

Emphysematous Pyelonephritis: A Twelve-year Review in A Regional Centre

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What's known on the subject? and What does the study add?

It is known that emphysematous pyelonephritis is a severe and life threatening illness that does not have a clearly defined treatment algorithm. This paper shows the experience of treating this disease over 12 years and reinforces that there remains a role for both minimally invasive therapy as well as extensive surgical intervention, but further research into this condition is required.

Abstract

Objective: To examine outcomes and prognostic features of patients admitted with emphysematous pyelonephritis (EPN) at a regional tertiary centre.

Materials and Methods: Nineteen patients with EPN were identified between January 2007 and December 2019. Patients were grouped into two "mild" (grade I or II); and "severe" (grade III or IV) based on their Huang and Tseng classification. The two groups were compared using Fisher's Exact tests to determine prognostic features associated with poor outcome, defined as extensive surgical intervention or death.

Results: Thirteen patients had mild disease and six patients had severe disease. 69% of patients had ureteric obstruction, 58% were diabetic, 26% were thrombocytopenic, and there was a female predominance (12:7). Poor outcomes were significantly more common in patients with severe disease (83%), versus mild disease (8%) ($p < 0.0001$). Half of the patients managed with sole medical management died (two of four patients) and only two patients required escalation to extensive surgical management, both of whom survived. Overall mortality during admission was 19%; encompassing three of six patients with severe disease (50%) and one of thirteen patients with mild disease (8%).

Conclusion: EPN is dangerous, requiring prompt recognition and intervention, and is of increasing importance given the aging population and increased prevalence of comorbidities associated with the disease. This study of the largest recorded cohort of patients with EPN in Australia it was found that poor outcomes were significantly more common in patients with high radiological-grade disease, and severe thrombocytopenia.

Keywords: Emphysematous pyelonephritis, urinary tract infections, nephrectomy, percutaneous nephrostomy, pyelonephritis

Introduction

Emphysematous pyelonephritis (EPN) is a rare but life-threatening infection, characterized by "necrosis of the renal and peri-renal tissues by gas-producing bacteria" (1). Patients with EPN usually present with fever, flank pain, pyuria, raised inflammatory markers and septic shock. Therefore, differentiating EPN from severe pyelonephritis on clinical

features alone is challenging. Hence, computerized topography (CT) is necessary for diagnosis.

An example of a system for radiological grading for the severity of EPN has been described by Huang and Tseng (2) in 2000, and is displayed in Table 1.

The grading system described above is frequently described in two groups, mild disease, encompassing class I and II grades, and

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severe, including classes IIIA, IIIB and IV. Example images from the study cohort are shown in Figure 1, displaying severe disease (class IIIB, left frame) and mild disease with concurrent ureteric calculus causing obstruction (class I, right frame).

Because of the severity and high mortality rate of EPN, early diagnostic CT and appropriate treatment are critical to prevent morbidity and mortality (3).

It is necessary that clinicians are familiar with poor prognostic features and signs of EPN as the average age of the general population increases and comorbid conditions that elevate both the risk of developing EPN and the risk of a poor outcome become more prevalent (4).

The primary purpose of this study was to validate the prognostic value of the radiological grading system for EPN. Secondary purposes were to provide evidence regarding the risk factors for poor outcomes and assist with clinical decision making.

Materials and Methods

An ethical waiver to report these cases was obtained from Hunter New England Human Research Ethics Committee (authorisation number: AU202007-19) for a retrospective audit performed on all imaging requests and reports, and all discharge summaries issued in our institution between January 1, 2007 and December 31, 2019 that contained the term "emphysematous pyelonephritis", "emphysematous pyelitis", as well as all patients coded with an unspecified variant of "pyelonephritis" as per the Intentional Classification of Disease.

Patient demographics were retrieved electronically and clinical, laboratory, treatment and post-treatment variables were identified by analysis of relevant medical records.

Patients with radiological Huang class I or II were classified as mild, and Huang class IIIa/b and IV were classified as severe, consistent with previous studies (5-7). The groups were compared with Fisher's Exact and T-testing for independent variables.

"Good" outcomes were defined as a response to medical and/or renal decompression. "Poor" outcomes were defined as extensive surgical intervention or death, which is consistent with outcome reporting described in a previous series (2,8).

Class	Description
Class I	Gas in the collecting system only
Class II	Parenchymal gas only
Class IIIA	Extension of gas into perinephric space
Class IIIB	Extension of gas into pararenal space
Class IV	EPN in a solitary kidney or bilateral disease

EPN: Emphysematous pyelonephritis

All imaging had previously been reviewed by consultant radiologists.

Results

Eighty-nine patients were identified from the medical records electronic review. Seventy patients were excluded: 62 with simple pyelonephritis, five with emphysematous cystitis, two with incomplete medical records, and one due to a pre-existing ureteric stent. Nineteen patients with EPN were identified for further investigation.

The demographics of the cohort are displayed in Table 2.

Twelve of the 19 patients (63%) were female and 11 patients had diabetes mellitus (DM) (58%). Median age was 65 years [interquartile range (IQR) 13] with no statistically significant difference in age between severity groups ($p > 0.1$).

All cases were unilateral; 11 cases were left sided (58%), one of which was a left pelvic transplant kidney.

Fourteen (74%) patients presented with septic shock; nine of those had mild disease and five had severe disease. Septic shock was defined according to local guidelines as two or more of the following criteria; temperature $>38\text{ }^{\circ}\text{C}$ or $<36\text{ }^{\circ}\text{C}$; heart-rate $>90\text{ bpm}$; respiratory rate $>25\text{ breaths/min}$ or $<10\text{ breaths/min}$; white cell count $>12.000\text{ mm}^3$ or $<3.000\text{ per mm}^3$ and systolic blood pressure $<90\text{ mmHg}$ (9). Six patients who presented with septic shock had poor outcomes (40%). All patients without evidence of septic shock had good outcomes.

The white cell count was elevated in 12 of the 19 patients (63%), and C-reactive protein (CRP) was elevated in all patients who were tested, with no significant difference in laboratory titer between the severity groups ($p > 0.1$).

Median age in years (IQR)	65 (IQR 13)
Male	7 (37%)
Diabetic males	4 (57%)
Female	12 (63%)
Diabetic females	7 (53%)
Diabetic total	11 (58%)
Ureteric obstruction	13 (68%)
Left side EPN	12 (63%)*
Right side EPN	7 (37%)
Haematuria on presentation	15 (79%)
Septic shock on presentation	14 (74%)
Immunosuppressed	13 (68%)
Hypoalbuminaemia ($<30\text{ g/L}$)	13 (68%)
Thrombocytopenia ($<150 \times 10^9/L$)	5 (26%)

*Includes single case of transplanted kidney, EPN: Emphysematous pyelonephritis, IQR: Interquartile range

Thrombocytopenia was present in five of 19 cases (26%) and was more common in those with severe disease (n=3; 50%). Statistical significance was reached with the degree of thrombocytopenia (p=0.041), but not with the frequency of thrombocytopenia (p>0.1) between the severity groups.

Hypoalbuminaemia was present in 13 of the 17 patients tested (77%), and in all cases of severe disease tested (n=5) however, there was no statistically significant difference between the two groups (p=0.051).

Elevated blood sugar levels (BSLs) were detected in 12 of the 18 patients tested (67%). Hemoglobin A1c (HbA1c) was performed in 10/11 patients with diabetes and was >7% (indicative of poor glycemic control) in nine cases (90%). For mild disease median BSL on presentation was 8.3 mmol/L (IQR 4.4 mmol/L), with a median HbA1c of 9.5% (IQR 3.4%). For severe disease median BSL was 10.5 mmol/L (IQR 6 mmol/L), with a median HbA1c of 7.4% (IQR 0.5%). However, subgroup analysis revealed no statistically significant difference in HbA1c or BSL on presentation between the severity groups (p>0.1).

Microbiological testing revealed organisms similar to those seen in pyelonephritis/urinary tract infection. Sixteen of 18 urine cultures were positive (90%) and 14 of 16 blood cultures were positive (88%).

The organisms cultured from urine were *E. coli* in 13/16 (72%), *Klebsiella pneumoniae* in 2/16 (11%) and mixed *Enterococcus aurogenes* and *Enterococcus faecium* in 1/16. Blood cultures grew *E. coli* in 12/14 (86%), and *Klebsiella pneumoniae* in 2/14 (14%).

Table 3 shows the treatment received by patients graded according to the Huang and Tseng (2) classification. Obstruction was identified in 13 cases (68%); of which 10 cases were caused by ureteric calculi, two by ureteric stricture, and one by a displaced ureteric stent. Of the 13 patients in the mild group, 11 had identified causes of obstruction (85%), compared with two of the six patients in the severe group (33%).

Percutaneous nephrostomy (PCN) was performed in eight patients of whom none required further escalation, including a patient who had EPN of a transplant kidney (grade IV).

Grading	Number (n=19)	Treatment	Outcome (Good vs. Poor)
Class I	5	3 x PCN	3 x Good
		1 x MM	1 x Good
		1x RS	1 x Good
Class II	8	3 x RS	2 x Good 1 x Poor*
		4 x PCN	4 x Good
		1 x MM	1 x Good
Class IIIA	3	2 x MM 1 x Palliation	2 x Poor 1 x Poor
Class IIIB	2	1 x SD	1 x Poor*
		1 x EN	1 x Poor*
Class IV	1	1 x PCN	1 x Good

MM: Medical management, PCN: Percutaneous nephrostomy, RS: Retrograde stent, EN: Emergency nephrectomy, SD: Surgical drainage, *Patient failed initial conservative/ decompressive management, highest intervention required displayed.

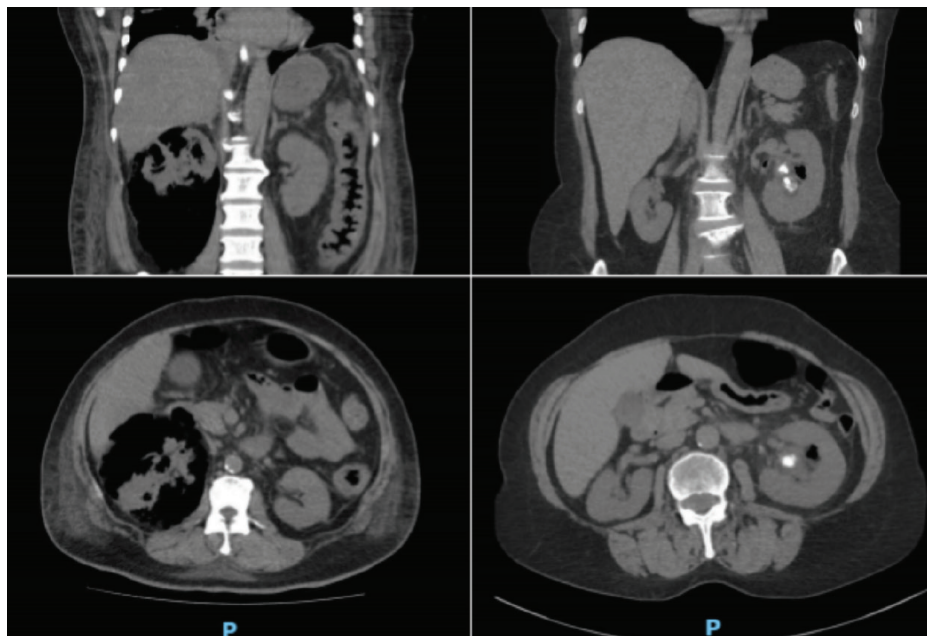


Figure 1. Severe disease (Class IIIB, left frame) and mild disease with concurrent ureteric calculus causing obstruction (Class I, right frame)

Double J (DJ) stents were inserted acutely in five patients. Of those, two patients responded without further intervention; one patient required escalation to open surgical debridement; and one case required subsequent emergency nephrectomy after continued haemodynamic instability. The final patient who underwent DJ stent insertion elected to pursue palliative management after minimal response to renal decompression and subsequently died. Subgroup analysis of patients undergoing PCN vs DJ stent insertion was performed and there was a statistically significant difference ($p=0.035$) in favour of PCN. Four patients were treated with medical management only; two were treated successfully and two died.

58% of patients ($n=11$) required admission to the intensive care unit (ICU): 65% ($n=8$) of patients with mild disease and 50% ($n=3$) of patients with severe disease. However, of the three patients with severe EPN who were not admitted to the ICU; one died in the emergency department 2 hours after presentation; another declined admission and subsequently died. The final patient had class IV disease according to the classification, with a pelvic transplant kidney that had gas only within the collecting system, but that patient had no evidence of significant sepsis. Of the 14 patients who presented with septic shock, 10 (71%) required ICU, while one patient who did not fulfill criteria for septic shock on presentation required ICU after developing persistent hypotension following PCN.

The median hospital length of stay (LOS) was eight days (IQR 20 days) for mild disease, and 16 days (IQR 27 days) for severe disease. The median ICU LOS was 2 days (IQR 2 days) for mild disease, and 1 day (IQR 7.8 days) for severe. There was no statistically significant difference in the ICU admission rate, ICU LOS, or hospital LOS between the severity groups.

Six of 19 patients had poor outcomes (32%). Four died (21%), and two required extensive surgery (11%). Of the patients who died, one patient with evidence of ureteric obstruction elected for immediate palliative management due to concurrent comorbidities, and another chose palliative management after failing to respond to renal decompression. Two patients died after failing to respond to medical management alone; one died within two hours of presentation to the hospital before further intervention could be instituted, the other declined more intensive treatment. All patients who died or required extensive surgical intervention initially presented in septic shock but this was not found to be statistically significant ($p>0.1$), likely due to inadequate power. Fifteen patients (79%) were discharged home after successful treatment, two of whom had required extensive surgical intervention. The majority of patients with poor outcomes were patients with severe disease based on radiological grading (5/6; 83%; $p<0.01$).

Discussion

EPN is a rare but life-threatening infection, characterized by "necrosis of the renal and peri-renal tissues by gas-producing bacteria" (1). It was first reported in 1898 by Kelly (10), and less than 800 cases have been reported worldwide to date. With the increasing prevalence of risk factors for the condition, it is likely that the incidence of EPN will increase (4). The mortality rate of EPN ranges from 11-42% (11-13), with a recent international meta-analysis reporting overall mortality of 19% (7).

DM is the most common predisposing factor and is present up to 95% of patients with EPN (14,15). This is thought to be due to high glucose concentrations and poor perfusion in the microenvironment providing ideal conditions for the growth of gas-producing bacteria (16). Ureteric obstruction has been implicated in 25-40% of cases (17).

Other risk factors for mortality reported include age, shock on presentation, poor glycemic control (defined as HbA1c $>7\%$), thrombocytopenia, and need for emergency nephrectomy (2,8,11,16,18,19).

The initial management of EPN requires intravenous antibiotics, aggressive fluid, and electrolyte resuscitation. Renal decompression through either PCN, or retrograde DJ stent insertion is used in an attempt for renal preservation, is particularly important in patients with chronic renal failure, solitary kidneys and transplant allografts (20,21). However, there are still those who advocate emergency nephrectomy of the affected kidney immediately after clinical stabilization, or if no improvement is achieved with initial treatment (22-24).

A systematic review of 10 retrospective studies reported a mortality rate of 50% with medical management alone compared to 13.5% with renal decompression with PCN (5). Other studies have reported successful treatment of severe disease (Class IV) with medical management alone, including cases of bilateral disease (20).

Huang and Tseng (2) reported in their seminal paper an overall survival rate of 81% however, almost 20% of all patients required EN. Jain et al. (8) reported cure in 90% of 72 patients, with 80% renal preservation. However, of those that underwent nephrectomy ($n=14$), 14% died. Shoiker et al. (23) reported that conservative management was successful in 92% of patients, however 30% of their cohort required subsequent nephrectomy of the affected kidney within four years. This shows that although surgical management can be effective in severe cases, escalation to invasive measures should be used as a last resort (2,7,14,23-25).

In our cohort 58% of patients had DM and proportionally more were women (12:7). *E. coli* was the most frequently isolated causative pathogen, as expected (26). The rate of

both DM and female predominance were lower than the rates reported in previous studies. Obstruction was present in 13 patients (68%), which is higher than the previously reported rate of 25-40% (17). 83% of patients with severe disease were diabetic (n=5) compared with 46% of patients with mild disease, but neither the presence of DM nor glycaemic control correlated with severity or outcomes, consistent with current literature (5,7).

There were more poor outcomes in patients with severe thrombocytopenia (p=0.041), but no difference in the prevalence of thrombocytopenia between the two groups (p>0.1). The laboratory values measured, including albumin, CRP and white cell count did not correlate with the outcome, consistent with prior findings (6,7,16). ICU admission was required in 58% of patients, which was slightly higher than 36.5% reported in some other series (27). Unusually, the rate of ICU admission was higher in the mild group compared to the severe group—though this is likely due to one early death, and one patient electing to withdraw care and the limitations with sample size.

Renal decompression was sufficient for treatment in most cases, consistent with current literature (5,7,8). PCN was effective in the treatment of all cases, whereas patients who underwent DJ stent insertion required escalation in 40% of cases. 60% of patients who underwent DJ stent insertion had poor outcomes, statistically significantly higher than those undergoing PCN insertion (p=0.035). Two patients failing to respond to renal treatment with extensive surgical intervention recovered well postoperatively and were discharged home without complication.

Four patients died (21%); two patients elected to withdraw care; one patient died before significant intervention could be instituted. There was a 50% cure rate for patients treated exclusively with medical measures, however there were more mortality (n=2) compared to those treated with renal decompression (n=1) or operative measures (n=1), consistent with the outcomes reported in previous analyses (8,11,24). Perhaps patients with a higher chance of mortality due to poorer baseline health were offered less invasive treatment options, hence causality cannot be inferred.

The rate of poor outcomes was statistically significantly higher in patients with severe disease based on the radiological grading systems (p=0.0005). This supports the validity of the radiological grading system categorizing patients into severe and mild disease. We found that higher grade disease had a trend toward higher mortality, longer overall hospital stay, higher morbidity, and more invasive intervention, though these were not found to be statistically significant - potentially secondary to inadequate power.

Study Limitations

We acknowledge that there are limitations of this study; it is underpowered due to the rarity of the disease, and there are biases present secondary to the retrospective retrieval of data. However, given that EPN is a rare and dangerous disease with an increasing number of susceptible individuals, all additions to the worldwide literature are beneficial to assist with the development of evidence-based guidelines for managing such a dangerous condition.

Conclusion

EPN is a life-threatening disease, but there is an increasing body of evidence that early treatment with renal decompression and intravenous antibiotics is sufficient in most cases. There are no established management guidelines for treating EPN, and opinions conflict regarding the efficacy and timing of conservative versus aggressive intervention. This is of particular significance given that there is a marked increase in the prevalence of risk factors and comorbid conditions, such as diabetes and chronic renal disease, in the context of an aging population.

In our experience, the radiological grading system described by Huang and Tseng is an effective prognostic tool. We found that most patients with EPN can be safely managed with antimicrobial therapy and renal decompression, preferentially with PCN insertion, including patients with Grade IV disease. Patients who present in septic shock with concurrent thrombocytopenia warrant close observation and aggressive surgical intervention if they fail to progress. However, further multi-centre series must establish treatment guidelines for this disease state.

Ethics

Ethics Committee Approval: An ethical waiver to report these cases was obtained from Hunter New England Human Research Ethics Committee (authorisation number: AU202007-19).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.S., A.B., Concept: B.S., S.N., Design: S.N., Data Collection or Processing: B.S., S.N., S.W., Analysis or Interpretation: B.S., Literature Search: B.S., S.N., Writing: B.S.

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