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Original Article

Clinical and economic impact of appropriate empirical antibiotic therapy in complicated intra-abdominal infections: A retrospective study

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ABSTRACT

Aims: To study the comparative efficacy of Piperacillin/Tazobactam (PIP-TAZ) and new fixed dose combination (FDC) of ceftriaxone + sulbactam + ethylenediaminetetraacetic 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 IAIs 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 IAIs treatments.

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1. Introduction

Multi drug-resistant gram-negative bacteria have emerged as a major threat to hospitalized patients and have been associated with wide range of mortality rates.[1–3] These organisms are highly efficient at up-regulating or acquiring genes that code for antibiotic resistance, especially in the presence of antibiotic selection pressure. Furthermore, they have available with them a plethora of resistance mechanisms, often using multiple mechanisms against the same antibiotic or using a single mechanism to affect multiple antibiotics.[4]

Intra-abdominal infections (IAIs) are common in clinical practice and comprise a wide variety of clinical presentations and differing sources of infection.[5] IAIs include many pathological conditions, ranging from uncomplicated appendicitis to fecal peritonitis. Most of the IAIs occur due to gram-negative bacilli, such as *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., and, to a lesser extent, *Pseudomonas aeruginosa* and other non-fermenting gram-negative bacilli.[6] IAI are classified into uncomplicated and complicated (cIAIs).[7] Uncomplicated IAIs involve infection to a single organ and does not proceed to peritoneum, whereas in cIAIs, the infectious process proceeds beyond the organ, and cause either localized peritonitis or diffused peritonitis.[8] Patients with uncomplicated IAIs can be managed with either surgical resection alone, or with antibiotics alone. However, treatment of cIAIs involves both source control and antibiotic therapy.[8]

Piperacillin/Tazobactam (PIP-TAZ) is a β-lactam/β-lactamase inhibitor combination with increased gram-negative spectrum and anti-pseudomonal activity. PIP-TAZ retains in vitro activity against broad-spectrum β-lactamase producing, many extended-spectrum β-lactamase-producing *Enterobacteriaceae* and many *Pseudomonas* isolates. It is believed to be a reliable option for the empiric treatment of high risk IAIs.[9] PIP-TAZ is commonly used in the treatment of IAIs.[10,11]

Over the last decade, resistance to β-lactams among these organisms mostly because of extended spectrum β-lactamases (ESBL) production has become common both in the hospitals, and more recently also in the community. These organisms often fail treatment with various β-lactam agents and thus carbapenems have become the drug of choice to treat such severe infections.[12,13] However, the emergence of novel β-lactamases with direct carbapenem-hydrolyzing activity has contributed to an increased resistance toward carbapenems. Carbapenem resistant *Enterobacteriaceae* (CRE) are particularly problematic given the frequency with which they cause infections,[14] the high mortality associated with infections caused by CRE.[1,15,16]

A new fixed dose combination (FDC) of ceftriaxone + sulbactam + adjuvant disodium edetate is a novel antibiotic adjuvant entity (AAE) approved by the Drug Controller General of India (DCGI) and increasingly used in Indian hospitals. AAE has been approved for the conditions such as Suppurative Otitis Media, Lower Respiratory Tract Infection, Urinary Tract Infection, Skin/Skin Structure Infection, Bone/Joint Infection, Bacterial Septicemia, IAIs and pre and post surgical infections. Various reports of the in vitro susceptibility studies[17] hint the possibility of this FDC to overcome the hurdles of both ESBL and metallo-β-lactamases (MBL) producers clinically. If effective in vivo clinical success is achieved by this FDC, then it can be a potent alternative to carbapenems in treating infections caused by the resistant bacteria.

Along with increasing mortality and morbidity rates, drug resistant gram negative bacterial infections also increase the duration of the hospital stay and higher health costs compared to those that result from infections with their antibiotic susceptible counter parts.[18] It is universally accepted that drug resistance results in prolonged hospitalization and higher economic costs compared to similar infections caused by antibiotic-susceptible gram negative bacteria.[19,20] In addition to significant morbidity and mortality for patients, IAIs consume substantial hospital resources. This is compounded by the potential misuse of antimicrobial agents that may result in suboptimal treatment, as well as encourage the selection and spread of antibiotic-resistant microorganisms in the health care setting. In view of all these aspects, we have conducted a retrospective study, comparing efficacy and the cost expenditures involved in IAI patients management with PIP-TAZ and new FDC of ceftriaxone + sulbactam + adjuvant disodium edetate.

2. Materials and methods

2.1. Study design

This multi-center, retrospective, observational study was performed in two hospitals at Aligarh, UP, India. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (and subsequent revisions) and to the current norm for observational studies. Due to the retrospective study design, informed consent was not deemed necessary.

2.2. Patient selection

Patients were identified by going through the patient case sheets of each recruiting hospital. All the case sheets of patients, who were admitted between March 2012 and December 2014 for cIAI were evaluated to shortlist the patients, who are meeting the eligibility criteria. Patients were eligible for inclusion if they (1) were hospitalized between March 2012 and December 2014, (2) had a primary discharge diagnosis suggesting any cIAIs; (3) underwent laparotomy, laparoscopy or percutaneous drainage of an intra-abdominal abscess and (4) FDC or PIP-TAZ used empirically as intravenous antibiotics. On the other hand, the patients, who were (1) on ventilator support, (2) diagnosed with resistant bacteria showing resistance toward any of the drugs (PIP-TAZ, FDC, meropenem and colistin), (3) in whom the PIP-TAZ/FDC therapy was given for less than 3 days were excluded from the study.

2.3. Patient analysis

A review and evaluation of each shortlisted patient's case sheet was performed, and all the key information such as gender, age, source of infection, causative pathogen, co-morbidities, patient lifestyle factors (smoking, alcoholism),