

Emphysematous Pyelonephritis Case Series From South India

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Introduction: Emphysematous pyelonephritis (EPN) is a rare, life-threatening necrotizing infection of the kidney. The mortality rate for EPN is as high as 25%. We conducted a retrospective study at MS Ramaiah Hospital between January 2011 and May 2016 to observe the clinical, biochemical, and microbiological patterns of EPN at our institute.

Methods: The clinical and laboratory data, imaging findings, and microbiological patterns of 51 patients chosen for the study were recorded. The data were analyzed to identify the prognostic variables that could predict the morbidity and mortality of patients with EPN, and the focus of this study was to determine risk factors for and outcomes of patients who presented with EPN and who required hemodialysis. Primary endpoints were successful treatment and all-cause mortality. Secondary endpoints included need for hemodialysis and the need for a specific treatment.

Results: There was an equal incidence among both sexes (median age: 59 years). Common symptoms were abdominal pain (94.11%), fever (83.2%), dysuria (74.5%), vomiting (72.54%), frequency of micturition (68.62%), oliguria, generalized weakness (66.67%), and breathlessness (66.67%); 98.03% (n = 50) of the patients had diabetes. The most common organism cultured was *Escherichia coli* (37.2%). Nineteen patients (37.2%) required dialysis; their mean age was 60.25 ± 11.74 years. Male sex, diabetes mellitus, shock, high serum creatinine at presentation, and uremic symptoms showed no statistically significant association. Indefinite hemodialysis was required by 12.5% of patients. The antibiotic-treated group had a 100% success rate, whereas the Double J (DJ) stenting group (Double J stent, Biorad, India) had 96.42% success rate.

Conclusion: Early diagnosis and broad spectrum antibiotics, together with an appropriately timed intervention, resulted in decreased mortality. Pain in the abdomen and renal angle tenderness were the most common clinical finding. *E coli* was the most found organism, and early use of broad spectrum antibiotics decreased mortality.

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mphysematous pyelonephritis (EPN) is a rare, severe life-threatening necrotizing renal parenchymal infection that is characterized by the production of intraparenchymal gas. Until the mid-1980s, the standard treatment was nephrectomy of the affected kidney because efforts in preserving the kidney by surgical methods led to mortality from 60% to 80%. However, in recent years, the mortality of EPN patients has decreased to 25% (1%-46%).¹

EPN occurs most commonly in women, and diabetic populations are at increased risk of infection. In

comorbidities are renal stone disease, structural abnormalities of the urinary tract, and immunosuppression. Although a high tissue glucose level could provide a favorable environment for the growth of gas-producing bacteria in patients with diabetes, this was not associated with increased mortality or need for the dialysis, even in patients with poorly controlled diabetes mellitus (glycosylated hemoglobin [HbA_{1c}] >8%).² Four factors have been implicated in the pathogen-

nondiabetic population, the common

Four factors have been implicated in the pathogenesis of EPN: (i) gas-forming bacteria; (ii) a high tissue glucose level (favoring rapid bacterial growth); (iii) impaired tissue perfusion (diabetic nephropathy can lead to additional compromise of regional oxygen delivery in the kidney, which results in tissue ischemia and necrosis, as well as nitrogen released during tissue

associated

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necrosis); and (iv) a defective immune response due to an impaired vascular supply. Ureteral obstruction causes local tissue ischemia that provokes infection. Calculi act as a nidus for infection, and also causes stagnation and reflux of urine.

Although there are no specific symptoms or signs to diagnose EPN, poor response to antibiotic treatment in patients with diabetes mellitus who are believed to have uncomplicated pyelonephritis should immediately arouse suspicion of this life-threatening infection. 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.

METHODS

This was a retrospective, observational study conducted at M.S. Ramaiah Medical College and its attached hospitals from January 2011 to May 2016. The data were obtained from the hospital electronic records using *International Classification of Disease* codes. The hospital medical records were searched electronically for EPN keywords using their *International Classification of Diseases, Ninth Revision* codes.

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 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 center after discontinuing treatment at the study center were excluded from the analysis. The chosen records were then assessed by the Departmental Committee for any incomplete records, and such subjects were also excluded from the study.

We collected various variables from our chosen subjects that were suspected to have any effect on clinical outcomes, based on our knowledge of similar studies. 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. The laboratory variables included hemoglobin, white blood cell count, platelet count, albumin, sodium, HbA_{1c}, serum creatinine levels, serum electrolytes, and the results of urinalysis, blood, and urine cultures. Once data were obtained, we first analyzed the key clinical and laboratory data that could serve as predictors for a need of hemodialysis and further outcomes. The antibiotic culture sensitivity reports were also analyzed. The study subjects were divided into 3 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 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 hemodynamics or a prolonged fever.

The key variables were defined per standard definitions used in the literature and are shown in Table 1.

Clinical, biochemical, and microbiological data were recorded in a tabular form. Data were analyzed using SPSS version 20.0 for Windows (IBM, Armonk, New York). Quantitative variables were expressed as mean \pm SD, whereas qualitative data were presented as the number of observations with percentages. Continuous data were compared by using Student's *t*-test. Paired data were analyzed by an independent sample *t* test. Univariate analysis was performed to identify risk factors of morbidity. A *P* value <0.05 was considered significant.

RESULTS

We identified a total of 54 patients during the study period who had a diagnosis of EPN. Of these 54 patients, we excluded 3 patients: 2 of them left the

	Tabl	e 1.	Definitions
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Parameter	Definition
Emphysematous pyelonephritis (EPN)	 In accordance with the classification system of Huang and Tseng,³ which is based on the extent of air seen on CT, patients were divided into the following 4 types of EPN: Class 1: Gas in the collecting system only; Class 2: Gas in the renal parenchyma without extension to the extrarenal space; Class 3: 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
Recurrent EPN	Both clinical presentation of sepsis and progressive lesions disclosed on the image study were noted within 3 months after adequate treatment of EPN
Thrombocytopenia	A platelet count <120,000/ml
Hypoalbuminemia	A serum albumin <3.0 g/dl
Hyponatremia	A serum Na <135 mEq/L
Severe hyponatremia	A serum Na <125 mEq/L
Shock	A systolic blood pressure <90 mm Hg
Anemia	Hb% <11 g/dl

CT, computed tomography; Hb, hemoglobin; Na, sodium.

CLINICAL RESEARCH

hospital before a complete workup and treatment initiation; and 1 patient who was diagnosed with EPN elsewhere was referred to our institution in a critically ill state and died within 2 hours of admission. Hence, these 3 patients were excluded from analysis due to incomplete data. The remaining 51 patients had all the necessary data required for analysis.

We divided the entire cohort of our patients into 2 broad categories; 1 group of patients was managed conservatively without any need for hemodialysis, and the other group required hemodialysis along with other standard medical treatment for EPN. Overall, 32 (62.74%) patients in our study were managed conservatively, and 19 (37.26%) patients required hemodialysis. The mean age of patients in the dialysis group was higher than those in the conservative group (60.25 \pm 11.74 years vs. 55.14 \pm 14.7 years); however, the difference failed to achieve statistical significance (P =0.715). The median age of women in the conservative management group (65.6%) was 53 years (range: 25-87 years), and the median age of men (34.4%) was 65 years (range: 46-75 years). However, in the dialysis group, there was a slight male preponderance, with men constituting 57.8% of the group and women constituting 42.2%. The median age of men in hemodialysis group was 58 years (range: 28-65 years), and the median age of women was 59 years (range: 50-60 years). Patient in dialysis group had a slightly higher incidence of renal calculi (10.5% in the hemodialysis group vs. 6.25% in the conservatively managed group), although this was not statistically significant. Depressed level of consciousness, shock, thrombocytopenia, and hypoalbuminemia all had a numerically higher incidence among the hemodialysis group of our study population, although these failed to achieve statistical significance (Table 2). Mean serum creatinine was higher and statistically significant in the hemodialysis group (4.75 mg/dl) versus the conservatively managed group (2.45 mg/dl). The overall prevalence of diabetes in our study was 98% (n = 50), with a median duration of 12 years (range: 2 months to 30 years). Median leucocyte count, hyponatremia, and positive urine culture did not have a statistically significant correlation.

The clinical symptoms observed in our study population were quite varied (Table 3). The 3 most common symptoms reported in the overall cohort of our study were abdominal pain (94.11%), fever (82.3%), and dysuria (74.5%). Other frequently reported symptoms were vomiting, (72.54%), frequency of micturition (68.62%), oliguria (66.67%), generalized weakness (66.67%), and shortness of breath (49.01%). Thrombocytopenia (42.1%), uremia (27.45%), depressed level

Table 2. Clinical and	epidemiological	characteristics of patients
with emphysematous	pyelonephritis	

Variable	Patient who required dialysis ($n = 19$)	Patient managed conservatively $(n = 32)$	<i>P</i> value
Mean age, yr	60.25 ± 11.74	55.14 ± 14.7	0.715
Women	8 (42.2)	21 (65.6)	0.083
Median age of women, yr	59 (50-60)	53 (25–87)	0.721
Men	11 (57.8)	11 (34.4)	0.091
Median age of men, yr	58 (28-65)	65 (46-75)	0.722
Diabetics, %	94.74	100	0.862
Uncontrolled diabetes, %	31.25	42.85	0.857
Patients with renal calculi	2 (10.5)	2 (6.25)	0.126
Depressed level of consciousness	6 (31.6)	2 (6.25)	0.071
Shock	3 (15.7)	2 (6.2)	0.056
Anemia	8 (42.1)	14 (43.7)	0.234
Median leucocyte count, cells/mm ³	15,905 (12,300-21,660)	13,925 (9642–16,450)	0.721
Median platelet count, Lakhs/mm ³	1.55 (0.65-3.33)	2.5 (1.1–3.3)	0.279
Thrombocytopenia	8 (42.1)	7 (21.8)	0.061
Hematuria, %	56.25	78.57	0.579
Mean serum creatinine, mg/dl	4.75	2.45	<0.0001
Mean albumin, g/dl	2	2.56	0.867
Hypoalbuminemia	5 (26.3)	7 (21.8)	0.075
Hyponatremia	13 (68.4)	18 (56.2)	0.786
Urine culture positive, %	68.75	53.57	0.986

Values are numbers (ranges), mean \pm SD, or number (%)

of consciousness (15.68%), and shock (9.80%) were considered to be features of a more severe form of the disease. One patient in our study had a stricture urethra, and 1 had a single kidney. None of the patients were on immunosuppressive therapy that could predispose them to infection. One patient had recurrent pyelonephritis. One patient presented with hyperkalemia-induced weakness. One patient was a pregnant woman in her second trimester who recovered well with antibiotics. Three patients (5.89%) had bronchopneumonia. One patient had a left psoas abscess with syndrome of inappropriate antidiuretic hormone secretion presentation.

The most common organism to be cultured from blood and urine was *Escherichia coli* (37.25%). The other organisms included *Enterococcus* species (5.88%), *Klebsiella pneumoniae* (5.88%), *Candida* species (5.88%), and *Proteus mirabilis* (1.96%). Urine culture was positive in 58.82% of patients, and 1 patient had a polymicrobial infection. *E coli* was the most common organism isolated from urine specimens (19 patients). Bacteremia occurred in 12 patients (31.37%), with polymicrobial bacteremia in 1 patient, *E coli* in 9

Table 3. Incidence of clinical symptoms in emphysematous pyelonephritis

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No.	Symptom	Affected ($N = 51$)
1	Abdominal Pain	48 (94.11)
2	Fever	42 (82.35)
3	Dysuria	38 (74.50)
4	Vomiting	37 (72.54)
5	Frequency of micturition	35 (68.62)
6	Oliguria	34 (66.67)
7	Generalized weakness	34 (66.67)
8	Shortness of breath	25 (49.01)
9	Anorexia	16 (31.37)
10	Uremic features	14 (27.45)
11	Malnutrition	13 (25.49)
12	Depressed level of consciousness	8 (15.68)
13	Jaundice	8 (15.68)
14	Shock	5 (9.8)
15	Itching	6 (11.76)
16	Hematuria	3 (17.64)
17	Giddiness	2 (3.92)
18	Pneumaturia	2 (3.92)
19	Renal angle tenderness: left	26 (50.98)
20	Renal angle tenderness: bilateral	8 (15.68)
21	Renal angle tenderness: right	4 (27.45)
22	Renal caliculi	4 (7.84)
23	Structural abnormalities	2 (3.92)

Values are numbers (%).

patients, Klebsiella in 2 patients, staphylococcus in 2 patients, and enterococcus in 1 patient (Table 4).

The final treatment of EPN in our study mainly included antibiotics alone or antibiotics with DJ stenting and/or nephrectomy when the previous treatment measures failed to show any favorable clinical response. Based on these data, we further analyzed our data by categorizing patients into 3 groups (Figure 1):

Group 1: Antibiotic alone treated group;

Group 2: Antibiotic with DJ stenting group; and

Group 3: Nephrectomy group.

All the patients in our study were started on antibiotics per institutional antibiotic protocol. Carbapenems (meropenem and imipenem), uredopenicillin (piperacillin with tazobactum), and third-generation cephalosporin and amino glycoside (amikacin) antibiotics were the most commonly prescribed antimicrobials for our study participants. The choice of antibiotic

Table 4. Causative organisms from blood, urine cultures

Urine culture		Blood culture	
No growth	21 (41.1)	No growth	35 (68.62)
E coli	19 (37.25)	E coli	9 (17.64)
Enterococcus	3 (5.88)	Enterococcus	1 (1.96)
Klebsiella	3 (5.88)	Klebsiella	2 (3.92)
Candida	3 (5.88)	Staphylococcus epidermidis	2 (3.92)
Proteus	1 (1.96)	Candida	1 (1.96)
Polymicrobial	1 (1.96)	Polymicrobial	1 (1.96)

Values are numbers (%).

at admission depended on the severity of sepsis, diabetic state, age, sex, and general condition (shock) of the patient. Blood cultures were taken before initiating antimicrobials for all our patients. No significant modification of the initial antimicrobial regimen took place after obtaining culture reports for most of our patients, except for 2 patients. One received tigecycline, and the other received amphotericin B. We observed that antibiotics alone were successful in treating EPN in 23 patients (45.10%). Twenty-seven (52.94%) of the patients in our study also required DJ stenting after initiating the appropriate antibiotic. Only 1 patient in our study did not respond to 2 previous treatment strategies and required emergency nephrectomy because of a rapidly deteriorating condition.

DISCUSSION

EPN is a rare, life-threatening necrotizing infection of the kidney that is characterized by an accumulation of gas in the renal parenchyma, peri-renal tissues, and/or in the collecting system.

In their study, Wan *et al.*⁴ showed that EPN is a disease that occurs more commonly in women, with a female/male ratio of 3:1. Lu *et al.*⁵ showed a striking female dominance in their study, with ratio of 12:1. Female preponderance is seen in almost all studies because women are more susceptible to urinary tract infections, except in renal transplantation cases. In our study, we did not see any gross difference in the incidence of disease between the two sexes, with a female/male ratio of only 1.3:1.

In their study, Huang and Tseng³ encountered fever in 79% of their patients, abdominal or back pain in 71%, nausea and vomiting in 17%, lethargy and confusion in 19%, dyspnea in 13%, and shock in 29%. In our study, we found that abdominal pain (94.11%) was the most common symptom, followed by fever (82.3%), dysuria (74.5%), vomiting (72.54%), frequency of micturition (68.62%), oliguria (66.67%), generalized weakness (66.67%), and shortness of breath (49.01%).

A meta-analysis reported that 52% of patients had left-sided EPN, 37.7% had right-sided EPN, and 10.2% had bilateral EPN.¹ Huang and Tseng³ reported that 67%, 25%, and 8% of EPN patients had left-sided, right-sided, and bilateral disease, respectively. In our study, 50.98% of patients had left-sided EPN, 27.45% had right-sided EPN, and 15.68% had bilateral EPN.

Diabetes mellitus, renal calculi disease, structural abnormalities of the urinary tract, and immunosuppression are commonly observed comorbidities of EPN. Prevalence of diabetes and renal calculi in our study was 98% and 7.84%, respectively. In their study,

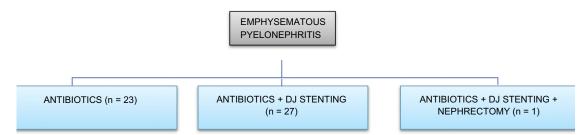


Figure 1. Treatment chart. DJ, Double J stent.

Huang and Tseng,³ reported that 96% of the patients had diabetes mellitus, and 22% had urinary tract obstruction. Lu et al.6 proposed that high tissue glucose levels could cause a fulminant course in patients with diabetes mellitus, because such high levels might provide gas-forming microbes in a microenvironment that is more favorable for growth and catabolism. In their study, Lu et al.⁵, showed that glycemic control had no prognostic significance. Studies concluded that glycemic control was not a prognostic factor in patients with EPN. Although high tissue glucose levels might provide a favorable environment in diabetic patients for the growth of gasproducing bacteria, an association with increased mortality or need for the dialysis was not found, even in patients with poorly controlled diabetes mellitus $(HbA_{1c} > 8\%).^2$

In their studies, Huang and Tseng,³ Wan *et al.*,⁴ and Pontin *et al.*⁷ showed that *E coli* was the most common causative organism for EPN, which was isolated in 47% to 90% of their patients; the other commonly involved organisms included *P. mirabilis*, Klebsiella, pneumoniae, *Enterococcus* species, and *Pseudomonas aeruginosa*. Urine cultures and blood cultures were positive in 58.82% and 31.37% of our study participants, respectively. The most common organism to be cultured from blood and urine was *E coli*. The other organisms included *Enterococcus* species (5.88%), *Klebsiella pneumoniae* (5.88%), *Candida* species (5.88%), and *P. mirabilis* (1.96%); 1 patient had polymicrobial infection.

Various studies focused on the factors that are associated with mortality of EPN. In 1 meta-analysis that included 7 study cohorts representing 175 patients with EPN, the overall mortality rate was 25% (range: 11%-42%).¹

Thrombocytopenia (42.1%), uremia (27.45%), depressed level of consciousness (15.68%), and shock (9.80%) were considered features of a more severe form of the disease in our patients. Olvera-Posada *et al.*⁸ concluded that altered consciousness, multiple organ failure, hyperglycemia, and elevated count of leukocytes were more frequent among patients dying from EPN. Huang and Tseng³ similarly reported that thrombocytopenia (46%), acute kidney injury (35%), depressed level of consciousness (19%), shock (29%), and extension of the infection into the peri-nephric space were significantly associated with mortality. In an Indian study, Kapoor et al.9 showed that altered mental status, thrombocytopenia, renal failure, and severe hyponatremia at presentation were associated with higher mortality rates, whereas extensive renal parenchymal destruction mandated the need for nephrectomy. In their study, Khaira et al.² also showed that shock at time of admission, serum creatinine >5.0 mg/dl, and disseminated intravascular coagulation were independent poor prognostic factors. Lu et al.⁶ reported that need for emergency hemodialysis, severe hypoalbuminemia (serum albumin <3 g/dl), and polymicrobial infections were poor prognostic factors for patients with EPN.

The treatment of EPN has changed over the years from radical nephrectomy to more conservative approaches that involve antibiotics and percutaneous drainage techniques due to better imaging modalities and early diagnosis with better antimicrobials. Huang and Tseng³ concluded that nephrectomy provided the best management of their 48 cases of EPN and should be promptly attempted for extensive EPN with a fulminant course (≥ 2 bad prognostic factors). In their studies, Dunn et al.¹⁰, and Cook et al.¹¹ showed that early nephrectomy was considered the treatment of choice for EPN, with a few reports that suggested increased mortality with medical therapy compared with surgery. In 1996, Chen et al.¹² reported that antibiotic therapy combined with CT-guided percutaneous drainage of EPN was an acceptable alternative to antibiotic therapy with surgical intervention. In the last 2 decades, more conservative approaches have decreased the mortality of EPN from 80% to 21%.^{13,14} The metaanalysis by Aboumarzouk *et al.*¹⁵ showed that compared with emergency nephrectomy, percutaneous drainage and medical management alone were associated with a significantly lower mortality rate. Misgar et al.¹⁶, Nagappan and Kletchko¹⁷, Grozel et al.¹⁸, and Tahir et al.¹⁹ showed successful nonsurgical management of bilateral EPN in their studies. In our study, we

Table 5. Radiological classification of EPN

Class of EPN	Total no of patients $(n = 51)$	Urological intervention (DJ stenting)	Outcomes
Class I	8	0	Recovered
Class II	30	14	2 patients progressed to ESRD
Class III	12	12	2 progressed to ESRD
Class IV	01	01	Required DJ stent and nephrectomy, eventually died.

 DJ stent, <code>Double J</code> stent; <code>EPN</code>, <code>emphysematous</code> <code>pyelonephritis</code>; <code>ESRD</code>, <code>end-stage</code> <code>renal</code> disease.

observed that antibiotics alone were successful for treatment of EPN in 23 patients (45.10%). Twenty-seven (52.94%) patients in our study also required DJ stenting after initiating the appropriate antibiotic.

Of our 51 patients, 8, 30, 12, 1 patients were in classes I, II, III, and IV of EPN, respectively (Table 5). Only 1 patient in our study did not respond to 2 of the treatment strategies and required emergency nephrectomy because of a rapidly deteriorating condition.

Conclusion

EPN is still a dangerous renal infection, but with high clinical suspicion and early initiation of therapy, it is potentially treatable, thus reducing both short- and long-term renal outcomes. Although EPN is a dreaded diagnosis, it is still a manageable menace.

DISCLOSURES

All the authors declared no competing interests.

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