurate sensitivity pattern and phenotypical detection of common antimicrobial resistance mechanisms. However, work is also being done for creating automated testing mechanisms for Elores as well, in the coming time.

Before going for full scale sensitivity testing at external tertiary care centers, multiple tests were conducted against a test panel of relevant bacteria early in clinical development. The target was to develop data on a sufficient range of clinically relevant bacteria to allow an assessment of the potential clinical efficacy of the antibacterial AAE for the intended indication, few of these studies were also published in various national and international journals. Studies of the spectrum of activity were conducted with parallel testing of antibacterial drugs such as Meropenem, Piptazo, Ceftriaxone etc.

CLSI breakpoints for Ceftriaxone were considered to evaluate the sensitivity patterns of Elores against tested gram negative bacteria. By definition, an organism is not considered sensitive unless the concentration of components of the antibiotic adjuvant entity attainable in the body exceeds that necessary to inhibit its growth *in-vitro*, and the same was confirmed by Elores PK/PD study as shared in previous chapter.
1. Antibiotic Sensitivity Pattern of Bacterial Pathogens in Rajeev Gandhi Cancer Hospital, Delhi

Author: Neelam Sachdeva

Abstract: We performed a retrospective, comparative study to evaluate efficacy outcomes of empiric Elores (ceftriaxone/sulbactam/EDTA) therapy compared with the meropenem, imipenem and piperacillin/tazobactam in patients suspected of bacterial infections. Among the isolates which showed the presence of bacteria, around 36.0% samples were of urine followed by sputum and blood which contributed to 15.7% and 11.5% respectively. Among the isolates, *Escherichia coli* (51.7%) was found to be the most dominant pathogen followed by *Klebsiella pneumoniae* (29.5%), *Pseudomonas aeruginosa* (15.0%), *Acinetobacter baumannii* (2.3%), and *Proteus mirabilis* (1.5%). Higher susceptibility rates were achieved with Elores in comparison with piperacillin/tazobactam and meropenem. Susceptibility pattern for imipenem was almost same as that for Elores. Piperacillin/tazobactam resistance was high in all the tested pathogens ranging from 54.0% (least in *P. aeruginosa*) to 100.0% (highest in *Proteus spp.*) when compared to Elores to which low resistance was observed ranging from 19.0% (least in *P. aeruginosa*) to 33.3% (highest in *A. baumannii*) was observed. Overall, the results of the present study strongly advocate the superiority of Elores over piperacillin/tazobactam and meropenem and an equivalence to imipenem. Elores can be a very effective alternative to treat against the deadly multi drug resistant gram negative bacteria, sparing penems as reserve drugs.
2. Efficacy of Ceftriaxone-Sulbactam-EDTA Combination in Immuno Compromised Patients in a Tertiary Care Cancer Centre

Authors: Sanjay Biswas, Vivek Bhatt and Rohini Kelkar
Journal: Journal of Drug Metabolism and Toxicology 2015, 6:4

Abstract

Introduction: The resistance to the antimicrobials has been increasing over the years and is varying from country to country. Among the causes of β-lactam antibiotic resistance, the production of ESBLs appeared to be most common. ESBLs are plasmid mediated and can be easily transmitted among members of enterobacteriaceae, thus facilitating the dissemination of resistance, not only to β-lactam, but to other commonly used antibiotics including aminoglycosides and quinolones. To overcome ESBLs resistance, carbapenem drugs have been introduced in clinical settings, although carbapenems resistance has been reported increasingly worldwide. Resistance in bacteria to carbapenems is due to the production of carbapenem hydrolyzing enzymes called carbapenemases, which is encoded by KPC, VIM and IMP genes. The aim of the present study was to compare the susceptibility pattern of ceftriaxone-sulbactam-EDTA(CSE) combination with other routinely used antibiotics in immunocompromised patients.

Materials and Methods: A total of 33930 clinical samples were received in the Dept. of Microbiology in 2014. All the samples were processed as per standard microbiological methods. Antimicrobial susceptibility testing of cefoperazone-sulbactam, ceftriaxone-sulbactam-EDTA, piperacillin-tazobactam, imipenem and meropenem of 195 Gram negative isolates, included in this study, were carried out by disc diffusion method as per CLSI guidelines. ATCC strains were used as standards. Interpretative criteria of Ceftriaxone were used for interpretation of CSE.

Results: Of the 33930 samples received, only 195 Gram negative isolates, from different clinical samples, were included in this study. Blood was the most common isolate followed by broncho-alveolar lavages, wound swabs and drain fluids. Escherichia coli was the commonest isolate followed by Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter spp. Carbapenems were the most sensitive antimicrobial followed by cefoperazone-sulbactam, ceftriaxone-sulbactam-EDTA and piperacillin-tazobactam.

Conclusions: Results obtained in the current study clearly demonstrates the good in-vitro activity of ceftriaxone plus sulbactam plus EDTA as compared to other β-lactam β-lactamase inhibitor combinations. The enhanced susceptibility of ceftriaxone+EDTA+sulbactam against different clinical isolates is likely to be associated with synergistic activity of ceftriaxone+sulbactam+EDTA. EDTA chelates the divalent ions, thus enhancing the susceptibility of ceftriaxone plus EDTA plus sulbactam towards different microorganisms. EDTA also enhances the susceptibility by altering the outer membrane permeability, which in turn increased penetration of drugs inside the bacterial cells.
3. *In Vitro* Antimicrobial Susceptibility of Ceftriaxone/Sulbactam/Ethylene Diamine Tetra Acetic Acid and Comparison to other Beta-Lactam/Beta-Lactamase Inhibitors, Carbapenems and Colistin against Gram Negative Bacteria

Authors: S. Jain, A. Gupta, V. Khare  

**Background:** Drug resistance against Gram Negative Bacteria (GNB) is increasing. Incidence of ESBL producing bacteria is around 70-80%. Carbanpenem resistance has also been reached 40-90% for the GNB. We are also obtaining Colistin resistant isolates. Resistance against Beta-lactam (BL)/beta-lactamase inhibitor (BLI) combinations is already very high. No new antibiotic or antibiotic group is in pipeline at least for the next 5-10 years. With this background the objective of this study is to compare *in vitro* susceptibility of new BL/BLI combination Ceftriaxone/Sulbactam/Ethylene diamine tetra acetic Acid (CSE) to Piperacillin/Tazobactam, Cefoperazone/Sulbactam, Cefepime/Tazobactam, Meropenem, Imipenem and Colistin.

**Methods & Materials:** Study was conducted on all clinical samples received from all critical care units between January 2014 and June 2015. Identification and susceptibility was done by Vitek 2 compact system. Susceptibilities of Ceftriaxone/Sulbactam/Ethylene diamine tetra acetic Acid and Cefepime/Tazobactam were done by disc diffusion method on the bases of CLSI guidelines. *Escherichia coli, Klebsiella* sp., *Pseudomonas* sp. and *Acinetobacter* sp. isolates were included in the study.

**Results:** *Escherichia coli* (324, 25%) was the most common bacteria isolated followed by *Klebsiella* sp. (309, 24%), *Pseudomonas* sp. (217, 17%) and *Acinetobacter* sp. (214, 17%) from all clinical samples. % susceptibilities were as given in table below.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of Isolates</th>
<th>CSE</th>
<th>Cefepime/Sulbactam</th>
<th>Piperacillin/Tazobactam</th>
<th>Cefoperazone/Tazobactam</th>
<th>Meropenem</th>
<th>Imipenem</th>
<th>Colistin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E.coli</em></td>
<td>324</td>
<td>67.4</td>
<td>77.3</td>
<td>46.5</td>
<td>57.9</td>
<td>73.1</td>
<td>72.7</td>
<td>99.5</td>
</tr>
<tr>
<td><em>Klebsiella</em> sp.</td>
<td>309</td>
<td>28.3</td>
<td>37.6</td>
<td>18.6</td>
<td>26.2</td>
<td>32</td>
<td>32</td>
<td>70.9</td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp.</td>
<td>217</td>
<td>43.1</td>
<td>64.1</td>
<td>40.6</td>
<td>46.9</td>
<td>52.4</td>
<td>50.3</td>
<td>93.8</td>
</tr>
<tr>
<td><em>Acinetobacter</em> sp.</td>
<td>214</td>
<td>24.3</td>
<td>13.9</td>
<td>11.3</td>
<td>23.6</td>
<td>12.5</td>
<td>11.8</td>
<td>95.8</td>
</tr>
</tbody>
</table>

**Conclusion:** Colistin was the most sensitive antimicrobial for all GNB. Carbapenem resistance was around 27% - 89%. CSE susceptibility was better than Piperacillin/Tazobactam and Cefoperazone/Sulbactam and comparable to Meropenem and Imipenem. Although the number of isolates included in this study were less in number, a larger study needs to be conducted. This is an *in vitro* susceptibility data hence study has to be conducted for clinical efficiency of CSE.
4. **Retrospective Analysis of Antibiotic Susceptibility and Resistance Patterns against Nosocomial Gram Negative Pathogens in Fortis Memorial Research Institute, Gurgaon**

**Abstract**
Antibiotic resistance is an alarming problem globally, especially in developing nations like India. This study was aimed to study the susceptibility pattern of nosocomial gram negative microbes towards meropenem, piperacillin+tazobactam, amikacin and ceftriaxone+ sulbactam+EDTA (Elores) in Fortis Hospital, Gurgaon, India. A total of 129 clinical isolates from various clinical specimens were collected. All the samples were processed under strict quality control measures and identified as per standard microbiological methods. Susceptibility study was done by the disc diffusion method according to the procedure of Clinical Laboratory Standard Institute guidelines. Among 129 samples tested, 85 samples showed the presence of infection and 44 were sterile. Among the isolates, *E. coli* (43.52%) was found to be the most dominant pathogen followed by *K. pneumoniae* (20%), *A. baumannii* (9.41%), *P. aeruginosa* (9.41%). However, other gram negative bacteria accounted for a cumulative share of 17.64%. Among the tested antibiotics, Elores was the most effective against all the tested pathogens with 87 to 100% susceptibility. Results of the meropenem were comparable to Elores against *P. aeruginosa* (100% susceptibility), and other gram negative bacteria (93.35), except *K. pneumoniae*, *E. coli* and *A. baumannii*. The susceptibilities of meropenem against *A. baumannii*, *E. coli* and *K. pneumoniae* were 62.5, 37.8 and 35.3%, respectively. The susceptibilities of piperacillin+tazobactam and amikacin varied 29 to 64% and 47 to 83%, respectively. Susceptibility to pathogens isolated from blood, sputum, urine, endotracheal secretion and broncho alveolar lavage showed poor response to all drugs studied except Elores. On the basis of our results we conclude that Elores is more effective than other tested antibiotics routinely used to treat gram negative bacterial infections.
5. **Comparative Assessment of Antibiotic Susceptibility Pattern of Gram Negative Pathogens Isolated from Intensive Care Unit Patients in Pune**

Authors: S. Arora and N. Munshi

Journal: British Microbiology Research Journal10(2): 1-9, 2015, Article no.BMRJ.18199

**Abstract**

**Introduction and Aim:** Extended spectrum ß-lactamases (ESBLs) and metallo-ß-lactamases (MBLs) production is one of the main means of the resistance developed by gram negative bacteria against ß-lactam antibiotics. The present study was carried out to evaluate the incidences of ESBL and MBL producers in gram negative bacteria isolated from Ruby Hall Clinic, Pune, Maharashtra, India and to evaluate the efficacy of drugs against these bacteria.

**Methodology:** 254 different samples collected from various sources were screened for the presence of bacterial pathogens. The pathogens were identified using selective media technique. The ESBL and MBL producer’s screening and the antimicrobial susceptibility testing (AST) of pathogens towards a new drug; Elores (ceftriaxone + sulbactam with adjuvant ethylene diamine tetra acetic acid, EDTA) in comparison with commonly used antibiotics like meropenem, imipenem, piperacillin-tazobactam and cefoperazone-sulbactam was carried out according to CLSI guidelines.

**Results:** Among 254 samples collected, 200 samples showed the presence of bacterial infections with *Klebsiella* sp. (39%) as the most predominant pathogens followed by, *E. coli* (32%) and *Pseudomonas* sp. (16.5%), *Acinetobacter* sp. (12.5%). Of the identified pathogens, 61% (122/200) were found to be ESBL producers and 4.5% (9/200) were MBL producers. Nearly, 3.5% (7/200) pathogens were both ESBL and MBL producers. However another significant number (66 isolates) of pathogens were identified as non-ESBL/ non-MBL producers. Further, our data showed that, Elores was highly susceptible (87 to 100%) followed by imipenem-cilastatin (30 to 67%), meropenem (33 to 68%), cefoperazone-sulbactam (24 to 70%) and piperacillin-tazobactam (4 to 81%) against gram negative bacteria.

**Conclusion:** The results of the present study concludes, that Elores is an useful option to treat the infections caused by carbapenemase producing multi-drug resistance gram negative bacteria.
6. Alarmingly Rising β-lactamase-mediated Meropenem Resistance in Nosocomial infections in Indian Hospitals

Authors: Shikha Chaudhary, Manoj Kumar, Rahul Gupta, Esha Walia and Anshika Gangal

Abstract:
Growing insensitivity to multiple antibiotic groups particularly beta-lactams has been a concern for past decade. The concerns of antibiotic resistance, lack of new antibiotics and limited therapeutic options led us to compare the susceptibility of a new antibiotic adjuvant entity Elores (Ceftriaxone + sulbactam + ethylene diamine tetra acetic acid, EDTA) with meropenem among gram negative organisms isolated from >1100 clinical samples obtained from various Indian hospitals during past six months. Out of total samples analyzed 923 samples showed the presence of infection and 281 samples were sterile. E. coli (44.2%) was found to be the most dominant pathogen followed by P. aeruginosa (18.2%), K. pneumoniae (10.9%), A. baumannii (9.0%), M. morganii (4.9%), P. mirabilis (4.8%), S. marcescens (3.0%), K. oxytoca (3.8%) and E. cloacae (1.2%). Higher success rates have been achieved with ceftriaxone+sulbactam+EDTA in comparison to meropenem. Use of meropenem in the light of alarmingly rising resistance (9 to 62 %) warrants restricted use and re-evaluation of the therapies where penems are used in high doses and to evaluate ceftriaxone+sulbactam+EDTA as an alternative. Results of meropenem was comparable to ceftriaxone+sulbactam+EDTA against M. morgannii, P. aeruginosa, and S. mercescens but in enterobacters ceftriaxone+sulbactam+EDTA exhibited around 3% to 33% higher susceptibility. We conclude that ceftriaxone+sulbactam+EDTA is much more effective against most of the multidrug resistant (MDR) pathogens and can be a better option against these pathogens.
7. Trend in Susceptibility Pattern to Commonly Used Antibacterial Agents and Role of Ceftriaxone + Sulbactam + Disodium Edetate Combination against Extended Spectrum Beta-Lactamase and Carbapenemase Producing Gram Negative Isolates

Authors: K Prasanthi, K Nagamani, PR Anuradha and DS Murty

Abstract
In the present study, we attempted to find the resistance pattern to antibacterial agents among extended spectrum beta-lactamases (ESBL) and carbapenemase positive isolates, obtained from different clinical specimens at Gandhi Medical College Hospital, Hyderabad, India. A total of 299 isolates consisting of 250 ESBL and 49 carbapenemase producing isolates were recovered from various samples collected from intensive care units (ICU) and wards. Antibiotic susceptibility study was done by the disc diffusion method according to the Clinical Laboratory Standards Institute guidelines. Out of 299 isolates, 281 (93.9%) were of enterobacteriaceae family and 18 (6.0%) were from non-enterobacteriaceae. Of enterobacteriaceae family, 184 (65.5%) were E. coli and 97 (34.5%) were K. pneumoniae. Among non-enterobacteriaceae, 9 of each were Acinetobacter spp and P. aeruginosa.

The most prevalent pathogen was E. coli followed by K. pneumoniae, and equal prevalence of Acinetobacter spp and P. aeruginosa. Ceftriaxone+sulbactam+disodium edetate (Elores) was the most effective drug showing 100% susceptibility to P. aeruginosa followed by E. coli (88.4%), K. pneumoniae (78%), Acinetobacter spp (66.6%). The comparator drugs showed low sensitivity up to 55%. Carbapenemase producers, showed 100% resistance to Meropenem. However, Elores showed sensitivity ranging from 50% to 58% in carbapenemases producing E.coli, K. pneumoniae and P. aeruginosa. This study provides important data for clinicians to plan the appropriate treatment regimen. As Elores showed better activity against both enterobacteriaceae and non-enterobacteriaceae family pathogens, it may be a useful option to treat the infections caused by these organisms.
8. Comparative Antimicrobial Efficacy Evaluation of a New Product Elores against Meropenem on Gram-Negative Isolates

Authors: Manoj Kumar, Shikha Chaudhary, Diljot Kumar Makkar, Neeru Garg, Sanjeev Kumar Chugh

Abstract

**Background and Objective:** Increased resistance of gram-negative bacteria towards most of the available antibiotics, especially beta-lactam antibiotics is a prime difficulty for the treatment of infections caused by these pathogens. In view of the fact that there is a continuous increase in the antibiotic resistance and the limited available therapeutic options, we aimed the present work to evaluate the antibiotic susceptibility pattern of 847 isolates towards meropenem and Elores (ceftriaxone+sulbcatam+and adjuvant ethylene diamine tetra acetic acid).

**Methods:** A total of 1180 clinical samples were collected from patients suspected of bacterial infection between January 2014 to June 2014. These samples were subjected for bacterial identification. Antibiotic susceptibility testing were carried out according to the recommendations of Clinical Laboratory Standards Institute (CLSI) guidelines.

**Results:** Among the samples which showed the presence of bacteria, around 29.04% samples were of sputum followed by urine and blood which contributed to 21.95% and 12.51%, respectively. *Escherichia coli* (39.55%) was found to be the most dominant pathogen, followed by *Pseudomonas aeruginosa* (19.12%), *Klebsiella pneumoniae* (12.39%), *Proteus mirabilis* (8.50%), *Klebsiella oxytoxa* (8.26%), Acinetobacter baumannii (5.31%), *Morganella morganii* (3.77%), *Serratia marcescens* (2.24%). The susceptibility of Elores was comparable with meropenem in some of the organisms, but Elores displayed higher susceptibility in *E. coli*, *A. baumannii*, *K. pneumoniae*, *P. mirabilis*, *K. oxytoxa*, *M. morganii* and *S. marcescens* which might be due to presence of metallo-beta lactamases in these isolates.

**Conclusion:** Overall, the results of this study strongly advocate the equivalent of Elores with meropenem and can be of very effective alternative to treat against the deadly multi drug resistant gram-negative bacteria.
9. Susceptibility Trend of Drugs Among Metallo β-lactamase Producing Strains of Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas aeruginosa in India

Authors: Manu Chaudhary and Anurag Payasi
Journal: International Journal of Advances in Pharmacy, Biology and Chemistry: 2015, 4(2); 303-312

Abstract
The current study was conducted to observe the prevalence of different types of metallo-β-lactamases (MBLs) and their variants among 849 clinical isolates obtained from various parts of India. Further, antibiotic susceptibility behaviour of these isolates to different antibiotics was analysed. Identification of isolates according to the standard microbiological techniques and VITEK-2. Susceptibility studies were carried out according to Clinical and Laboratory Standards Institute guidelines. Phenotypic screening confirmed that out of 1361 isolates, 849 (62.4%) isolates were MBL producers. The highest number of MBL producers was from Pseudomonas aeruginosa (235/347; 67.7%) followed by Klebsiella pneumoniae (88/131; 67.2%), Escherichia coli (151/254; 59.4%) and Acinetobacter baumannii (371/629; 58.9%). PCR results revealed the occurrence of NDM type MBLs were the predominant (n= 412), followed by IMP type (n= 245) and VIM type (n= 192). Susceptibility results demonstrated that approximately 94.1%, 93%, 93.2% and 91% of E. coli, A. baumannii, K. pneumoniae and P. aeruginosa isolates were susceptible to CSE1034. The susceptibilities of penems (meropenem, imipenem+cilastatin) and piperacillin+tazobactam were <45% and <16%. Interestingly, none of the isolates were found to be susceptible to amoxicillin + clavulanic acid and cefoperazone + sulbactam. Results of the present study indicate that CSE1034 appeared to be the most efficacious and majority of the isolates were susceptible to CSE1034 appeared to be the most efficacious and majority of the isolates were susceptible to CSE1034 and can be a potent antibacterial agent for the treatment of severe bacterial infections caused by MBL producing organisms.
10. Molecular Characterization and In Vitro Susceptibilities of ß-Lactamase Producing Escherichia coli, Klebsiella Species, Acinetobacter baumannii, Pseudomonas aeruginosa and Staphylococcus aureus to CSE1034 and other ß-Lactams

Authors: Manu Chaudhary, Anurag Payasi

Abstract

Objective: To study the prevalence of extended-spectrum ß-lactamases (ESBLs) among 663 clinical isolates obtained from various parts of India and to study the occurrence of different variants of ESBLs among these isolates.

Methods: Phenotypic characterization and susceptibility studies were performed according to the methods described in Clinical and Laboratory Standards Institute guidelines. The occurrence of ESBL variants was analyzed with PCR using the previously reported primers.

Results: Among the six hundred sixty three isolates, the identified isolates were Acinetobacter baumannii (72), Escherichia coli (218), Klebsiella pneumoniae (30), Klebsiella oxytoca (63), Pseudomonas aeruginosa (264) and Staphylococcus aureus (16). PCR results revealed that approximately 89.0% of Pseudomonas aeruginosa isolates were positive for ESBL followed by Escherichia coli (85.3%), Klebsiella pneumoniae (76.6%), Klebsiella oxytoca (73%), Acinetobacter baumannii (72.2%) and Staphylococcus aureus (31.2%). The overall prevalence of ESBL was 82.5%. The presence of TEM type ESBLs were the predominant (in 186 isolates), followed by SHV (138), OXA (92), CTX-M (65), AmpC (33), KPC (28) and blaZ (5). Of the drugs involved in the study, CSE1034 was found to be the most efficacious against all of ESBL positive clinical isolates showing susceptibility approximately 95.7% with minimal inhibitory concentration values between 0.125 and 8.000 µg/mL for all strains tested. The susceptibilities of penems (meropenem and imipenem and cilastatin) ranged between 83% and 93% for all the isolates. The susceptibilities of other drugs like piperacillin and tazobactam, amoxicillin and clavulanic acid, cefoperazone and sulbactam were <45% for all the isolates.

Conclusions: Results of the present study indicated that majority of the isolates were susceptible to CSE1034 and it could be a potent antibacterial agent for the treatment of severe bacterial infections caused by such organisms.
Abstract

Background: In the visage of multidrug resistance among gram negative bacilli, we look forward to carbapenem group of drugs as empiric choice in seriously ill patients. However, increasing resistance to carbapenems, the last resort, is of growing concern for all. It’s high time to look beyond carbapenems and emphasize on carbapenem sparsers.

Objective: This study is to find the susceptibility pattern of the novel adjuvant antimicrobial CSE 1034, a combination of ceftriaxone+sulbactam+disodium edetate for the current ESBL and MBL isolates in a tertiary care centre.

Materials and Methods: A total of 823 gram negative bacterial isolates were obtained from different clinical specimens during the period of March, 2013 to October, 2013. The overall prevalence of metallo beta lactamase producing gram negative organisms was 11 percent (n=91). We included a total of 141 clinical isolates for this study.

Results: Among 141 clinical isolates, 50 isolates (35%) were ESBL producers and 91 (65%) were MBL producers. Maximum numbers of ESBL producers were identified in Escherichia coli followed by Klebsiella pneumoniae, Acinetobacter baumannii and Proteus spp. Maximum numbers of MBL producers were identified in Klebsiella pneumoniae followed by Pseudomonas aeruginosa. CSE 1034 (ceftriaxone+sulbactam+disodium edetate) showed fairly good in-vitro susceptibility for these ESBL and MBL producing isolates. It exhibited 64% to 100% susceptibility and 18% to 22% intermediate sensitivity to ESBL producing isolates and 42% to 89% susceptible and 10% to 51% intermediate response to MBL producing isolates.

Conclusion: With increasing resistance to the commonly prescribed drugs used to treat infections caused by variety of gram negative organisms, ceftriaxone+sulbactam+disodium edetate, a novel Antibiotic Adjuvant Entity (AAE) may be a promising option.
12. False Susceptibility of Antibiotics to Carbapenemase Producers and Means to Overcome

Authors: Manu Chaudhary and Anurag Payasi

Abstract:
The aim of this study was to identify the reason for frequent failure of carbapenems and β-lactam and β-lactamase inhibitor combination drugs in clinical settings despite susceptibility. For this different isolates collected from clinical specimens were tested for susceptibility and identification of carbapenemase producers was done by phenotypic method (Modified Hodge Test). Further, phenotypic results were compared with the gold standard PCR results to assess accuracy of the results. A total of 541 isolates collected from various centres across India including *Escherichia coli* (n=154), *Klebsiella pneumoniae* (n=161), *Acinetobacter baumannii* (n=103) and *Pseudomonas aeruginosa* (n=123) were included in the study. These isolates were tested for susceptibility according to Clinical and Laboratory Standards Institute (CLSI) methods and then screened for carbapenemase following the same guidelines. The isolates were then subjected to Modified Hodge Test with and without zinc sulfate with subsequent confirmation with the genotypic assay. Out of 541 clinical isolates, 464 isolates were identified as probable carbapenemase producers. Further phenotypic screening of these isolates, only 316 (68.1 %) isolates were found to be positive to MHT. After addition of zinc into MHT sensitivity of the test was improved and now 431 (92.9 %) isolates were found to be positive to MHT indicating it is 24.8 % more effective compared to MHT without zinc sulfate. Subsequently, when 316 MHT positive isolates were screened through PCR, 30 % (95/316) isolates showed false positive and 19.6 % (29/316) isolates showed false negative, results indicating higher degree of false positive and negative results are associated with MHT. However, with the addition of zinc sulfate to MHT, false positive and negative results are minimized significantly. Among the tested drugs, Elores appeared to be the most efficacious with 90.9 % to 95.4 % susceptibility to carbapenemase producing organisms. Interestingly, penems (meropenem and imipenem plus cilastatin) exhibited higher resistance varing from 90 % to 96.1 %. For the proper treatment of patients, it is important to use simple and reliable tests for identification of carbapenemase producing clinical isolates among gram negative organisms. This study showed that the MHT technique is highly sensitive for detecting carbapenemases after addition of zinc. When susceptibility of various drugs were tested against carbapenemase producing isolates, Elores was found as the most efficacious drug.
13. Synergy of a Novel Antibiotic Adjuvant Entity Against Multi Drug Resistant Enterobacteriaceae

Abstract
In the present investigation, we investigated the in vitro interaction of ceftriaxone plus sulbactam with disodium edetate, a Non Antibiotic Adjuvant (NAA) against selected clinical isolates and in vitro susceptibility studies were also performed. The isolates were tested against a range of ratios of ceftriaxone and sulbactam using a microdilution checkerboard method. Having determined the appropriate ratios of ceftriaxone plus sulbactam, effect of various concentration of disodium edetate were also studied using the microdilution checkerboard method. All the results were analysed with the Fractional Inhibitory Concentration (FIC) indices. Susceptibility studies were carried out according to the Clinical and Laboratory Standards Institute (CLSI) methods. Results of this study demonstrated that 2:1 ratio of ceftriaxone and sulbactam was the more synergistic with FIC index values 0.4281, 0.4023, 0.4124 and 0.4325 for E. coli, A. baumannii, P. aeruginosa and K. pneumoniae. The synergicity of ceftriaxone and sulbactam was enhanced significantly with increasing concentration of disodium edetate and produced the lowest FIC index (<0.2) at 10 mM of disodium edetate in all positive controls as well as clinical isolates. Further, the synergy between ceftriaxone plus sulbactam with disodium edetate (Elores) was confirmed by broth dilution, time kill curve and agar diffusion methods. In broth dilution method, Elores (ceftriaxone+sulbactam+disodium edetate) produced 4 to 5 fold lower MIC when compared with ceftriaxone plus sulbactam. Approximately 104 log of killing reduction was observed with synergistic ratio of Elores in time kill curve study. This study suggests that, Elores could be an alternative regimen in combating antibiotic resistance among multi drug resistant enterobacteriaceae.

Authors: Manu Chaudhary and Anurag Payasi
14. Changing Trends of Commonly Used Intensive Care Unit Antibiotics due to Differential Membrane Permeability in Resistant Escherichia coli Collected in EASE Programme

Abstract
In order to understand resistance pattern of Escherichia coli clinical isolates, the outer membrane permeability trend of different antibiotics was studied. The outer membrane permeability of Elores was compared with other commonly used intensive care unit (ICU) drugs being used in the treatment of various infections caused by resistant E. coli. A total of fifty three isolates collected under EASE programme from North Indian hospitals, fifteen extended spectrum β-lactamases (ESBL) positive clinical isolates of E. coli were included in the study. Michaelis constants (Km) and maximal rates of substrate hydrolysis (Vmax) were determined from Lineweaver-Burk plot. Permeability coefficient was determined using the method described by Zimmermann and Rosslet. Elores demonstrated the lowest Vmax/Km ratio further indicating its lower affinity (high Km 209.9 ± 17.4 µM) towards β-lactamase or more stability against β-lactamase enzyme. The other comparator drugs including penems, colistin, β-lactam and β-lactamase inhibitor combinations exhibited three to ten folds higher Vmax/Km ratio compared to Elores indicating very high affinity for β-lactamase induced degradation. Elores penetrated the outer membrane of ESBL producing resistant E. coli with permeability coefficient approximately 1.8, 2.2, 6.9, 2.5 and 2.3 times higher than imipenem plus cilastatin, meropenem, colistin, cefoperazone plus sulbactam, piperacillin plus tazobactam, respectively. The increased penetration of the Elores leads to higher periplasmic concentration of the drug resulting in reduced MIC. Our results clearly demonstrated that Elores exhibited the highest permeability coefficient, enhanced penetration, greater stability and periplasmic concentration leading to higher susceptibility towards resistant E. coli compared to other drugs. Therefore, Elores can be considered as an empiric drug of choice for the treatment of infections caused by E. coli positive with ESBL.
15. *In vitro* Susceptibilities of 116 Clinical Isolates of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* to Conventional and New Antibacterial Agents

Authors: Manu Chaudhary, Shailesh Kumar, Anurag Payasi

**Abstract**

The antibiotic susceptibility patterns of 116 clinical isolates of *A. baumannii* and *P. aeruginosa* to a CSE1034 and other conventional antibiotic were examined. CSE1034 was found to be most active antibacterial agent against metallo-ß-lactamase (MBL) positive isolates with 100% susceptibility of both *P. aeruginosa* and *A. baumannii* and demonstrated variable susceptibility to extended spectrum-ß-lactamase (ESBL) (81.82 to 85.72%) and ESBL+MBL (90.63 to 94.73%) positive isolates of *P. aeruginosa* and *A. baumannii* compared to other drugs. The MIC of CSE1034 was found to be between 2 to 16 µg/ml for the 92.64% of the isolates of *A. baumannii* and only 7.35% isolates exhibiting MIC 32 to >128 µg/ml and 4 to 16 µg/ml for 79.16% of clinical isolates of *P. aeruginosa* remaining 20.83% isolates exhibiting MIC 32 to >128 µg/ml. These results suggesting that CSE1034 can be considered as a drug of choice for the treatment of these infections.
16. Prevalence and Antimicrobial Sensitivity of Extended-Spectrum ß-Lactamase Producing Gram Negative Bacteria from Clinical Settings in India from 2010-2012

Authors: Manu Chaudhary, Shailesh Kumar, Anurag Payasi

Abstract

There has been a steady increase in the incidence of extended-spectrum ß-lactamase (ESBL) producing pathogens. Coupled with the increasing prevalence rates and their association with high morbidity and mortality, the ESBL producing organisms are considered a major public health issue. The objective of the present study was to monitor the prevalence rates of ESBL producing organisms in clinical settings and to identify the changes in their sensitivity patterns towards commonly used antibiotics. A retrospective surveillance study was conducted in 5 centers spread across the country from 2010 to 2012. A total of 2500 clinical isolates were collected from the patients suffering from various infections and ESBLs were confirmed by Clinical and Laboratory Standards Institute (CLSI) methods. The ESBL isolates were subjected to antibiotic susceptibility testing against selected antibiotics. Out of the 2500 isolates, 1325 were found to be ESBL positive indicating a prevalence rate of 53% ESBL producers. The most predominant ESBL producer was Escherichia coli (64.2%) followed by Klebsiella pneumoniae (60.1%), Pseudomonas aeruginosa (37.4%) and Acinetobacter baumannii (17.1%). Among the antibiotics tested in the study, the ESBL producers indicated the highest percentage of resistance to amoxicillin plus clavulanic acid (64-79%) followed by piperacillin plus tazobactam (47-59%). A high incidence of resistance among ESBL producers was also observed against carbapenems such as imipenem plus cilastatin (23-36%) and meropenem (26-34%). However, most of the ESBL producing pathogens were highly susceptible to tigecycline, colistin and Elores (ceftriaxone+sulbactam with adjuvant EDTA). The present study indicated an alarming rise in incidence of ESBLs in clinical settings.

The ESBLs were highly resistant to ß-lactam and ß-lactamase inhibitor combinations such as amoxicillin plus clavulanic acid and piperacillin plus tazobactam, but most of these were sensitive to colistin, tigecycline and Elores. Decreased sensitivity against carbapenems and high incidence of ESBL producers in the present study advocates the judicious use of carbapenems and preserve it as reserve drug.
17. Elores : A New Antibiotic Adjuvant Entity Active Against Metallo-ß-Lactamases Producing Organisms

Authors: Manu Chaudhary, Anurag Payasi

Abstract
The aim of the present study was to investigate the prevalence of New Delhi metallo-ß-lactamase (NDM-1) in multi-drug resistant enterobacteriaceae particularly Escherichia coli and Klebsiella pneumoniae and in non fermenting gram-negative bacilli (Acinetobacter baumannii and Pseudomonas aeruginosa) in India and compared the antibacterial activity of Elores with other ß-lactam antibiotics against these NDM-1 producing isolates. Phenotypic characterization of the isolates was done using imipenem and imipenem+EDTA (ethylene diamine tetra acetic acid) disc diffusion method. The prevalence of NDM-1 among these isolates was studied using polymerase chain reaction (PCR). Antibiotic susceptibility study was performed according to the Clinical Laboratory Standards Institute method (CLSI). Out of the five hundred forty one isolates, four hundred sixty four isolates (85.7 %) were found to be carbapenem resistant. Further screening of these isolates revealed approximately 81.7 % (379/464) isolates were found to be NDM-1 positive through PCR method. Elores appeared to be most active antibacterial agents with 95.0% susceptibility to NDM-1 positive K. pneumoniae followed by A. baumannii (94.0%), E. coli (93.5%) and P. aeruginosa (92.8%), however, it showed 1 to 2% resistant and 3 to 6 % intermediate response to these isolates. Among the penems (imipenem+cilastatin, doripenem and meropenem), imipenem plus cilastatin showed 100% resistant to A. baumannii, P. aeruginosa and K. pneumoniae against NDM-1 producing isolates whereas doripenem exhibited 5.5% susceptibility and 79.6% resistant to E. coli followed by A. baumannii (4.5% susceptibility, 86.5% resistance), K. pneumoniae (1.6% susceptibility, 91.6% resistance) and P. aeruginosa (1.2% susceptibility, 95.2% resistance) while meropenem showed 1 to 2% susceptibility, 88 to 97% resistance and 1 to 8% intermediate response against E. coli, K. pneumoniae, A. baumannii and P. aeruginosa. Piperacillin plus tazobactam demonstrated 88 to 93 % resistance, and 6 to 7 % intermediate response and only 1 to 3 % susceptibility response. In conclusion, Elores was the most active which showed 92 to 95 % susceptibility therefore can be a potent antibacterial agent for the treatment of infections caused by carbapenemase producing A. baumannii.
18. Inhibition of ATPase Activity by Elores

Authors: Manu Chaudhary, Anurag Payasi

Abstract
Efflux of antibiotics by AcrAB-tolC efflux pump is an important factor for antibiotic resistance. The activity of this efflux pump depends upon metabolic energy which is provided by ATP (adenosine triphosphate) hydrolysis via ATPase enzyme. Therefore, the present experiment was planned to study the effect of various chemicals such as EDTA, sodium borate, sodium salicylate and various drugs on ATPase activity. A total of sixteen E. coli clinical isolates were used in this study. All these isolates were subjected to re-identification and characterization for the presence of acrA, acrB and tolC genes responsible for AcrAB-tolC efflux pump. Results of this study demonstrated that the significant inhibition of ATPase activity was observed at 8, 9 and 10 mM concentrations of EDTA, sodium borate and sodium salicylate respectively. We observed Elores significantly inhibited the ATPase activity which was comparable with colistin and tigecycline. However other drugs could not demonstrate significant effect on ATPase activity. In conclusion, ethylene diamine tetra acetic acid (EDTA) and Elores appeared to be the most efficient in inhibiting the ATPase activity as compared to other chemicals and drugs. It is therefore postulated that immediately after the inhibition of ATPase activity, the activity of efflux pump would be decreased as a result enhanced activity of Elores in the efflux overexpressed positive strains. We further assume that inhibition of ATPase activity by EDTA is the result of the chelation of calcium needed for the activity of ATPases.
19. In vitro Susceptibilities of Clinical Isolates of *Escherichia coli* and *Klebsiella* species to CSE1034 and Other β-Lactams

Authors: Manu Chaudhary, Shailesh Kumar and Anurag Payasi

**Abstract**
Infections are becoming difficult to treat with commonly used antibiotics when caused by extended spectrum β-lactamase (ESBL)- and metallo-β-lactamase (MBL)-producing organisms. In recent years, the antibiotic resistance against ESBL-producing organisms has increased at an alarming rate. To overcome the antibiotic resistance caused by ESBL producers, carbapenems were introduced in clinical settings. However, carbapenem resistance among the members of the enterobacteriaceae family has been reported globally.
20. Incidence, Prevalence and Control of Multidrug Resistant (MDR) Carbapenemase Producing *Acinetobacter baumannii* in Indian Intensive Care Units

Authors: Manu Chaudhary and Anurag Payasi

Abstract

**Objective:** The objective of present study was to conduct a microbial surveillance in India to find the prevalence of carbapenemases producing genes among multidrug resistant *Acinetobacter baumannii* isolates from various clinical specimens of ICU patients and to evaluate the comparative antimicrobial susceptibility of Elores with other drugs among these strains.

**Methods:** Phenotypic characterization of isolates was carried out by the disc diffusion method. The prevalence of carbapenemase producing gene was studied using polymerase chain reaction (PCR). Antibiotic susceptibility study was performed according to the Clinical Laboratory Standards Institute method (CLSI, 2009) in all carbapenemase producing clinical isolates.

**Results:** Among the four hundred and fifty four (454) isolates, three hundred and seventy one (371) (81.71%) isolates were found to be carbapenemase producing. Further screening of these isolates revealed that approximately 86.5% (321/371) isolates were carbapenemase positive via PCR method. The highest percentage of carbapenemase producers were confirmed via PCR in urine specimen 95.1% (137/144) followed by respiratory secretion 91.6% (11/12), blood 82.6% (95/115), pus 79.7% (55/69), and fluid 74.1% (23/31).

In non-fermentor carbapenemase producing *A. baumannii*, none of the antibiotics yielded percentage susceptibility >40% except Elores which showed 93–96% susceptibility. Colistin appeared to be the second most active antibiotic with 21–32% susceptibility followed by tigecycline (21–25%), doripenem (9–14%) and each of imipenem and meropenem (1–4%). None of the isolates was found to be susceptible to piperacillin plus tazobactam. Interestingly, penems (doripenem, imipenem and meropenem) exhibited 71–91% resistant and 6.8–14.3% intermediate response to carbapenemase producing *A. baumannii* isolates.

**Conclusion:** Results of the present study revealed that Elores was the most active amongst commonly used antibiotics in ICU settings, which showed 93–96% susceptibility, therefore can be a potent antibacterial option for the treatment of infections caused by carbapenemase producing *A. baumannii*. 
21. Rising Antimicrobial Resistance of *Pseudomonas aeruginosa* Isolated from Clinical Specimens in India

Authors: Manu Chaudhary and Anurag Payasi
Journal: Journal of Proteomics & Bioinformatics 6, 2013: 005-009

**Abstract**
The rising antibiotic resistance against commonly used drugs is of great concern. Drug susceptibility testing and Polymerase Chain Reaction (PCR) assay were used to determine the antibiotic susceptibility patterns and prevalence of genes encoding extended-spectrum-ß-lactamases (ESBLs) and metallo-ß-lactamases (MBLs) among 515 isolates of *Pseudomonas aeruginosa* isolated from various clinical specimens. Susceptibility of isolates to seven antibiotics was tested using disc diffusion method according to the guidelines defined by Clinical Laboratory Standard Institute. Isolates showing resistance to any of the two cephalosporins (ceftriaxone, ceftazidime and cefotaxime) were subjected to PCR for the prevalence of ESBL and MBL gene characterization. Out of the 515 isolates, 235 (45.63%) were considered as ESBL positive; 87 (16.89%) were MBL positive and 74 (14.36%) had co-produced both ESBL and MBL. The frequency of TEM-type, SHV-type and AMP-C type ESBLs were 45.10, 26.0, and 28.93%, respectively. Among the MBLs, the frequency of distribution of NDM-1, IMP-1 and VIM-1 was 24.13, 28.73 and 47.12%, respectively. The rate of susceptibility of ESBL producing *P. aeruginosa* towards various antibacterial agents were as follows: piperacillin+tazobactam (84.3%), doripenem (83.8%), ceftriaxone plus ethylene diamine tetra acetic acid plus sulbactam; Elores (74.1%), imipenem (66.5%), meropenem (54.7%), ceftazidime (44.8%) and cefepime (28.5%). Isolates harboring MBL and ESBL+MBL genes were resistant to almost all antibiotics except Elores (97.3 and 95.1% susceptibility) and doripenem (11.3 and 19.5% susceptibility). From the above results, it can be concluded that Elores was highly potent against MBL producing *P. aeruginosa*. However, susceptibility of Elores to ESBL producing *P. aeruginosa* was comparable to piperacillin plus tazobactam.
22. Role of CSE1034 in Bacterial Lipids and Polysaccharides Involved in Biofilm Formation: A Comparison with Other Drugs

Authors: Chaudhary Manu and Anurag Payasi

Abstract
In the present investigation minimum inhibitory concentration (MIC) and minimum biofilm eradication concentration (MBEC) and CSE1034 (Sulbactomax) was compared with piperacilline+tazobactam, amoxyclav, ceftriaxone, ceftriaxone+sulbactam and cefoperazone+ sulbactam in planktonic and sessile cells of Acinetobacter baumannii, Enterobacter cloacae and Pseudomonas aeruginosa. MICs were determined by broth microdilution method with a final inoculum size of 106 cfu/ml of plaktonic cells. MBECs were measured using a calgary biofilm device method to establish a co-relation with biofilm breaking efficacy of different drugs. The MICs for CSE1034 ranged from 0.5 to 4.0 µg/ml and for other antibacterial drugs ranged from 2 to 32 µg/ml. The MBEC for CSE1034 ranged from 8 to 16 µg/ml and for other antibacterial agents, it ranged from 64 to 4096 µg/ml. The CSE1034 exhibited approximately 5 logs reduction in the number of bacteria present in biofilm when compared with other antibacterial agents. When total lipid and total polysaccharide contents were compared, CSE1034 showed 90 and 84% reduction, respectively. The enhanced efficacy of CSE1034 in the eradication of biofilm infection is due to presence of EDTA which helps in the destabilizing of the barriers responsible for the development of biofilm as well as antibiotic resistance. In conclusion, combining of ceftriaxone+sulbactam with EDTA can significantly reduces the MIC and MBEC values against selected organisms. Hence, CSE1034 could be one of the best choices to eradicate the biofilm caused by these organisms.
Abstract

*Pseudomonas aeruginosa* is an opportunistic bacterium which has been shown to have multi-drug resistance against fluoroquinolones, β-lactams, and aminoglycosides. In this investigation, we studied the effect of different concentrations of ethylene diamine tetra acetic acid (EDTA) on MexA-MexB-OprM efflux pump and subsequent changes in susceptibility and expression. Next, we examined, the expression of mexAB gene following treatment with half of minimum inhibitory concentration (MIC) of drugs. Our results revealed that 10 mM EDTA significantly reduced MIC of all drugs; moreover, the higher reduction (8 fold) was observed with CSE1034. MexA and MexB expression was down regulated at 2.93 and 3.21 fold, respectively with 10 mM EDTA. When the same concentration of EDTA was incorporated with drugs, the CSE1034 down regulates 5.64 and 5.94 fold expression of mexA and mexB, respectively. Moreover, meropenem treated groups exhibited 2.63 and 3.12 fold down regulation in the expression of the genes. However, treatment with piperacillin plus tazobactam, amoxicillin plus clavulanate, cefoperazone plus sulbactam and imipenem plus cilastatin did not produce changes in the expression of MexAB-OprM. Hence, CSE1034 could be one of the best choices to treat infections caused by microorganisms that overexpressed MexAB-Opr-M as compared to other drugs. Furthermore, use of EDTA disodium at appropriated concentrations can be regarded as a safe strategy to fight against the menace caused by the efflux pumps.
24. A Novel Approach to Combat Acquired Multiple Resistance in *Escherichia coli* by using EDTA as Efflux Pump Inhibitor

Authors: Manu Chaudhary, Shailesh Kumar and Anurag Payasi


**Abstract**

*Escherichia coli* is one of the leading pathogen responsible for severe ICU infections and have evolved a variety of strategies to resist antibiotics. A single resistance mechanism may diminish susceptibility to several therapeutic drugs allowing the survival of bacteria in their niches. Among the various resistance mechanisms, antibiotic removal from the bacterial cells by efflux pumps is most common. There are a number of reports indicating antibiotic resistance because of efflux pump in bacteria is increasing significantly. Therefore, antibiotic efflux pumps are thought of as attractive therapeutic targets, where their inhibition can restore antibiotic activity.
25. Molecular Characterization and Antimicrobial Susceptibility Study of *Acinetobacter baumannii* Clinical Isolates from Middle East, African and Indian Patients

Author: Manu Chaudhary

Abstract
The aim of the present investigation was to characterize the prevalence of extended-spectrum β-lactamases (ESBLs) and metallo β-lactamases (MBLs), and to study the antibiotic susceptibility profile among 250 clinical isolates of *Acinetobacter baumannii*. Phenotypic characterization was carried out by double disc synergy method and the prevalence of ESBLs and MBLs antibiotic resistant determinants were analyzed with Polymerase Chain Reaction (PCR). Susceptibility studies were performed by disc diffusion method according to Clinical and Laboratory Standards Institute guidelines 2009. Among the two hundred fifty isolates, two hundred nine isolates (83.6%) were positive for ESBLs whereas one hundred sixty seven isolates (79.9%) were positive for both ESBLs and MBLs. Moreover, five isolates (2.3%) which were positive for MBL on disc diffusion test, but negative in PCR showed MBL activity by spectrophotometric assay. Susceptibility study showed that all of the isolates were found to be more susceptible to ceftriaxone plus ethylene diamine tetra acetate plus sulbactam (90-93%), followed by meropenem (50-53%), imipenem (42-45%), cefoperazone plus sulbactam (40-42%), piperacillin plus tazobactam (38-42%) and amoxicillin plus clavulanic acid (28-31%). Among the ESBLs, TEM-types were varied from 82 to 87% followed by SHV-types (67-78%), CTX-M types (60 to 67) and OXA types (51 to 56%) in all of the isolates. Among the MBLs, NDM-1 varied from 40 to 49% followed by IMP-1 (51 to 55%), VIM-1 (55 to 59%) and KPC (47 to 55%) in all of the isolates. Moreover, results of the present study revealed that all of the clinical isolates were susceptible to ceftriaxone plus EDTA plus sulbactam and can be a potent antibacterial agent for the treatment of severe bacterial infections caused by *A. baumannii*. 
Prospective Study for Antimicrobial Susceptibility of *Escherichia coli* Isolated from Various Clinical Specimens in India

**Abstract**

The aim of the present work was to study the prevalence of extended-spectrum \(\beta\)-lactamases (ESBLs) and metallo-\(\beta\)-lactamases (M\(\beta\)Ls) among 464 *E. coli* clinical isolates obtained from various clinical specimens; and to study the susceptibility of various drugs against *E. coli* isolates. Phenotypic characterization and susceptibility studies were performed according to the methods described in Clinical and Laboratory Standards Institute guidelines (CLSI, 2010). The prevalence of ESBLs and M\(\beta\)Ls was analyzed with Polymerase Chain Reaction (PCR), using the previously reported primers. Among the four hundred sixty four isolates, 186 (40.08%) isolates were ESBLs positive, 75 (16.16%) isolates were M\(\beta\)Ls positive, and 80 (17.24%) were both ESBLs and M\(\beta\)Ls positive. The remaining 123 (26.50%) were non ESBLs and M\(\beta\)Ls. TEM-types ESBLs (blaTEM-1, blaTEM-2, and blaTEM-50) were found in approximately 57% isolates. The prevalence of SHV-types, CTX-M-types and OXA-type was 29.03, 11.82 and 2.15%, respectively. Among the M\(\beta\)Ls, the frequency of distribution of NDM-1, IMP-1, VIM-1 and KPC-types was 37.39, 21.33, 18.66, and 22.66%, respectively. In general, 92.6% *E. coli* isolates were susceptible to ceftriaxone plus EDTA plus sulbactam (CSE1034), followed by meropenem (74.4%), imipenem (71.2%), piperacillin plus tazobactam (52.1%), cefoperazone plus sulbactam (46.0%) and amoxycillin plus clavulanic acid (23.6%). Similarly, amoxycillin plus clavulanic acid showed the highest percentage of resistance (72.8%), followed by cefoperazone plus sulbactam (43.6%), piperacillin plus tazobactam (39.3%), imipenem (23.3%), meropenem (20.3%) and ceftriaxone plus EDTA plus sulbactam (CSE1034) (2.5%). Results of the present study revealed that most of the clinical isolates were susceptible to ceftriaxone plus EDTA plus sulbactam (CSE1034), and can be a potent antibacterial agent for the treatment of severe bacterial infections caused by *E. coli*. 

Authors: Manu Chaudhary and Anurag Payasi

27. Comparative Efficacy of Antibiotics in Biofilms Eradication Formed by ESBL and non ESBL Producing Micro-Organisms

Authors: Manu Chaudhary and Anurag Payasi

Abstract
Growth of bacterial cells within a biofilm complicate the treatment of infections. Therefore, in the present study biofilm eradication efficacy of (ceftriaxone and sulbactam plus EDTA; CSE1034) was compared with ceftriaxone alone, ceftriaxone plus EDTA and ceftriaxone plus sulbactam against biofilms of ESBL producing Escherichia coli, Klebsiella pneumoniae and Salmonella typhi. Susceptibility testing of each drug was performed on planktonic and biofilm cells in non ESBL producing and ESBL producing strains according to the recommendations of clinical and laboratory standards institutes guidelines. CSE1034 inhibited the growth of planktonic cells of non ESBL producing strains with minimum inhibitory concentration (MIC) from 0.25 to 1.0 µg/ml; the minimum biofilm eradication concentration (MBEC) values ranged from 8 to 32 µg/ml where as ESBL producing strains MIC values were 2 to 4 times higher and corresponding MBEC values were higher by 4 to 8 times. When biofilms of ESBL producing organisms were treated with the half MBEC of drugs, CSE1034 decreased 3 log of bacteria present in biofilm when compared with ceftriaxone, ceftriaxone plus EDTA and ceftriaxone plus sulbactam. In conclusion, combination of CSE1034 acts synergistically and reduces the MIC and MBEC values, significantly. One dimensional polyacrlamide gel electrophoresis of extracellular proteins revealed distinct difference in protein expression of the group treated with CSE1034. Hence, CSE1034 at low concentration showed greater efficacy in the eradication of biofilm as compared to other two drugs and could be one of the best choices to eradicate the biofilm infections caused by these organisms as compared to other drugs.
Preclinical studies refer to the testing of a drug in animals before trials may be carried out in humans. During preclinical drug development, the drug’s toxic and pharmacological effects need to be evaluated through *in vitro* and *in vivo* laboratory animal testing. The companies are supposed to develop a pharmacological profile, determine toxicity in at least two species of animals and conduct short-term toxicity studies. Various preclinical requirements exist for different kinds of laboratory animal studies. Information gathered in preclinical studies are used as evidence and support in applications for the approval of new drugs to respective drug authority of the country. Before testing a drug in humans, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are *In Vitro* and *In Vivo*.

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug should be tested in people. In the preclinical stage, the regulatory authorities generally ask, at a minimum, that sponsors: Develop a pharmacological profile of the drug; Determine the acute toxicity of the drug in at least two species of animals, and conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.

During preclinical drug development, evaluation of Elores toxicity and pharmacologic effects was done through multiple *in vitro* and *in vivo* laboratory and animal tests. Initial studies against ESBL and MBL producing pathogens were followed by another set of studies including evaluation of the role of EDTA on QT prolongation in rabbit, genotoxicity screening was performed, as well as investigations on comparative efficacy of Elores vs Ceftriaxone in pneumonia induced rats, and the evaluation of toxicity of the drug’s metabolites in Swiss albino mice and Sprague Dawley rats, most of the studies were published and this concluding chapter carries abstracts from those preclinical and animal studies. There is no ‘one size fits all’ approach to the design of preclinical studies. Rather, the preclinical studies must be tailored to the specific investigational agent and the proposed clinical trials. While most of the regulatory authorities do not prescribe a standard set of tests for all experimental agents, the USFDA has issued guidelines for the selection of preclinical studies, most of which were considered and fulfilled during Elores preclinical studies.
1. Evaluation of Genotoxicity of CSE1034 by Ames and In vitro Chromosomal Aberration Tests

Authors: M Chaudhary, A Payasi

Abstract

Purpose: To evaluate the genotoxicity of CSE1034, a novel antibiotic adjuvant entity, using bacterial reverse mutation assay (Ames test) and in vitro chromosomal aberration test.

Methods: Reverse mutation test was carried out using four strains of *Salmonella typhimurium* (TA 98, TA100, TA1535 and TA1537) and one strain of *E. coli* [WP2 (uvrA)], while chromosomal aberration test was done with cultured Chinese hamster lung (CHL) cells. Reverse mutation test was carried out in a dose range of 0.0015 to 0.16 ìg/plate in triplicate with and without S9 activation.

Results: No significant increases in the number of revertants were observed at the dose levels where antibacterial effects were not noted. CSE1034 caused no increase in the number of chromosomal aberrants at dose levels of 0.34, 0.69, 1.37, 2.75 and 5.50 mg/ml in the absence and presence of metabolic activation.

Conclusion: Based on the above observations, it can be concluded that CSE1034 has no mutagenic activity.

Keywords: CSE1034, reverse mutation, antibiotic adjuvant entity, chromosomal aberration, mutagenic.
2. **Acute Intravenous Toxicity Study of Disodium EDTA in Swiss Albino Mice**

Authors: Manu Chaudhary, Parveen Kumar, Satish Kumar and Vinod Kumar M.

**Abstract**
The study was conducted to determine the acute toxicity of disodium EDTA upon slow intravenous injection in mice. The study was conducted at four dose levels and all doses were administered by slow injection in the lateral tail vein. All animals were observed upto 14 days after dosing for clinical signs of toxicity. Animals in the vehicle or disodium EDTA group showed normal gain in body weight. No clinical signs of pathological significance were recorded in this study. Mortality was not found in any group. Gross necropsy revealed that all organs appeared completely normal and were comparable to control in all the groups treated with disodium EDTA. Based on these observations, it was concluded that administration of disodium EDTA by slow intravenous injection does not produce any visible signs of toxicity upto doses of 120 mg/kg.

**Keywords:** Disodium EDTA, Elores, acute toxicity.
3. **Acute Toxicity Studies of Fixed Dose Combination of Ceftriaxone + Sulbactam + Ethylene Diamine Tetra Acetic Acid in Swiss Albino Mice And Sprague Dawley Rats**

Authors: Manu Chaudhary, Anurag Payasi
Journal: International Journal of Medicine and Medical Science, August 2013, ISSN:2051-5731, Vol.46, Issue.2

**Abstract**
The acute toxicity study of Ceftriaxone + Sulbactam + Ethylene diamine tetra acetic acid was investigated to offer a solution for the treatment of bacterial infection caused by beta lactam resistant pathogens. A single intravenous injection at the dose levels of 50 mg/Kg, 250 mg/Kg and 500 mg/Kg body weight were administered to Swiss albino mice and Sprague dawely rats (both male and female), where as control groups received normal saline. General behaviour, signs of toxicity, body weight, food and water consumption, and mortality were observed daily for 14 days. At the end of the study, hematological, biochemical, morphological and microscopic parameters were also determined. No toxicological meaningful difference, hazardous symptoms or death were observed in the acute toxicity test which indicates that a single i.v dose of Ceftraixone+sulbactam+EDTA combination at the dose levels of 50 mg/Kg, 250 mg/Kg and 500 mg/Kg body weight was not lethal in both mice and rats (male/female), and suggest a safe use in humans.
4. Catering ESBL Resistance Challenge Through Strategic Combination of Ceftriaxone, Sulbactam and Ethylene Diamine Tetra Acetic Acid

Authors: Manu Chaudhary, Sudaroli M, Shailesh Kumar, Krishna Raju

Abstract
Resistant development in ESBLs producing bacteria to third generation cephalosporin has emerged with alarming rapidity in recent years and become major cause of concern worldwide. Therefore, in order to cater growing resistance problem, combination of third generation cephalosporin with beta-lactam inhibitors and Ethylene diamine tetra acetic acid, was studied. The in vitro antibacterial efficacy of various concentration of ceftriaxone + sulbactam and effective dose determination study of EDTA against various ESBLs producing micro organisms such as *Escherichia coli* (MTCC-739), *Klebsiella pneumoniae* (MTCC-109), *Pseudomonas aeruginosa* (MTCC-1688), and *Staphylococcus aureus* (MTCC-737) were investigated. From the AST and MIC report it was found that the 2:1 ratio has very good bactericidal activity in comparison to other ratios under study. It was found that ceftriaxone and sulbactam combination along with 3mg/ml of Disodium EDTA has significant (p<0.001) bactericidal activity as compared to ceftriaxone and sulbactam alone. It was concluded that the ceftriaxone + sulbactam in the ratio of 2:1 along with EDTA disodium (3 mg/ml) lowers MIC to >8 fold and possess synergy against the most ESBL producing micro organisms. The combination was found to have beneficial property against troublesome strains and might be considered as a promising therapy for severe infections to overcome resistance.
5. Role of CSE1034 in Bacterial Lipids and Polysaccharides Involved in Biofilm Formation: A Comparison with Other Drugs

Authors: Chaudhary Manu and Anurag Payasi

Abstract
In the present investigation minimum inhibitory concentration (MIC) and minimum biofilm eradication concentration (MBEC) and CSE1034 (Sulbactomax) was compared with piperacilline+tazobactam, amoxyclave, ceftriaxone, ceftriaxone+ sulphactam and cefoperazone+ sulphactam in planktonic and sessile cells of Acinetobacter baumannii, Enterobacter cloacae and Pseudomonas aeruginosa. MICs were determined by broth microdilution method with a final inoculum size of 106 cfu/ml of planktonic cells. MBECs were measured using a calgary biofilm device method to establish a co-relation with biofilm breaking efficacy of different drugs. The MICs for CSE1034 ranged from 0.5 to 4.0 µg/ml and for other antibacterial drugs ranged from 2 to 32 µg/ml. The MBEC for CSE1034 ranged from 8 to 16 µg/ml and for other antibacterial agents, it ranged from 64 to 4096 µg/ml. The CSE1034 exhibited approximately 5 logs reduction in the number of bacteria present in biofilm when compared with other antibacterial agents. When total lipid and total polysaccharide contents were compared, CSE1034 showed 90 and 84% reduction, respectively. The enhanced efficacy of CSE1034 in the eradication of biofilm infection is due to presence of EDTA which helps in the destabilizing of the barriers responsible for the development of biofilm as well as antibiotic resistance. In conclusion, combining of ceftriaxone+ sulphactam with EDTA can significantly reduces the MIC and MBEC values against selected organisms. Hence, CSE1034 could be one of the best choices to eradicate the biofilm caused by these organisms.

Keywords: Lipopolysaccharide, lipid, log reduction, antibacterial agent.
Abstract
Pneumonia caused by *Klebsiella pneumoniae* is important due to its high morbidity and mortality. This infection causes acute inflammation in the lung is characterized by increased activity of neutrophils, generate free radical and decreased the endogenous anti-oxidant defense system. CSE1034 is a novel fixed dose combination drug of ceftriaxone plus sulbactam with VRP1034. The aim of this investigation was to compare the efficacy study of CSE1034 drug vs ceftriaxone alone in pneumonia induced rat model. For pneumonia infection in animal model, doses were standardized at concentration $10^2$ to $10^6$ CFU/ml of *Klebsiella pneumoniae*. Total thirty two male rats (150 ± 5 g) were randomly selected and divided into four groups of eight animals each. Group I was normal saline treated; group II was pneumonia infected; group III was infected plus ceftriaxone treated and group IV was infected plus CSE1034 treated. Pneumonia infection was induced in all group except group I via intranasal instillation, at concentration (log 10$^6$ CFU/ml) for 15 days. Infection was confirmed by raised body temperature, bacterial count, cell count and cytokine (TNF-α, IL-6) parameters in blood. After confirmation of infection, CSE1034 and ceftriaxone drugs treatment were started for 15 days. At the end experiment, blood and lung tissue were collected and measured the biochemical and enzymatic parameters in all group. The finding showed that a significant decrease lactate dehydrogenase activity, malonaldialdehyde, total protein, albumin, nitrate, tumor necrosis factor-Symbol, interleukin-6 levels and bacterial count along with increase reduced glutathione level in lung homogenate of CSE1034 treated group as compared to pneumonia induced and ceftriaxone treated groups. These findings suggested that CSE1034 is effective than ceftriaxone which reduced bacterial count and enhanced endogenous antioxidant status along with reduces, inflammatory response during pneumonia infection.
7. Protective Role of Ceftriaxone plus Sulbactam with VRP1034 on Oxidative Stress, Hematological and Enzymatic Parameters in Cadmium Toxicity Induced Rat Model

Authors: Vivek Kumar Dwivedi, Anuj Bhatanagar and Manu Chaudhary

Abstract
We investigated the protective role of ceftriaxone plus sulbactam with VRP1034 (Elores) on hematological, lipid peroxidation, antioxidant enzymatic activities and Cd levels in the blood and tissues of cadmium exposed rats. Twenty-four male rats were divided into three groups of eight rats each. The control group received distilled water whereas group II received CdCl₂ (1.5 mg/4 ml/body weight) through gastric gavage for 21 days. Group III received CdCl₂ and was treated with ceftriaxone plus sulbactam with VRP1034 for 21 days. The hematological, biochemical, lipid peroxidation levels and enzymatic parameters were measured in plasma and tissues (brain, liver and kidney) of all groups. The Cd, Zn and Fe levels were measured in blood and tissues of all groups. Our findings showed significantly decreased cadmium (p<0.001), malonaldehyde (p<0.001) and myloperoxidase (MPO) levels along with significantly increased hemoglobin (p<0.01), RBC (p<0.05), hematocrit (p<0.05) levels and all antioxidant enzymatic activities (SOD, CAT, GR, GPx) in plasma and tissues of ceftriaxone plus sulbactam with VRP1034 treated group as compared to cadmium exposed group. Delta aminolevulinatedehydratase (δ-ALAD) activity was significantly (p<0.001) increased in the blood of ceftriaxone plus sulbactam with VRP1034 treated group as compared with cadmium exposed group. The levels of hepatic and renal parameters were significantly (p<0.001) decreased in ceftriaxone plus sulbactam with VRP1034 treated group as compared to cadmium exposed group. These findings indicate that ceftriaxone plus sulbactam with VRP1034 acts as a potent free radical scavenger and exhibits metal chelating properties that reduce free radical mediated tissue injury and prevent dysfunction of hepatic and renal organs during metal intoxication.

Keywords: cadmium toxicity, hematological and biochemical parameters, oxidative stress and enzymatic parameters, hepatic and renal tissues, Elores
8. Kinetic Studies of Metallo-ß-Lactamase NDM-1
Authors: Manu Chaudhary, Anurag Payasi
Journal: International Journal of Medicine and Medical Science, August 2013, ISSN:2051-5731, Vol.46, Issue.2

Abstract
Kinetically metallo-ß-lactamases (MBLs) have a broad substrate spectrum profile and are capable of hydrolysing a range of substrates. In this study we described the steady-state kinetic parameters (Km, Vmax, Ki, and Kcat) of NDM-1 with the Line weaver Burk plot. NDM-1 producing Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia and Pseudomonas aeruginosa were used in this study. Results of inhibition constant (Ki) study revealed that Ki is directly proportional to MIC, reflecting that low Ki value of drugs represent enhanced susceptibility towards microorganisms. The NDM-1 enzyme showed good affinity (low Km, ranged from 25±2 to 148±14 µM) for imipenem plus cilastatin, meropenem, cefoperazone plus sulbactam and piperacillin plus tazobactam whereas Elores, tigecycline and colistin demonstrated lower affinity (high Km ranged from 303±23 to 335±27, 238±18 to 275±21 and 238±22 to 271±22 µM, respectively) for NDM-1 isolated from A. baumannii, E. coli, K. Pneumonia and P. aeruginosa. The catalytic efficiency (Kcat/Km) for Elores ranged 0.054 to 0.065 which is >65% (or >1.5 fold) lower than those of tigecycline and colistin whose catalytic efficiencies were 0.098 to 0.11 and 0.095 to 0.106 µM-1S-1 respectively. Low affinity of Elores towards NDM-1 degradation alongwith very weak catalytic activity (17-22 S-1) makes NDM-1 inefficient in hydrolysing this antibiotic. Further, it is also evident that NDM-1 enzyme had 6 to 7 fold higher catalytic efficiency for imipenem and meropenem and 32 to 61 fold higher catalytic efficiency for cefoperazone plus sulbactam and piperacillin plus tazobactam compared to Elores. These results clearly indicate that ß-lactam plus ß-lactamase inhibitor (BL plus BLI) combinations such as cefoperazone plus sulbactam and piperacillin plus tazobactam are more rapidly hydrolyzed by NDM-1 enzyme followed by imipenem, meropenem, tigecycline and colistin. From the above it can be concluded that Elores, a novel antibiotic adjuvant entity, is the most stable amongst tested antibiotics which are commonly used in Intensive Care Unit (ICU) for treatment of carbapenem-resistant Enterobacteriaceae (CRE) infections and is effective against NDM-1 enzymes. Therefore, use of Elores for the infections caused by NDM-1 positive isolated would be the best choice.

Keywords: Elores, Metallo-ß-lactamases (MBLs), NDM-1, Non-antibiotic adjuvant.
9. Therapeutic and Safety Study of Intravenous Disodium EDTA on QT Prolongation and Serum Electrolytes in Rabbit

Abstract
Disodium EDTA may causes hypocalcemia and Intravenous disodium EDTA can increase risk for corrected QT interval (QTc) prolongation, torsades de pointes (TdP) and sudden death. We studied the safety dose of disodium EDTA on QT prolongation and serum electrolytes in rabbit. Total twelve male rabbits were distributed into two groups of six animals each. Group I and II animals were treated with 8.78 and 11.36 mg/kg body weight of disodium EDTA respectively via intravenous route. Electrocardiogram (ECG) tracing was recorded in these groups at 5, 10, 15 and 30 minutes intervals before and after post administration of respective doses of disodium EDTA. Heart rate (HR), QT, Qtc (by bazett’s formula) were calculated. Serum electrolytes were also measured in these groups before and after post administration of disodium EDTA. The results revealed that no mortality were found in group I (8.78 mg/kg body weight) and group II treated (11.36 mg/kg body weight) animals. Clinical signs of toxicity (pain and etiching etc) were found only in group II treated animals. HR, QT and QTc intervals were found significantly (p<0.001) alteration along with significant change in calcium, magnesium and potassium levels of group II treated animals as compared to baseline value and group I at different intervals. So these findings, suggested that the dose 8.78mg/kg of disodium EDTA is safe through intravenous route which did not affect the serum electrolytes and QT prolongation in rabbit.

Authors: Chaudhary M., V.K. Dwivedi*
10. **Sub-Acute Toxicity Study of Fixed Dose Combination of Sulbactomax (Ceftriaxone-Sulbactam) in Swiss Albino Mice and Wistar Rat**

Authors: Tamta, A.; Chaudhary, M.

**Abstract**
The present study investigated safety/toxicity profile of Sulbactomax (Ceftriaxone-Sulbactam for injection), a fixed dose combination, in Mus musculus mice and SD rats at three dose levels, 10, 50 and 150 mg kg⁻¹ ranging from asymptomatic to high dose. Sulbactomax was introduced in order to enhance the antimicrobial efficacy and to combat resistance towards beta-lactamase producing bacteria. The combination has been reported to be highly effective as well as synergistic for many resistant strains and carry the potential for its usage in empirical therapy for various bacterial infections. To establish the safety profile of combination, 28 days repeated dose sub-acute toxicity study was conducted on mice and rat (male and female). Various hematological parameters were studied in addition to physiological and biochemical parameters in order to study toxicity profile of Sulbactomax. There were no signs of toxicity observed at any of the dose levels used in this study. Animals from control and different treated groups exhibited normal body weight gain throughout the dosing period of 28 days. No mortality was observed in any of the treatment groups during the course of whole study. Hematological as well as biochemical parameters were unaltered at all three dose levels in Sulbactomax treated rat and mice. From the present study, it can be concluded that Sulbactomax (the fixed dose combination of Ceftriaxone-Sulbactam) is safe even at the dose level which is several folds of the intended human dose.
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