EVALUATION OF CEFTRIAXONE WITH DISODIUM EDTA IN A COMBINATION TO TREAT ACUTE EMPHYSEMATOUS PYELONEPHRITIS

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Abstract:

Background: Emphysematous pyelonephritis (EPN) is an acute necrotizing infection of upper urinary tract distinguished by the presence of gas in renal parenchyma and peri-renal tissue. There is a rapid increase in multi drug resistant strains across the globe, especially in the southeast asian region, including India, where extended-spectrum β-lactamase (ESBL) prevalence varies between 17% and 70%. Ceftriaxone and disodium ethylene diamine tetra acetic acid (EDTA) is a novel combination active against multidrug-resistant Gram-negative pathogens. Infections due to EPN and ESBL producers range from uncomplicated urinary tract infections to life-threatening sepsis.

Methods: We investigated 11 cases in the present retrospective study. These patients were diagnosed as EPN produced by ESBL bacteria. The cases were followed from 6 to 20 months. Among the 11 patients 9 were female and 2 were male. All were diabetic and treated with 1 week ELORES followed by Faropenem for 7 days decreasing the chances of renal failure requiring haemodialysis and nephrectomy. The clinical and laboratory data, imaging findings, and microbiological patterns of 11 patients were recorded.

Results: Of the 11 cases in the present study, 9 patients showed progress with 1 week of ELORES followed by Faropenem. 1 underwent percutaneous nephrostomy and delayed nephrectomy. 1 patient underwent Nephrectomy,

Conclusion: The study clearly demonstrates the decreased nephrectomy rate when the drug combination is used. This retrospective study with a small sample number needs further validation with a multivariable analysis and with a higher number of cases.

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1. Introduction

Emphysematous pyelonephritis (EPN) is defined as an acute, necrotizing, and critical infection of the renal parenchyma and adjoining tissues, mainly distinguished by the presence of gas in the parenchyma, collecting system, perinephric and paranephric tissue. Risk components related with EPN were well categorised, diabetes mellitus being the most common implication. Sepsis is a significant infection and continue to be a common cause of mortality and morbidity in developing countries. The most affected being the younger population and the causative organisms likely to be Gram-negative and atypical pathogens. Four main attributes involved in the pathogenesis of the disease is well documented: Infection produced by gas-forming bacteria, chronically increased glucose levels, changes in the perfusion of peripheral tissues, and defects in the immune response. Gram-negative enteric non obligatory anaerobic microorganisms mainly cause this condition. The most frequent causative microorganism reported in EPN is Escherichia coli (E. coli) in 60%-70% of the cases. The presence of Enterobacteriaceae, such as E. coli, Klebsiella pneumoniae and Proteus spp., under anaerobic conditions cause diverse acid fermentation of glucose, leading to the pathway of gas formation in EPN. The evolution of uropathogens resistant to the initial antibiotic treatments is a significant complication in healthcare practice.

Inadequate response to antibiotic therapy in patients with diabetes mellitus who have uncomplicated pyelonephritis should immediately arouse suspicion of this life-threatening infection since no specific symptoms or signs to diagnose EPN. A prompt computed tomography (CT) scan of the abdomen should be taken to confirm the diagnosis and to plan treatment. The treatment of EPN has changed over the years from radical nephrectomy to more conservative approaches, such as antibiotics and percutaneous drainage techniques, due to the availability of better imaging modalities. A surge has recently been noted in extended-spectrum beta-lactamase (ESBL) producing microorganisms in urinary tract infections. The production of ESBL provide a natural resistance to penicillins, cephalosporins, and aztreonam, restricting the therapeutic action on these bacterial infections. Not much of observations were reported on the microbiological factors as predictors of clinical responses or outcomes. The prevalence of ESBL-producing microorganisms and their clinical significance in EPN are not well known from this part of the country. The aim of the present study is to elucidate the efficacy of Ceftriaxone and disodium ethylene diamine tetra acetic acid fusion (ELORES) for 7 days followed by Faropenem for a week given to our patients.

2. Methods

This was a retrospective, observational study conducted at Bharath Medical College and Hospital from January 2021 to August 2022. EPN is a gas-forming infection of the kidney. We analysed 11 cases in the present study. These patients were diagnosed as EPN caused by ESBL bacteria. 11 cases of EPN, all were diabetic were treated with 1 week ELORES followed by Faropenem. All the cases were followed up from 6 to 20 months. Among the 11 patients 9 were female and 2 were male patients.

Acute kidney injury (AKI) is defined by a sudden loss of excretory kidney function. AKI is part of a range of conditions summarized as acute kidney diseases and disorders (AKD), in which slow deterioration of kidney function or persistent kidney dysfunction is associated with an irreversible loss of kidney cells and nephrons, which can lead to chronic kidney disease (CKD). By definition, AKD persisting for >3 months is referred to as chronic kidney disease (CKD). Acute Kidney Injury was observed in 2 patients (defined as increased serum creatinine > 0.2), Chronic Kidney Disease was seen in 5 cases, Normal Renal function was observed in 4 patients (6,7,22) (Table 3).

Based on the extent of air seen on CT, (Table 1) we selected patients of Grade 1 and grade 2 class of EPN (9). All patients who were admitted to the Department of Nephro-Urology for management of EPN were chosen for the study after fulfilling the study criteria. Those patients with Grade 3 and 4 of EPN, incomplete data, patients who died of a suspected diagnosis of EPN before the diagnosis was confirmed, or

patients who had an early transfer to another centre after discontinuing treatment at the study centre were excluded from the analysis. We collected demographic characteristics and clinical information, underlying medical conditions, laboratory findings, imaging findings, types of management, and patient outcomes. The clinical features included signs and symptoms at presentation, and the hemodynamic and mental status of the patients (Table 2). The laboratory variables included hemoglobin, white blood cell count, platelet count, albumin, sodium, HbA1c, serum creatinine levels, serum electrolytes, and the results of urinalysis, blood, and urine cultures.

We first analysed the key clinical and laboratory data that could serve as predictors for a need of haemodialysis and further outcomes. The antibiotic culture sensitivity reports were also analysed. The study subjects were divided into three treatment groups, that is, those on antibiotics alone, those who underwent Double J (DJ) stenting (Double J stent, Biorad, India) in addition to receiving antibiotics, and finally, those patients who underwent percutaneous nephrostomy and nephrectomy despite receiving antibiotics and DJ stenting. Nephrectomy was considered if patient had progressive or persistent lesions detected on imaging, and if they had clinical manifestation of unstable hemodynamic or a prolonged fever (Table 4).

DJ stenting was performed with local anaesthesia for the improved patients. No death occurred in the study. In our study the common feature present in all patients was abdominal pain, dysuria, vomiting and fatigue. 9 cases were found with frequent micturition, 10 cases with jaundice. Other common characteristics were haematuria (4), anorexia (4), shock (4), uremic features (6), renal angle tenderness on the left (6). Few cases were observed with renal angle tenderness on the right (3), renal calculi (3), breathlessness (2), Itching (2), Oliguria (2), bilateral renal angle tenderness (2), single cases with Pneumaturia and structural abnormalities were noted (1) (Table 2).

3. Results

Of the 11 cases studied in the present study, all received ELORES with Faropenem and DJ Stenting. 9 patients improved with 1 week of ELORES followed by Faropenem and D J Stenting, 1 case had Nephrectomy, 1 underwent percutaneous nephrostomy and delayed nephrectomy.

Table 1: Based on the extent of air seen on CT, patients were categorised into the following 4 types of EPN Classification Ref: 9

Class 1	Gas in the collecting system only
Class 2	Gas in the renal parenchyma without extension to the extrarenal space
Class 3A	extension of gas or abscess to the peri-nephric space;
Class 3B	extension of gas or abscess to the pararenal space;
Class 4	Bilateral EPN or a solitary kidney with EPN

Table 2: Serum Creatinine and Urea Levels Observed in our Patients:

Mean serum creatinine, mg/dl (Nonacute Kidney Injury (AKI) and Chronic Kidney Disease (CKD)	1.1 ±0.2
Mean serum creatinine, mg/dl AKI	1.8-2.3
Mean serum creatinine, mg/dl CKD	3-4
Mean Normal Urea level mg/dL	5-20
Mean Urea, mg/dl AKI	55-65
Mean Urea, mg/dl CKD	75-85

Table 3: Treatment given to the patients: ELORES: {IV Ceftriaxone 1-2g IV qday + EDTA – 37 mg qday (3,24,27)}

Patient Number	**Gender**	**Co-morbidities**	**Antibiotics received** ELORES (7days) + Faropenam (7days)
1	Male	DM+CKD	ELORES+Faropenam+Nephrectomy
2	Male	DM	ELORES+Faropenam+Percutaneous Nephrostomy+Nephrectomy
3	Female	DM+CKD	ELORES+Faropenam+DJ Stenting
4	Female	DM+CKD	ELORES+Faropenam+DJ Stenting
5	Female	DM+CKD	ELORES+Faropenam+DJ Stenting
6	Female	DM+CKD	ELORES+Faropenam+DJ Stenting
7	Female	DM+AKI	ELORES+Faropenam+DJ Stenting
8	Female	DM+AKI	ELORES+Faropenam+DJ Stenting
9	Female	DM+AKI	ELORES+Faropenam+DJ Stenting
10	Female	DM+AKI	ELORES+Faropenam+DJ Stenting
11	Female	DM+AKI	ELORES+Faropenam+DJ Stenting

Figure 1: Gender wise Distribution:

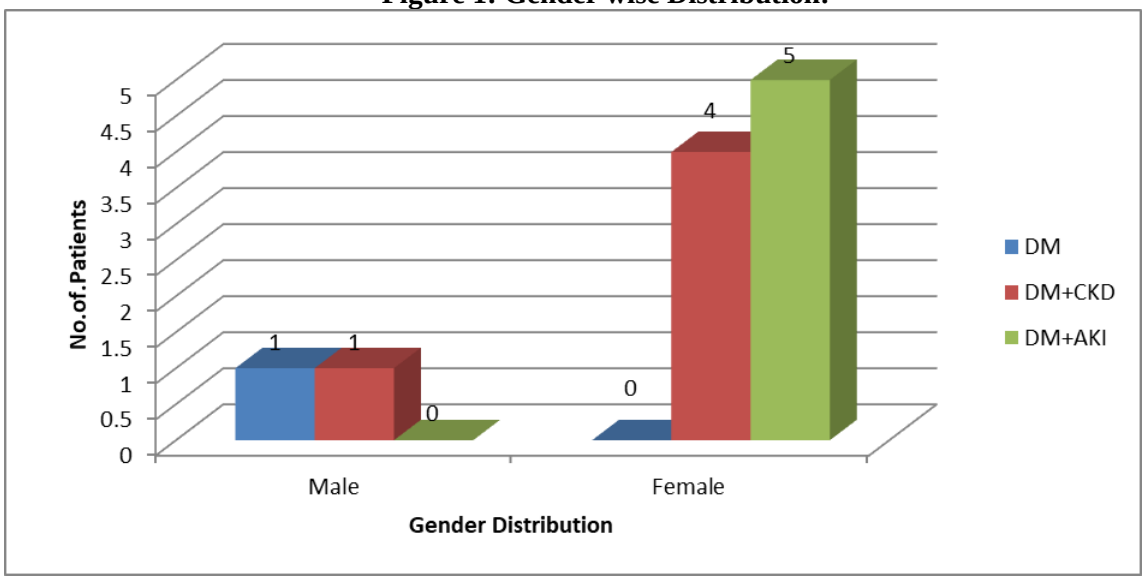
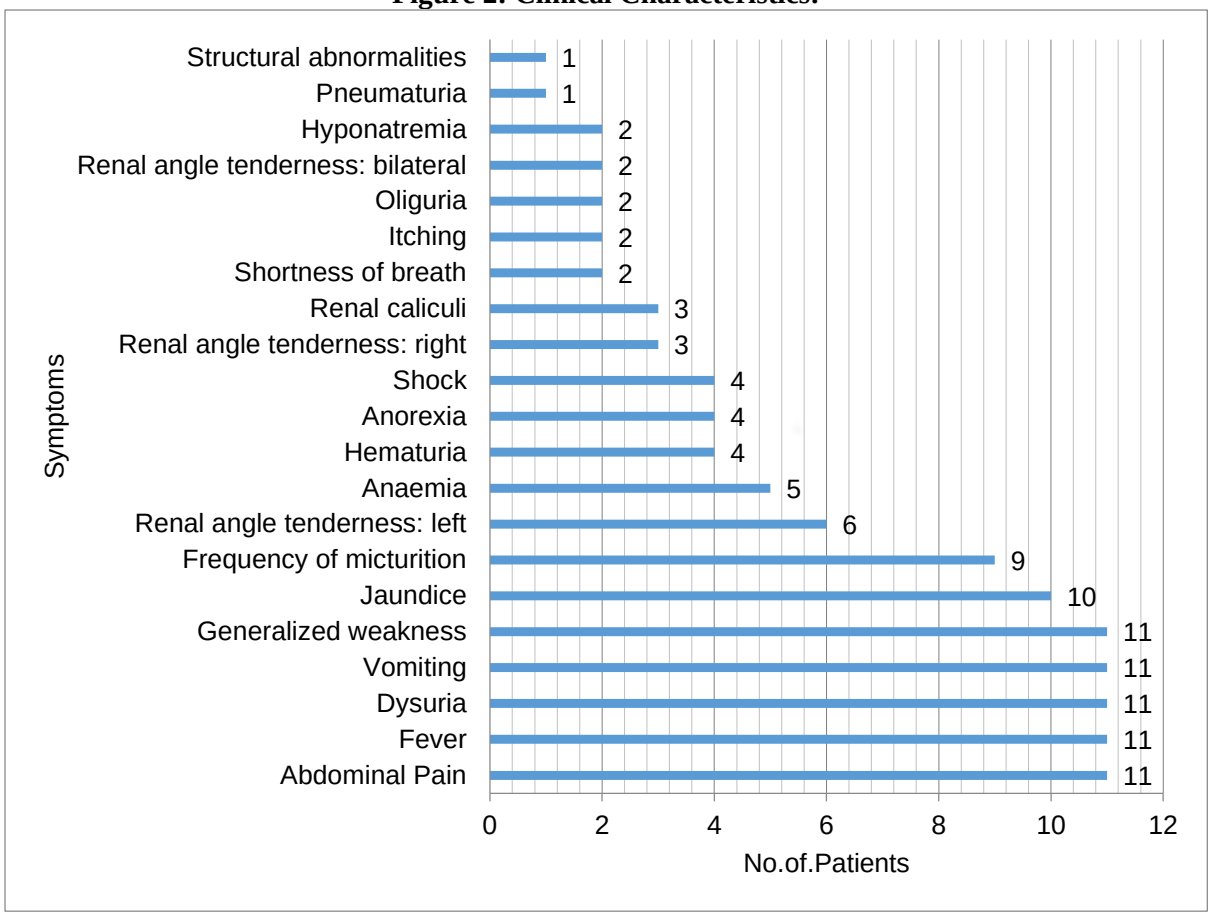


Figure 2: Clinical Characteristics:



4. Discussion

EPN is a fatal necrotizing infection of the kidney that is identified by an accumulation of gas in the renal parenchyma, peri-renal tissues, and/or in the collecting system. In our study female patients were dominant. Female preponderance is seen in almost all studies because women are more susceptible to urinary tract infections (16). Our study population is less. We have planned for a larger study done prospectively with multivariate analysis which will authorise further efficacy of the drug combinations (Figure 1).

Wan et al. reported that EPN is a disease that arise more commonly in women, with a ratio of 3:1. Lu et al.5 observed a distinct female predominance in their study, with ratio of 12:1. In our study, we observed a gross difference in the incidence of disease between the two sexes, with a female/male ratio of only 9:2 (Table 1).

In the studies of Dunn et al., and Cook et al., they documented that initial nephrectomy was considered the main treatment for EPN, with a few reports that recommended elevated mortality with medical intervention compared with surgery. In 1996, Chen et al. documented that antibiotic treatment with CT-aided percutaneous drainage of EPN was a suitable method to antibiotic therapy without surgical intervention. In the last 2 decades, more stable strategies have decreased the mortality of EPN from 80% to 21% (Table 2). Huang and Tseng reported that thrombocytopenia, acute kidney injury, depressed level of consciousness, shock, and extension of the infection into the peri-nephric space were significantly associated with mortality. Even though the study population is less, we observed all the clinical features as seen in the study by Huang and Tseng (Table 3).

An Indian study by Kapoor et al. reported that altered mental status, renal failure, and acute hyponatremia at presentation were associated with higher mortality rates. Extensive renal parenchymal destruction mandated the need for nephrectomy. In our study 1 case necessitated

nephrectomy at admission, 1 case needed percutaneous nephrostomy at admission, but due to non-improvement needed nephrectomy later leading to delayed nephrectomy. In one of the study by Khaira et al. observed that shock at time of admission, serum creatinine >5.0 mg/dl, and disseminated intravascular coagulation were determinants of poor prognosis. In the present study, 2 cases presented with increased creatinine level more than 0.3 was observed (Figure 2).

Huang and Tseng (11) established that nephrectomy provided the best treatment of 48 cases of EPN and should be considered for extensive EPN which is resistant to higher antibiotics. The treatment of EPN has changed over the years from complete nephrectomy to more safe strategies apply antibiotics and percutaneous drainage procedures. This is due to better imaging procedures and improved antimicrobials. EPN is still a fatal renal infection, but with increased clinical suspicion and early intervention; it is curable, thus decreasing both short- and long-term renal consequences.

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