Ukrainian Journal of Nephrology and Dialysis

Scientific and Practical, Medical Journal

Founders:

- State Institution «Institute of Nephrology NAMS of Ukraine»
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Research article

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doi: 10.31450/ukrjnd.4(72).2021.10

Clinical profile, management and outcomes of class IV emphysematous pyelonephritis in a tertiary care center: A retrospective descriptive study

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Citation: Manjunath R, Bennikal M, Dasar SK, Patil ST. Clinical profile, management and outcomes of class IV emphysematous pyelonephritis in a tertiary care center: A retrospective descriptive study. Ukr J Nephr Dial. 2021;4(72):78-85. doi: 10.31450/ukrjnd.4(72).2021.10

Abstract. *Class IV Emphysematous pyelonephritis (EPN) is a life-threatening infection of the kidney, and there is sparse data on immediate and long-term outcomes of medical management. The study aimed to review the clinical presentation, diagnosis, immediate and long-term outcomes of medical management, and outcome of patients presenting with class IV EPN*

Methods. This retrospective study was conducted in a tertiary care center in Dharwad, India. The study included class IV EPN patients admitted to the hospital between Jan 2012 to Dec 2019. The factors studied were demographics, comorbidities, radiological investigations, clinical presentation, urine, blood and pus culture, and sensitivity and treatment history. Immediate and long-term outcomes of medical management were determined. Descriptive analysis of the data was conducted. Continuous variables were presented as mean ± standard deviation and discrete variables in terms of number (%).

Results. Twenty-one patients with class IV EPN, with a mean age of 55.7 ± 13.5 years, were analyzed. The majority were males (M: F 15:6). The patients were followed up for 32.70±21.12 months. Fever, flank or abdominal pain, and acute kidney injury were observed in all 21 patients, while nausea and/or vomiting and dysuria were seen in 16 (76.2%) patients. E. Coli was the most common pathogen found. Double J stenting was done in 20 (95.2%) patients; Ultrasonography guided aspiration 8(38.1%) and percutaneous drainage in 5 (23.8%) patients. One (4.8%) patient died during the first episode and 3(19%) others due to recurrent infection and end-stage renal disease.

Conclusions. Class IV Emphysematous pyelonephritis can be managed successfully by minimally invasive modalities. However, long-term morbidity and mortality risks are still negative.

Key-words: *emphysematous pyelonephritis, kidney, Escherichia coli, double J stent, acute kidney injury.*

Article history:
Received September 11, 2021
Received in revised form October 02, 2021
Accepted October 12, 2021

Conflict of interest statement. The authors declare no competing interest.

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УДК 616.61-002.3-07-08

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Клінічний профіль, лікування та наслідки емфізематозного пієлонефриту IV класу в центрі третинної допомоги: ретроспективне описове дослідження

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Резюме. *Емфізематозний пієлонефрит IV класу (ЕПН) є небезпечною для життя інфекцією нирок. Метою дослідження було проаналізувати клінічну картину, діагностику, короткострокові та віддалені результати лікування та наслідки пацієнтів із IV класом EPN.*

Методи. Це ретроспективне дослідження було проведено в центрі третинної допомоги в Дхарваді, Індія. Дослідження включало пацієнтів з ЕПН IV класу, які були госпіталізовані з січня 2012 року по грудень 2019 року. Досліджуваними факторами були демографічні показники, супутні захворювання, дані комп ютерної томографії, клінічна картина, культуральне дослідження сечі та крові, а також чутливість до антибіотиків і наслідки лікування. Визначено безпосередні та віддалені результати медичного менеджменту.

Результати. До дослідження залучено медичну документацію 21 пацієнта з ЕПН IV класу, середнього віку 55,7 ±13,5 років. Більшість становили чоловіки (М: Ж 15:6). Хворі спостерігалися протягом 32,70±21,12 міс. Лихоманка, біль у костовертебральному куті та гостре ураження нирок спостерігалися в усіх пацієнтів, а нудота/блювання та дизурія – у 16 (76,2%) пацієнтів. Найбільш поширеним збудником була кишкова паличка. Стентування виконано 20 (95,2%) хворим; у 5 (23,8%) пацієнтів аспірація під контролем ультразвукового дослідження та черезшкірне дренування; 1 (4,8%) пацієнт помер під час першого епізоду та 3 (19%) хворих через рецидивну інфекцію та термінальну стадію ниркової недостатності.

Висновки. Емфізематозний пієлонефрит IV класу можна успішно лікувати за допомогою малоінвазивних методів. Однак довгострокові ризики захворюваності та смертності залишаються прогнозонегативними.

Ключові слова: *емфізематозний пієлонефрит, нирка, кишкова паличка, стентування, гостре ураження нирок.*

Introduction. Emphysematous pyelonephritis (EPN), first defined by Kelly and MacCallum in 1898, is a rare but life-threatening, acute suppurative infection of the kidney. It is characterized by gas production within the renal parenchyma, collecting system, or perinephric tissue [1]. EPN is an uncommon condition where many studies have reported a wide range of clinical profiles and causative organisms. There are no specific symptoms or signs to diagnose EPN [2]. E. Coli and Klebsiella spp. are the most common causative organisms, but the exact pathogenesis is poorly understood [3].

Nephrectomy was the standard treatment used in the 1990s [2]. A meta-analysis suggested conservative treatment to be a significant risk factor for mortality in patients with EPN, where the mortality was reported to be 11–42% [4]. However, with the improvement of computed tomography (CT) based diagnosis and advances in multi-disciplinary intensive care, the treatment of EPN has changed over the years to more conservative approaches, such as antibiotics and percutaneous drainage techniques [2, 5].

Class IV is a severe variant among the various classes of EPN and has traditionally been treated with nephrectomy in the past. There are few reports of class IV EPN treated with renal preservation strategy by medical management alone without nephrectomy. However, the long-term outcome of medical management is not known. Hence, **this study aimed** to review the clinical features and presentation, causative organisms, diagnosis, management, and immediate and long-term outcome of patients presenting with class IV EPN.

Subjects and Methods. This retrospective study was conducted at SDM College of Medical Sciences and Hospital, a tertiary care center in Dharwad, India. The electronic medical records of all EPN patients admitted to the hospital between Jan 2012 -Dec 2019 were reviewed. All adults (>18years of age) diagnosed with class IV EPN at our hospital were included in the study. Ethical clearance was obtained from the institutional review board (with number SDMCDSIEC No2021/Medical/Nephrology/S/01), and the personal patient details were de-identified to protect patient privacy. The study followed the tenets of the Declaration of Helsinki.

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Diagnosis of EPN was based on the initial ultrasound evidence of gas in the renal parenchyma, confirmed by a CT scan of the abdomen in all patients. We included only class IV EPN cases based on CT findings described by Huang and Tseng [6]. The bilateral EPN or EPN in a solitary kidney was also defined as class IV EPN. Broad-spectrum antibiotics were used initially and later on modified as per microbiological culture reports. Standard treatment protocols for fluid resuscitation and insulin therapy, as deemed essential, were used.

The factors studied were patient-related factors, such as demography, comorbidities, clinical presentation, and treatment history; radiological investigations, including the side of involvement, ultrasound (US) and CT findings, treatment-related factors, like duration of hospital stay, management of patients, need of ventilation support; urine, blood, and pus culture and sensitivity and other relevant investigations.

The outcomes studied were severity of the disease, renal replacement therapy requirement, immediate recovery or mortality, recurrence of urinary tract infection during follow-up, and eGFR during follow-up. The severity of acute kidney injury was graded as per AKIN classification, and chronic kidney disease (CKD) was based on the KDIGO classification [7].

Descriptive analysis of the data was conducted. Continuous variables were presented as mean ± standard deviation and discrete variables in terms of number (%).

Results. ***Demographic and clinical data.*** A total of 21 cases of class IV EPN were included in the study. The mean age of patients was 55.71±13.53 years, where most participants were males 15 (71.4%). Diabetes was the most common comorbidity (57.1%) present. Seven (33.3%) patients had urinary tract infections in the past, and eight (38.1%) patients had a history of renal stone disease.

The mean duration of symptoms before diagnosis was 6±2.31 days with a range of 3–10 days. The prominent clinical manifestations included fever 21 (100%), flank/ abdominal pain 21 (100%), nausea/ vomiting 16 (76.2%), dysuria 16 (76.2%), shock 7 (33.3%), hematuria 7 (33.3%) and encephalopathy 5 (23.8%). All the patients had acute kidney injury (AKI) (Table 1).

Table 1

Demographic characteristics and clinical profile of emphysematous patients (n=21)

Variables	Frequency	Percent
Age (Mean ±SD)	55.71 ±13.53	
Body Mass Index (Mean ±SD)	23.92 ±5.03	
Sex		
Male	15	71.4
Female	6	28.6
Tobacco consumption	7	33.3
Existing comorbidities		
Diabetes	12	57.1
Hypertension	7	33.3
Chronic kidney disease	11	52.4
Ischemic heart disease	3	14.3
Past history of Renal stone disease	8	38.1
Past Urinary tract infection	7	33.3
Clinical features		
Fever/Febrile	21	100.0
Flank/Abdominal pain	21	100.0
Nausea/vomiting	16	76.2
Dysuria	16	76.2
Gross hematuria	7	33.3
Pneumaturia	3	14.3
Shock	7	33.3
Encephalopathy	5	23.8
Diabetic ketoacidosis	2	9.5
Acute kidney injury	21	100.0

Microbiologic data. The urine culture and sensitivity showed *E. coli 6* (28.6%) and *Pseudomonas 3* (14.3%) to be the most commonly occurring microorganisms. Polymicrobial infection was also observed in 3 patients. *E. coli 5* (23.8%) and *Klebsiella 4* (19.0%) were the most common organisms identified on blood culture. The culture of pus from the wound or percutaneous drainage was positive in 8 patients (Table 2).

Table 2

Causative organisms from blood, urine and wound/pus (n=21)

Variable	Frequency	Percent
Urine culture		
Negative	6	28.6
E. coli	6	28.6
Enterobacter	2	9.5
Pseudomonas	3	14.3
Klebsiella	1	4.8
E. coli and *Pseudomonas*	1	4.8
E coli and *Proteus*	1	4.8
E coli and *Enterococcus*	1	4.8
Blood culture		
Negative	11	52.4
E coli	5	23.8
Pseudomonas	1	4.8
Klebsiella	4	19.0
Culture of pus collected during aspiration or PCD or PCN		
Negative	3	14.3
E. coli	2	9.5
Enterobacter	1	4.8
Proteus	2	9.5
Klebsiella	2	9.5
E. coli and *Enterococcus*	1	4.8

Radiological data. Computer Tomography (CT) scan of abdomen and pelvis showed bilateral EPN in 17 (81.0%) patients and solitary kidney EPN in other patients. Hydroureteronephrosis was observed in 11 patients, kidney stone in 7 patients, and prostate hypertrophy in 2 patients. EPN was associated with emphysematous cystitis in 2 (9.5%) of 21 patients (Table 3).

Table 3

Diagnosis of EPN (n=21)

Variables	Frequency	Percent
CT features		
Bilateral	17	81.0
Right solitary functioning kidney with absent left kidney	1	4.8
Horse shoe kidney	1	4.8
Left solitary functioning kidney with contracted right kidney	1	4.8
Right solitary functioning kidney with contracted left kidney	1	4.8
Hydroureteronephrosis (HDUN)		
Left	3	14.3
Right	2	9.5
Bilateral	5	23.8
Right solitary functioning kidney	1	4.8

Continuation of Table 3

Variables	Frequency	Percent
Stone		
Staghorn	3	14.3
Pelvic Ureteric Junction Obstruction (PUJO)	1	4.8
Ureteric	2	9.5
Left	1	4.8
Non-stone obstruction (Prostate)	2	9.5
Emphysematous Cystitis	2	9.5

Diabetic Retinopathy changes were observed in dilated fundus examination in 11/12 diabetic patients. The changes observed were mild in two, moderate in five, severe in three, and proliferative retinopathy in one patient. Cardiac echocardiography was normal in 16 (76.2%) patients. Ischemic heart disease (IHD) with low ejection Fraction (30%-35%) was observed in 2 (9.5%) and 3 (14.3%).

Treatment. All patients were treated conservatively and 20 (95.2%) of them were treated with Double-J stent, 8 (38.1%) patients with ultrasonography-guided aspiration, and 5 (23.8%) with percutaneous nephrostomy (PCN). At the same time, only three (14.3%) patients required mechanical ventilation, 11 (52.4%) patients required hemodialysis support (Table 4).

Table 4

Management of EPN patients (n=21)

Variable	Frequency	Percent
Double-J stent	20	95.2
Ultrasonography guided aspiration	8	38.1
Percutaneous nephrostomy (PCN)	5	23.8
Percutaneous tube drain (PCD)	1	4.8
Necrosed Papilla retrieved during intervention	7	33.3
Ionotrope support required	5	23.8
Requirement of Dialysis	11	52.4
Mechanical ventilation support needed	3	14.3

Study Outcomes. The mean days of hospitalization of patients were 10.9±3.99 days. The immediate outcome was assessed at the time of discharge from the hospital. There was one death during the hospitalization period. Ten patients recovered completely. Out of eleven patients with dialysis-dependent AKI, 8 (38.1%) patients were dialysis independent at the time of discharge, 2 (9.5%) were still dialysis-dependent. Out of twenty-one patients, 20 were discharged under stable conditions.

The patients were followed up to 32.70±21.12 months (mean± SD). The long-term outcome was assessed at the time of the last follow-up. 3 (14.3%) patients died, 4 (19%) patients developed end-stage renal disease, and 13 (61.9%) patients were alive.

GFR was assessed at the last follow-up date. Only 3 (14.3%) patients had a normal renal function. Furthermore, all other patients developed CKD (Table 5).

Table 5

Short-term and long-term outcomes in the EPN patients

Variable	Frequency	Percent
Immediate outcome (n=21)		
Death	1	4.8
Complete recovery from infection	10	47.6
Discharged Dialysis independent	8	38.1
Discharged Dialysis dependent	2	9.5

Continuation of Table 5

Variable	Frequency	Percent
Estimated glomerular filtration rate (eGFR) at last follow up (n=20)		
Normal renal function	3	14.3
CKD1	2	9.5
CKD2	5	23.8
CKD3	4	19.0
CKD4	2	9.5
CKD5D	4	19.0
Long term outcome (n=20)		
Alive	13	61.9
End-Stage Renal Disease	4	19.0
Death	3	14.3
Recurrence of UTI during follow-up (n=20)	7	33.3

Discussion. Emphysematous pyelonephritis (EPN) is a rare, severe necrotizing disease of the renal parenchyma with a significant associated risk of mortality and morbidity [8]. Patients with EPN require multidisciplinary care because of its life-threatening nature. Out of all the classes of EPN, class IV is a severe variant. Hence, the study sought to review the clinical presentation, causative organisms, diagnosis, management, and outcome of patients presenting with class IV EPN.

The mean age of the patients in our study was 55.71 ±13.53 ranging from 25-74 years. EPN usually presents in the fourth and fifth decades of life or even later, which is evident in our study as well [9-11]. In the present study, males were more affected than females (M: F= 2.5:1). Most of the series have reported female preponderance [9, 12]. Some studies have reported that EPN was as much as six times more common in females when compared to males [13-17]. This contradictory finding could be due to the small sample size and only class IV disease studied.

The factors that predispose the development of EPN are known to be a combination of high tissue glucose concentrations, impaired tissue perfusion, and the presence of gas-producing organisms [18, 19]. In the present study, diabetes was the most common comorbidity 12 (57.1%) present. Seven (33.3%) patients had urinary tract infections in the past, and 8 (38.1%) patients had a history of renal stone disease. Diabetes mellitus and renal obstruction have been implicated with EPN [2, 10]. The high tissue glucose level is known to act as a substrate for the micro-organisms to produce hydrogen and carbon dioxide by fermentation. Glucose is the most favorable substrate for gas-producing organisms; thus, EPN is more prevalent in patients with diabetes. However, in non-diabetic patients, urinary albumin is thought to substitute for glucose [18]. Moreover, non-diabetic patients with EPN were found to have a higher incidence of urinary obstruction and also showed varying degrees of immunologic impairment [20].

Additionally, the microvascular changes were observed in fundus examination in 11 patients and cardiac dysfunction in five patients. These changes suggest that the patients had microvascular changes predisposing them to tissue ischemia, which could have predisposed them to develop EPN. Hydroureteronephrosis was observed in 11(52.38%) patients, kidney stone in 7 patients, non-stone prostate obstruction in 2 patients, and EC in 19(90.5%) patients. Previous studies have suggested that impaired tissue perfusion in patients with diabetes and may be aggravated by the presence of urinary tract obstruction [13, 21, 22]. The unrelieved urinary tract obstruction may increase pelvicalyceal pressure and compromise renal circulation [13]. It is possible that urinary tract obstruction and decreased renal vascular supply due to diabetes might have contributed to the development of EPN in our patients.

Another possible predisposing factor could have been the presence of acute kidney injury. All the patients in our study had AKI. AKI was one of the predisposing factors proposed by Huang and Tseng6 to contribute to a poor outcome of EPN. Patients with AKI are known to have a mixed etiology with sepsis, ischemia, and nephrotoxicity. The potential causes of AKI are a focal mismatch between oxygen and nutrient delivery (because of impaired microcirculation) to the nephrons and increased energy demands (due to cellular stress) [23].

Analysis of causative agent revealed that E. coli was the most common isolated pathogen in our study, which was in agreement with previous studies [2, 9, 14, 16] Klebsiella and Pseudomonas were other common pathogens causing EPN, albeit to a lesser extent than *E. coli*. This finding was also reported in many previous studies [12, 13, 19]. Therefore, initial antimicrobial therapy should target gram-negative bacteria as they are the most common causative organisms [9]. However, the antibiotic of choice should be based on a local antibiogram.

The ideal treatment modality for EPN remains controversial [9, 15]. While historically, nephrectomy was the conventional treatment of choice [25], the focus has now shifted toward a more conservative approach. DJ stenting, USG guided aspiration, and PCN was the most common management method used in our study. Das et al have reported their experience with urinary drainage in the form of DJ stenting or PCN in fifteen patients; all of them recovered with conservative treatment. Karthikeyan, V. S., et al. in their study reported PCD or DJ stenting as the preferred initial treatment [5, 26]. Several case reports show better outcomes by conservative management [2, 27]. DJ stenting or PCN in EPN patients presenting with hydroureteronephrosis or any other obstructions. Many studies have suggested that any indication of a ureteric obstruction must be managed by percutaneous nephrostomy or a ureteric stent unless nephrectomy is indicated [20, 28].

In the present study, the immediate survival rate in our study was 95.2%, which was quite remarkable compared to other studies. After the mean follow-up period of 32.70±21.12 months, the long-term outcome showed the survival rate to be 80.95%. Misgar, R. A., et al. had a survival rate of 88.5% [29]. The survival rate in the study by Fatima, R., et al. was 86.3%and 95% of patients in the study by Irfaan, A. M., et al. survived the illness [10, 24]. A recent meta-analysis by Aboumarzouk, O. M., et al. showed that the mortality rate was approximately 18% [19]. However, the patients in these studies presented with less extensive disease (CT grading) and less follow-up period, thereby accounting for good clinical outcomes in these studies. Even though all Class IV EPN were managed by conservative treatment, the patients in our study had good outcomes both in the short and long term,

Limitations. A retrospective single-center study with a small number of patients is the limitation of the study. However, it would be challenging to include many patients prospectively because EPN is a rare entity. Moreover, our patients also had prolonged follow-up (32.70±21.12) compared to other case series, and long-term renal and patient outcomes are delineated. A multi-centric prospective study with many patients would further elaborate morbidity and mortality during the long-term follow-up.

Conclusions. Emphysematous pyelonephritis is a life-threatening condition and must be suspected in diabetic patients with fever, flank pain, and urosepsis. The diagnosis of EPN can most clearly be made with a CT scan. EPN can be successfully managed with a minimally invasive approach. The antibiotic therapy based on microbial culture and drainage procedure is sufficient for managing class IVEPN cases. At present, the role of nephrectomy in the management of EPN is minimal. Among the drainage procedure, DJ stenting in our study showed a good outcome. Ultrasound-guided aspiration and PCN were also done in selected cases. Multi-centric prospective studies with a larger sample size are required to substantiate the study findings further.

Conflicts of Interest: All authors report no conflicts of Interest

Contribution

Manjunath R, Patil ST: Contributed to study design, preparation of the manuscript, and final revision;

Manjunath R, Bennikal M, Patil ST: Retrieval of data, and wrote parts of the paper;

Manjunath R, Patil ST: Data analysis and interpretation;

Dasar SK, Patil ST: A critical review of the manuscript and intellectual contribution.

All the authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Acknowledgments. We Acknowledge the department of Urology, SDM College Of Medical Sciences And Hospital, SDM University, Karnataka, India for their involvement in the clinical care of the patients.

Availability of data and material. The data that support the findings of this study are available on request from the corresponding author.

Financial support: none.

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