

Clinical profile and successful outcomes of conservative and minimally invasive treatment of emphysematous pyelonephritis

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Citation: Karthikeyan VS, Manohar CMS, Mallya A, Keshavamurthy R, Kamath AJ. Clinical profile and successful outcomes of conservative and minimally invasive treatment of emphysematous pyelonephritis. Cent European J Urol. 2018; 71: 228-233.

Article history

Submitted: Dec. 31, 2017

Accepted: April 12, 2018

Published online: April 16, 2018

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Introduction Emphysematous pyelonephritis (EPN) is a rare clinical entity, characterized by gas in the renal system, due to an acute, fulminant and potentially fatal necrotizing process with varying clinical presentations. It is much more aggressive than uncomplicated pyelonephritis, with the mortality of 20–40% in the contemporary meta-analysis.

Material and methods A retrospective record review of inpatients at the Institute of Nephro Urology, Bangalore, India (2007–2014), who were treated after EPN was diagnosed with the aid of a CT (computed tomography) scan.

Results Sixty-six patients (M:F 27:39) treated for EPN over the past seven years with the mean (\pm SD) age of 52.32 (\pm 12.48) years were analyzed. Median (interquartile range) duration of hospital stay was 8 (11.25) days with 4 (6%) patients requiring intensive care unit admission (median, IQR = 5.5, 1.5 days) of whom two passed away due to septicemia. Fifty-six (84.85%) patients were diabetics, forty (60.6%) patients had estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m², 6 (9.1%) patients had eGFR <30 ml/min/1.73 m² including 3 (4.5%) with eGFR <15 ml/min/1.73 m² requiring hemodialysis and twenty-two (33%) had thrombocytopenia. Fifty (75.76%) patients were classified as Huang and Tseng Class 2, 7 (10%) as Class 3 with perinephric abscess requiring open drainage and 9 (13.64%) had bilateral EPN (Class 4). Majority (43; 65%) responded to piperacillin-tazobactam treatment. Double J stenting was done in 17 (25.76%) patients, percutaneous drainage in 5 (7.58%) patients and nephrectomy in 2 (3%) patients.

Conclusions Although EPN historically carries high morbidity and mortality, modern day medical management with timely intervention in the form of urinary drainage is effective and curative in most patients resulting in a low mortality rate.

Key Words: pyelonephritis \leftrightarrow anti-bacterial agents \leftrightarrow stents \leftrightarrow nephrostomy \leftrightarrow percutaneous \leftrightarrow nephrectomy

INTRODUCTION

Emphysematous pyelonephritis (EPN) is a urologic emergency caused by a life threatening necrotizing infection of the kidney leading to an accumulation of gas in the renal parenchyma and perirenal tissue [1]. The term emphysematous pyelonephritis was coined by Schultz and Klorfein in 1962, although

Kelly and McCallum reported the first case of EPN in 1898 [2, 3]. EPN requires special attention due to the life threatening complications, especially sepsis [1]. Until the mid-1980s, nephrectomy was the standard treatment as the non-surgical treatment led to mortality of 60–80% [3, 4, 5]. With the improvement of computed tomography (CT) based diagnosis and advances in the multi-disciplinary intensive

care, mortality has been reported to be 20–40% in a meta-analysis [1]. Over the last three decades, many studies reported a wide range in mortality and risk factors. Conservative management was proposed as a risk factor for mortality [1]. We performed this study to assess the clinical profile, risk factors and mode of presentation, organisms and antibiotic sensitivity pattern, role of surgical interventions, associated morbidity and mortality and efficacy of conservative management in adult outpatients with EPN requiring hospitalization at the Institute of Nephro Urology, Bangalore, India.

MATERIAL AND METHODS

This was a retrospective study done at a tertiary care referral urological center in South India in the Department of Urology, from 2007 to 2014. Institute research review board approval was obtained. It included sixty-six patients diagnosed to have EPN on CT of the kidneys, ureters and bladder. CT was done within twenty-four hours of suspected EPN diagnosis if the patient was hemodynamically stable. Hemodynamic stability was defined as the heart rate less than 100 beats per minute, systolic blood pressure of more than 100 mm Hg, diastolic blood pressure of more than 60 mm Hg and oxygen saturation of more than 95%, without oxygen supplementation, enabling the patient to be shifted to the CT console. The following

factors were studied: patient related factors, such as demography, side of involvement, duration of the disease, comorbidities, mode of presentation, past and treatment history; radiological investigations, including side of involvement, ultrasound (US) and CT findings, CT severity grading, presence of a perinephric abscess, presence of calculi or obstruction in the kidney; treatment related factors, like duration of hospital stay, medical and surgical management, intensive care unit (ICU) admission, type and duration of antibiotics administered; renal parameters, complete blood count, urine culture and sensitivity and other relevant investigations; as well as surgical interventions such as double J (DJ) stenting, percutaneous nephrostomy (PCN), percutaneous (PCD) or open drainage or a nephrectomy [3]. CT severity grading system proposed by Huang et al. was used (Table 1) [3]. Charlson comorbidity index (CCI) was calculated for each patient [6]. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease formula and patients were classified based on KIDGO (Kidney Disease: Improving Global Outcomes) guidelines [7, 8].

RESULTS

A total of sixty-six patients were included in the review. The mean age was 52.35 ± 12.48 years with a male to female ratio of 1:1.4 (27:39). Most (48 out of 66; 72.7%) patients were in the 31–60 years age group. The median (interquartile range – IQR) duration of symptoms was 8 (25) days (range: 1–180). The most common presentation was fever in forty-nine (74.2%) patients, flank pain in forty-five (68.2%), vomiting in twenty-two (33.3%), hematuria in 3 (4.5%) and pneumaturia in 1 (1.5%) patient. The classic triad of fever, flank pain and vomiting was seen in seventeen (26%) patients. On physical examination, twenty (30.3%) patients had tachycardia (heart rate: >100 beats per min), 6 (9.1%) had hypotension (systolic blood pressure <90 mm Hg), costovertebral angle tenderness was seen in thirty-five (53%) patients and the kidney was enlarged and palpable in sixteen (24.2%) patients.

Systemic comorbidities were observed in a significant proportion of patients. Diabetes mellitus (DM) was seen in fifty-six (84.8%) patients, thirty-six (54.5%) of whom were female. Seven (10.6%) patients had hypertension, 3 (4.5%) had ischemic heart disease and 2 (3%) had chronic obstructive pulmonary disease. Eight (12.1%) patients had prior urologic surgeries – 2 (3%) underwent percutaneous nephrolithotomy, 4 (6.1%) had ureteric surgery (endoscopic and open) and 2 (3%) underwent open pyelolithotomy. The me-

Table 1. Computed tomography severity grading of emphysematous pyelonephritis (EPN) [3]

Class of EPN	Grade description
1	Gas in the collecting system
2	Gas in the renal parenchyma
3	A – Gas and/or abscess in the perinephric space
	B – Gas and/or abscess in the pararenal space
4	Bilateral EPN or EPN in solitary kidney

Table 2. Classification of patients with emphysematous pyelonephritis (EPN) based on Charlson Comorbidity Index (CCI)

CCI	Males N, %	Females N, %	Total
0	1 (25)	3 (75)	4
1	4 (33.3)	8 (66.7)	12
2	3 (20)	12 (80)	15
3	11 (61.1)	7 (38.9)	18
4	6 (46.2)	7 (53.8)	13
5	2 (50)	2 (50)	4
Total	27 (41)	39 (59)	66

Table 3. Classification of patients based on Huang and Tseng classification

Class	Males N, %	Females N, %	Total
2	19 (38)	31 (62)	50
3	4 (57.1)	3 (42.9)	7
3A	3 (42.8)	1 (14.3)	
3B	1 (14.3)	2 (28.6)	
4	4 (44.4)	5 (55.6)	9
Total	27 (41)	39 (59)	66

N – 66

Table 4. Biochemical abnormalities at patient presentation

Biochemical abnormality	Males N, %	Females N, %	Total
Anemia	25 (43.1)	33 (56.9)	58
Dyselectrolytemia	25 (45.5)	30 (54.5)	55
Hyperglycemia	19 (37.3)	32 (62.7)	51
Estimated GFR <60 ml /min/1.73 m ²	20 (50)	20 (50)	40
Leukocytosis	19 (47.5)	21 (52.5)	40
Thrombocytopenia	7 (31.8)	15 (68.2)	22
Elevated ESR	9 (39.1)	14 (60.9)	23

*Total exceeds 66 due to multiple abnormalities in same patient
N – 66; GFR – glomerular filtration rate; ESR – erythrocyte sedimentation rate

dian (IQR) time gap between the surgery and development of EPN was eighty (267) days. A larger proportion of female patients had a higher CCI (Table 2). Most of our patients (46; 69.7%) had CCI ranging from 2–4. In our study, twenty-two (33%) patients had right-sided involvement, thirty-five (53%) had left-sided and (14%) bilateral involvement.

All patients had a diagnostic CT of the kidneys performed. Twenty (30.3%) patients had ipsilateral hydronephrosis or hydroureterosis, 6 (9.1%) patients

had a renal abscess and 7 (10.6%) had a perinephric abscess. Contralateral pyelonephritis was seen in 6 (9.1%) patients and bilateral EPN was observed in 9 (13.6%) patients in our study. One patient had emphysematous cystitis. As per Huang and Tseng classification, fifty (75.8%) patients had class 2 EPN, 7 (10.6%) had class 3 EPN and 9 (13.6%) had class 4 EPN (Table 3) (Figure 1). Females contributed to thirty-one (31/50; 62%) of class 2, 3 (3/7; 42.9%) of class 3 and 5 (5/9; 55.5%) of class 4 EPN (Table 3). At presentation, twenty-six (39.4%) patients had an eGFR >60 ml/min/1.73 m² and forty (60.6%) patients had an eGFR <60 ml/min/1.73 m². Out of these patients with acute kidney injury, 6 (9.1%) patients had eGFR <30 ml/min/1.73 m², including 3 (4.5%) patients with eGFR <15 ml/min/1.73 m² at presentation, requiring hemodialysis. Electrolyte imbalance (altered sodium, potassium or chloride) was seen in fifty-five (83.3%) patients, hyperglycemia (random blood sugar – RBS>180 mg%) at presentation in forty-one (62.1%), anemia (hemoglobin <12 g% in male and <11 g% in female) in fifty-eight (87.9%), leukocytosis (total count >11000/mm³) in forty (60.6%), thrombocytopenia (platelets <100 000/mm³) in twenty-two (33.3%) and elevated erythrocyte sedimentation rate (>10 mm at 1 hour) was seen in twenty-three (34.8%) patients (Table 4).

Culture grew bacteria in thirty-one out of sixty-six (47%) patients. Escherichia coli was the most common isolate in twenty-five (25/31; 80.6%) patients and twenty-one (84%) were females. The other organisms isolated were Enterococcus species in 5 (5/31; 16.1%) patients, Citrobacter species and Candida albicans in 1 (1/31; 3.2%) patient each. Insignificant bacteriuria was observed in fifteen (15/66; 22.7%) patients. Antimicrobial sensitivity was available in thirty-one (31/66; 47%) patients. Piperacillin-tazobactam (18/31; 58.1%) had the least resistance followed by meropenem (16/31; 51.6%), amikacin

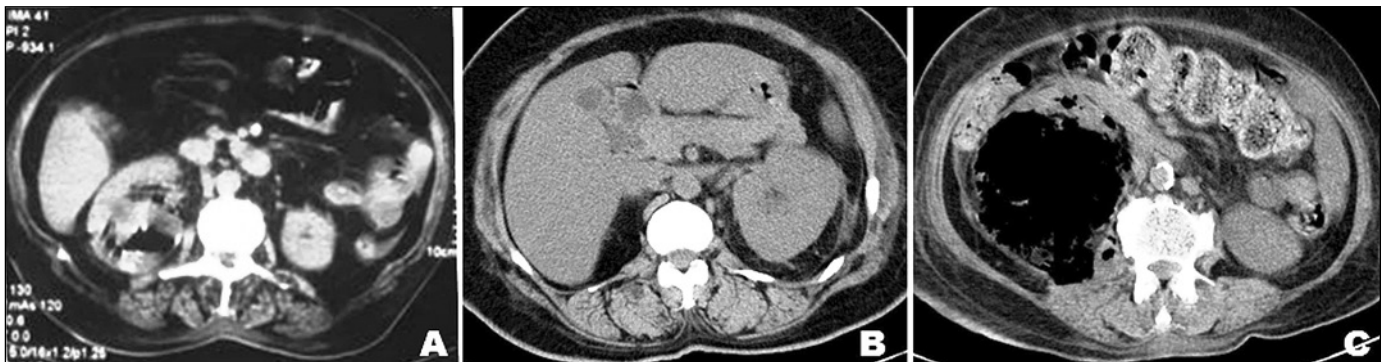


Figure 1. Emphysematous pyelonephritis. A. Gas in the right renal parenchyma (Grade 2). B. Gas in the left perinephric space (Grade 3A). C. Extensive gas and abscess in the right pararenal space (Grade 3B).

and cefoperazone-sulbactam (14/31; 45.2% each), ceftriaxone (10/31; 32.3%) and imipenem, gentamicin and levofloxacin (5/31; 16.1% each).

Some patients received multiple medications. Majority (43; 65.2%) of them responded to piperacillin-tazobactam. Other antibiotics used were ceftriaxone-sulbactam (27; 41%), cefoperazone-sulbactam (22; 33.3%), meropenem (18; 27.3%) and amikacin (16; 24.2%). Surgical treatment was done in thirty-two (48.5%) patients and they underwent thirty-four procedures. Unilateral stenting was done in twelve (37.5%) patients, bilateral stenting in 5 (15.6%), percutaneous drainage in 8 (25%), incision and drainage in 7 (21.9%) and open simple nephrectomy in 2 (6.3%) patients. Two patients underwent PCD after DJ stenting. Patients were discharged on oral antibiotics based on urine culture and sensitivity or oral fluoroquinolones or third generation cephalosporins if urine culture was sterile. The total duration of antibiotic treatment was 3–4 weeks.

The median (IQR) duration of hospital stay was 11.26 (6.16) days and median (IQR) duration of ICU stay was 0.38 (1.43) (range: 0–7) days. ICU stay was longer in CT class 3 and 4 ($p = 0.035$). The median (IQR) length of hospitalization in male was 10.52 (6.17) and in female was 11.77 (6.18) days. The median (IQR) was 0.26 (1) days in male and 0.46 (1.67) days in female. Length of hospitalization (LOH) was taken as a marker for morbidity as the number of patients expired was too little to assess the risk factors. Patients with hypertension (Likelihood ratio – LR = 10.4, $p = 0.028$), acute kidney injury (LR = 10.13, $p = 0.013$) and ischemic heart disease (LR = 7.84, $p = 0.049$) had a higher LOH. Only 2 (3%) patients (1 male and 1 female) passed away due to septic shock. The first patient had xanthogranulomatous pyelonephritis with DM for thirty years, hypertension, superimposed acute on chronic kidney disease (CKD) on maintenance hemodialysis (HD) for 8 years, had a palpable kidney with thrombocytopenia (93000/cc) and presented with class 2 EPN. The second patient had DM for fifteen years, post bilateral ureterolithotomy with a history of fifty-six bouts of acute kidney injuries, (AKI) received HD and had a long duration of symptoms (3 months). She presented with class 4 EPN. Both patients had hypotension at presentation and were started on meropenem at admission. No intervention could be done due to sepsis and hemodynamic instability. The intensive care length of hospitalization (LOH) was 4 and 2 days respectively.

Among 56 (84.8%) patients with DM, the median (IQR) RBS was 224 (151) mg%. All 7 patients who underwent incision and drainage for a perinephric abscess were diabetics ($p = 0.007$). Potassium abnormalities were seen in twenty-seven out of fifty-six (48.2%) diabetics – hypokalemia in fifteen out of

twenty-seven (55.6%) diabetics and hyperkalemia in twelve out of twenty-seven (44.4%) diabetics. Only one non-diabetic had hyperkalemia ($p = 0.045$). Medical renal disease was seen more commonly in diabetics ($p = 0.047$). The median (IQR) duration of DM was 1 (9.9) year in males and 3 (5.2) years in females. The median (IQR) LOH was 9 (10) days for males and 10 (9) days for females.

Only 2 (3%) patients died. Antibiotics and supportive care sufficed in thirty-four out of sixty-six (51.52%) patients and surgical procedures were performed in thirty-two out of sixty-six (48.48%) patients. Failure of conservative management happened only in two patients where intervention was not possible due to hemodynamic instability. Nephrectomy was done only in two out of the thirty-two surgical procedures (6.25%) and 3% (2/66) of the total population. There was 100% (32 out of 32) success with surgical intervention and 94.12% (32 out of 34) success with conservative management with respect to mortality.

DISCUSSION

Clinical presentation of EPN is similar to uncomplicated pyelonephritis. High tissue glucose, impaired immune system, gas-forming organisms, ureteral obstruction and impaired vascular supply have been proposed as factors in the pathogenesis of EPN [3, 9, 10]. Most cases occur in diabetics with poor glycemic control while a minority occurs due to urinary obstruction. In literature, 75–100% of EPN have been shown to be due to gas-forming organisms like *Escherichia coli*, *Klebsiella* species, *Clostridium* species, *Candida* species, *Aspergillus* species, *Cryptococcus* species and amebae [11–15]. We observed that gas-forming organisms caused EPN in 84.84% of our patients.

Urinary tract obstruction has been reported to cause EPN in 25–40% patients [12]. In our study, urinary tract obstruction was identified in 28.13% of patients. It was due to ureteral obstruction and local tissue ischemia. Obstructive calculi form a nidus of infection, causing stagnation or reflux of urine with lack of laminar flow in the ureteral system and ascending infection. Renal papillary necrosis has also been found to cause urinary tract obstruction and EPN [12]. Hypertension induces ischemia due to arteriosclerosis and glomerulosclerosis [16]. In our study, hypertension was seen in 10.6% of patients. Female patients (59%) outnumbered male (41) patients because of their increased susceptibility to urinary tract infections [16]. *E. coli* (82%) and *Klebsiella* species (12%) are the most common organisms [17]. In our study, *E. coli* was seen in 39% patients.

The overall mortality from EPN has been reported to range from 19–25% [1]. Meta-analysis suggests

Table 5. Comparison of factors contributing to mortality with literature

Factors	Kapoor et al. [19]	Aswathaman et al. [16]	Falagas et al. [1]	Present study
Grade 4 EPN	Nil	3/9 (33%)	OR 2.85 (p <0.01)	1/9 (11.1%)
Thrombocytopenia	4/5 (80%)	7/12 (58.3%)	OR 22.68 (<0.001)	1/22 (4.55%)
Conservative treatment alone	0/4 (0)	Not mentioned	OR 2.85 (p <0.02)	2/34 (5.88%)
Hemodialysis	Not mentioned	3/4 (75%)	Not mentioned	0/6 (0)
Delay in presentation >15 days	Not mentioned	4/5 (80%)	Not mentioned	1/18 (5.6%)
Diabetes mellitus	5/5 (100%)	93% diabetics with 9/41 (21.95%) death	OR 0.32 (p – NS)	1/56 (1.8%)

EPN – emphysematous pyelonephritis; OR – odds ratio.

that conservative treatment alone, type I, bilateral EPN, as well as thrombocytopenia are risk factors for a fatal outcome in patients with EPN [1]. In a systematic review by Soman et al., medical management alone resulted in 50% mortality, medical management with emergency nephrectomy in 25%, medical management with percutaneous drainage in 13.5% and medical management with percutaneous drainage and elective nephrectomy in 6.6% [18]. In our study, the mortality was 3%. In our study, class 4 EPN was seen in 14% of patients but only 1 patient with class 4 EPN succumbed. Conservative treatment with fluid resuscitation and antimicrobials was effective in 51.52%. Thrombocytopenia was observed in 33.33%, but only 1 patient with thrombocytopenia died.

Class 4 EPN was reported in 33% and found to have odds of 2.85 for mortality [1, 16]. However, we observed a mortality of 3% only. Thrombocytopenia has been associated with odds of 22.68 and in up to 80% mortality [1, 16, 19]. Conservative treatment was identified to have OR of 2.85 for mortality [1]. Aswathaman et al identified that 75% of patients needed hemodialysis but in our study we observed that 5.6% (1/18) patients died [14]. Delay in presentation beyond 15 days contributed to 80% mortality [16]. However, only 5.6% of our patients with this delay died. DM was seen in 84.8% of our patients and 93% of patients in the Aswathaman et al. study were diabetics. They observed 21.95% deaths but in our study only 1.8% deaths were associated with DM [16]. In another study, 100% mortality was observed with DM and EPN [19]. These details have been summarized in Table 5.

With advances in cross-sectional imaging, interventional radiology and antimicrobial therapy, better outcomes have resulted in the management of EPN. We observed that conservative management with initial fluid resuscitation and broad-spectrum antibi-

otics and later antibiotic treatment based on culture is successful. Lu et al. have reported third-generation cephalosporins as the recommended initial drug in their patients with EPN and carbapenem in patients with prior hospitalization or antibiotic use; patients needing emergency hemodialysis or developing disseminated intravascular coagulation [20]. In our patients, we observed that the bacteria were sensitive to piperacillin-tazobactam and meropenem in most patients, while they were resistant to gentamicin and levofloxacin in many patients. The success of conservative management has been reported in small case series and few case reports [21–25]. We found that PCD or DJ stenting, as the preferred initial treatment was helpful in our patients with EPN. Das et al. have reported their experience with urinary drainage in the form of DJ stenting or PCN in fifteen patients, all of whom were cured [26]. Extensive or fulminant disease with hemodynamic compromise will require nephrectomy. In our study, the need for nephrectomy was observed only in 3% of patients. Patients undergoing nephrectomy have been found to have less favorable outcomes and conservative management has been associated with better survival and better overall performance [24].

CONCLUSIONS

A high index of clinical suspicion is needed in sick elderly diabetics with fever of unknown origin or clinical presentation suggestive of urinary tract infection. Prompt CT imaging is vital in establishing the diagnosis and ruling out other causes of intra-abdominal sepsis. Early and aggressive resuscitation, empirical antimicrobial therapy and a drainage nephrostomy tube are imperative for a positive clinical outcome.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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