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ORIGINAL RESEARCH

Emphysematous Urinary Tract Infections in Regional Australia: Retrospective Review of Risk Factors, Microbiology, Management and Outcomes from 38 Cases

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Background: Emphysematous urinary tract infections (EUTI) are a dangerous and rare complication of urinary tract infection. Recent advances in management have reduced mortality and need for emergency nephrectomy. However, there remains a paucity of data concerning this condition in a regional Australian setting, despite a high observed incidence at our institution. We aimed to evaluate the risk factors, microbiological profile, clinical management, and outcomes of emphysematous urinary infections in our center.

Methods: A retrospective review of all patients diagnosed with EUTI in a single regional hospital over a 5-year period in rural Australia.

Results: Thirty-eight cases of EUTI were identified. Diabetes (76%) and female gender (79%) were common risk factors. *E. coli* was the most common organism (n = 26; 68%), followed by *K. pneumoniae* (n = 5; 13%). About 62% of patients were indigenous or Torres Strait Islander, and 55% were from a rural or remote locality. About 52% of patients required acute surgical intervention, 16% required admission to the intensive care unit (ICU). All patients were managed with a nephron-sparing approach and none required nephrectomy, with only a single EUTI-related mortality encountered. There was a high rate of antimicrobial resistance encountered (76%) with extended spectrum beta-lactamase-producing *E. coli* identified in 15% of patients.

Conclusion: Our retrospective study of EUTI provides the first Australian data regarding this rare disease, particularly in a regional setting. Despite high rates of antimicrobial resistance, a low mortality rate was achieved using a nephron-sparing approach.

Keywords: emphysematous pyelonephritis, emphysematous cystitis, antimicrobial resistance, risk factors

Introduction

Emphysematous urinary tract infections (EUTI) are a rare complication of urinary tract infection (UTI) and are classified according to their anatomical location (Figure 1). Emphysematous cystitis (EC) is an acute inflammatory condition affecting the mucosa and muscle of the bladder, resulting in intramural gas locule formation. Emphysematous pyelonephritis (EPN) describes gas within the upper urinary tract, which is further classified using the Huang-Tseng scale.[1] Gas within the collecting system only is considered Type I EPN, also termed emphysematous pyelitis (EP).[2] Gas within the renal parenchyma is classified as Type II EPN, gas extending beyond the parenchyma as Type III, and gas-forming renal infection bilaterally or within a solitary kidney is classified as Type IV. Diagnosis is based upon non-contrast computed tomography (CT) findings.

The pathogenesis of EUTI is secondary to the action of facultative anaerobes that produce gas from glucose,[1,3,4] and therefore has a strong association with poorly controlled diabetes. Other risk factors include female gender, impaired host immunity, urinary tract obstruction, chronic kidney disease and alcohol misuse.[5–7] Microbiological patterns are similar to typical UTI, with organisms *E. coli* most commonly reported (47–81% of cases), followed by *Klebsiella pneumoniae*

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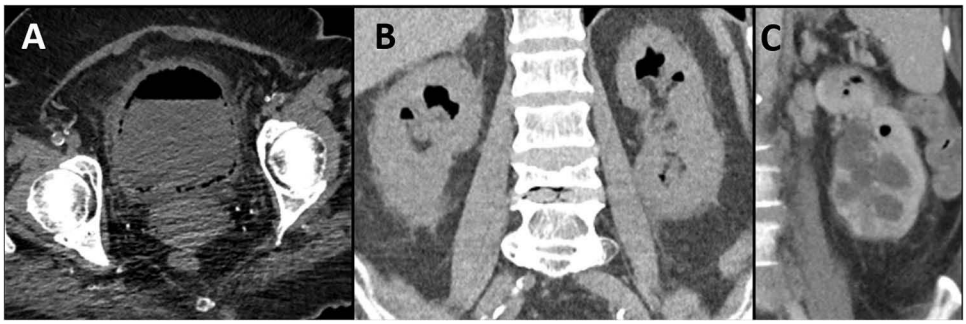

Figure 1 CT-imaging demonstrating spectrum of EUTI as classified by anatomical location. Emphysematous cystitis (**A**): axial section showing gas within the bladder lumen and wall. Emphysematous pyelitis, bilateral (**B**): coronal section showing gas within the renal calyxes. Emphysematous pyelonephritis, left (**C**): coronal section demonstrating gas within the left renal parenchyma. The collecting system is dilated secondary to obstruction.

(6–30% of cases). Other commonly implicated pathogens include *P. mirabilis, C. albicans, enterococcus species*, and *pseudomonas* species.[1,8–14] There is limited published data regarding antimicrobial resistance patterns in EUTI. Trujillo-Santamaría et al (2022) reported extended-spectrum β-lactamase (ESBL) rates of approximately 50%, and Lu et al (2014) detected fluoroquinolone resistance in approximately 40% of pathogens.

EC is the least severe form of EUTI, with non-specific clinical manifestations similar to those of typical UTI, ranging from asymptomatic to severe urosepsis.[15,16] About 90% of patients are successfully managed with medical therapies alone, with a mortality rate of 7%.[17]

The features of presentation of EPN are similar to those of standard pyelonephritis, including flank pain, dysuria, and fever.[7] These infections can be severe, and rapid progression to septic shock may occur, with further clinical manifestations including acid-base disturbance, electrolyte imbalance, renal dysfunction, impaired consciousness, thrombocytopenia, and hyperglycemia.[6,7] A meta-analysis totaling 628 cases of EPN of all types reported a pooled mortality rate of 18%.[11]

Literature regarding EP as a distinct entity is scarce with historical case series showing mortality rates of about 20%.[18] Contemporary data regarding EP, now classified as Huang-Tseng Type I EPN, shows a much more favorable prognosis, with mortality ranging from 0 to 3%.[6,19]

Gas formation within or beyond the renal parenchyma (EPN Type II or III) is the most severe form of EUTI and carries a worse prognosis. A recent multi-center study showed a mortality rate of 23% across 186 such cases.[6] Smaller case series have reported mortality rates ranging from 20% to >70%.[2,5,20–22] Overall mortality has decreased over time, likely reflecting improvements in quality of care and advancements in management techniques.[23]

Historically, emergency nephrectomy was the accepted treatment for severe EPN,[1,18,22,24] however studies from recent decades have shown dramatic improvements in survival by utilizing medical management and percutaneous drainage (PCD).[7,9,14,25] A nephron-sparing approach, consisting of thorough medical management, relief of ureteric obstruction where present, and/or percutaneous drainage is now the recommended method of treatment, with open drainage or emergency nephrectomy reserved for cases that fail to respond to minimally invasive measures.[7,11,12,21,23,26]

Whilst there has been significant advancement in the management of EUTI in recent years, it remains an uncommon and dangerous pathology. There is no published data regarding this disease in Australia, and limited literature regarding outcomes in regional settings. Antimicrobial resistance patterns in EUTI are also poorly reported. Due to the high observed incidence of EUTI at our center, we aimed to characterize the risk factors, microbiological profile, antimicrobial resistance patterns, management strategies, and outcomes in a cohort of patients EUTI, to aid clinicians who may encounter this disease in a similar setting.

Methods

A retrospective review was completed on all cases of EUTI referred to the Urology unit at Cairns Hospital, Queensland, Australia, from 2016 to 2021. All patients aged >18 years who were admitted with signs and symptoms of UTI plus CT-confirmed gas within the urinary system were included. Anonymized data were extracted from review of the patients'

electronic medical records, including demographics, medical history, laboratory and microbiological results, medical imaging, clinical course and follow-up.

All patients were initially managed with broad-spectrum antibiotic therapy, intravenous fluid resuscitation, bladder catheterization and medical supportive therapy as required. In cases where imaging was suspicious for obstruction of the upper renal tract, urgent cystoscopic retrograde ureteric stent insertion was performed under general anesthesia.

The Huang-Tseng system was used to classify the pattern of gas in the upper urinary tract. For this study, Type I EPN was referred to as emphysematous pyelitis in accordance with local protocols. Additionally, bilateral EP was grouped with standard EP cases rather than being assigned a Type IV classification to avoid confusion. As there were no cases of Type III EPN or bilateral renal parenchymal gas formation, the Type II EPN cases are simply referred to as EPN for the purpose of this study.

Multiple-drug resistant and extensively drug resistant organisms were defined as per Magiorakos et al (2012), and extended spectrum beta-lactamase-producing *E. coli* strains were identified by the local microbiologist.[27]

Descriptive statistical analysis was performed using IBM SPSS Statistics version 31.0 (IBM Corp., Armonk, NY, USA). For categorical variables, percentages were calculated. For continuous variables, mean and standard deviation (SD) were calculated.

Ethical approval was granted by the Far North Queensland Human Research Ethic Committee (EX/2024/QCH/105547), which waived informed consent due to negligible risk. Approval was not granted for data sharing. This study complies with the Declaration of Helsinki, as well as applicable data protection and privacy regulations.

Results

Patient Characteristics

During the study period 38 patients were identified of which 30 patients were female. The patient and pathology characteristics are summarized in Table 1. The mean age was 63.4 years (range 46–78 years). Infections consisted of EC (n = 14; 26%), EP (n = 26; 69%), and EPN (n = 2; 5%). Both EPN cases were Huang-Tseng classification Type II. Six patients (23%) with EP had bilateral disease, and four EP patients (15%) had concurrent EC. Diabetes was a risk factor in 29 patients (76%). For patients with diabetes, the mean percentage hemoglobin A1c on presentation was 9.8% (range 5.6 to 14.5%). Two patients were immunosuppressed: one was taking long-term steroids for polymyalgia rheumatica, and the other was on active chemotherapy for lymphoma. Four patients with EP had urinary tract instrumentation within four weeks of presentation. Four patients had previous documented hospital admissions for EUTI. About 55% of patients lived in a rural or remote locality.

Microbiological Profile

The microbiological profile of patients with EUTI is shown in Table 2. *E. coli* was the most common organism (n = 26; 68%), followed by *K. pneumoniae* (n = 5; 13%). For seven patients (23%), urine cultures demonstrated bacteria with no antibiotic resistance. Multiple-drug resistant organisms were identified in nine patients (24%). Extended spectrum beta-lactamase (ESBL)-producing *E. coli* strains were identified in four patients (15% of *E. coli* strains). There were no extensively-drug resistant strains isolated.

Patient Management and Clinical Outcomes

The management approaches utilized are summarized in Table 3. Thirty-two patients (84%) were managed on a ward whilst six patients had severe sepsis requiring intensive care management (EC n = 1; EP n = 5). Twenty patients (52%) required surgical intervention during their admission. Of the EP patients, 18 (70%) were managed with insertion of an indwelling ureteric stent. Of these, four patients had obstruction due to a ureteric calculus; 14 patients were stented to facilitate drainage of infection due to the presence of hydronephrosis. In all of patients managed with a stent, turbid urine or frank pus was drained from the kidney on stent insertion. One of the two patients with EPN required stenting to relieve obstruction. In one patient with EP, the etiology was likely due to a retained stent following previous management of urolithiasis. Following administration of intravenous antibiotics, the stent was removed prior to discharge. Mean length

Table 1 Patient Characteristics and Anatomical Patterns of Emphysematous Urinary Tract Infections

Patient Characteristics	n	%	mean	SD
Gender				
Female	30	78.9		
Male	8	21.1		
Age (years)			63.4	11.8
Indigenous or Torres Strait Islander	24	63.2		
Locality				
Urban/suburban	17	44.7		
Rural	5	13.2		
Remote	16	42.1		
LOS (days)			7.6	11
Diabetic	29	76.3		
HbA1c (%)			9.83	2.96
Immunocompromised	2	5.2		
Chronic kidney disease	12	31.5		
End-stage renal failure	4	10.4		
Recent urinary tract instrumentation	4	10.4		
Previous EUTI	4	10.4		
Pathology				
Emphysematous cystitis	14	36.8		
Isolated	10	26.3		
In combination with emphysematous pyelitis	4	10.4		
Emphysematous pyelitis	26	68.4		
Left	12			
Right	8			
Bilateral	6			
Emphysematous pyelonephritis	2	5.2		
Left	2			

Table 2 Organisms Isolated from Urinary Cultures of Emphysematous Urinary Tract Infections

Organism	n	%
E. coli	26	68.4
K. pneumoniae	5	13.2
Mixed enteric species	3	7.9
P. mirabilis	1	2.6
S. agalactiae	1	2.6
E. faecalis	1	2.6
Candida spp.	1	2.6

Notes: more than one organism was isolated in several patients.

of hospital stay was 7.6 days (range: 1 to 70 days). Complications and mortality are summarized in Table 4. One patient with EP and EC developed osteomyelitis of the pubis requiring prolonged out of hospital intravenous antibiotics. There was only one mortality (3%) secondary to EP: a 78yo male with severe comorbidities including end-stage renal disease and ischemic heart disease, which limited his ceiling of care to ward-based therapies. After failing to respond to 48 hrs of conservative management, the decision was made in conjunction with family to transition to palliative measures.

Table 3 Initial Management of Emphysematous Urinary Tract Infections, Categorized by Anatomical Locations

Initial Management	Isolated EC (n = 10)	EP (n = 26)	EPN (n = 2)	Total
Non-operative	90% (n = 9)	27% (n = 7)	50% (n = 1)	17
Insertion of ureteric stent	10% (n = 1)	70% (n = 18)	50% (n = 1)	20
Removal of ureteric stent		3% (n = 1)		1
ICU Admission	10% (n = 1)	19% (n = 5)		6

Abbreviations: EC, emphysematous cystitis; EP, emphysematous pyelitis; EPN, emphysematous pyelonephritis.

Table 4 Complications and Mortality Secondary to Emphysematous Urinary Tract Infections, Categorized by Anatomical Locations

Complication	Isolated EC (n = 10)	EP (n = 26)	EPN (n = 2)	Total
Recurrent gas-forming UTI		15% (n = 4)		4
Pubic bone osteomyelitis		3% (n = 1)		1
Functional decline post-sepsis		3% (n = 1)		1
Emphysematous UTI-related mortality:				
Palliation secondary to multiple comorbidities		3% (n = 1)		1

Abbreviations: EC, emphysematous cystitis; EP, emphysematous pyelitis; EPN, emphysematous pyelonephritis.

One patient with EP had a partial staghorn calculus that required subsequent elective admission for percutaneous nephrolithotomy. One patient with emphysematous cystitis presented with chronic painless urinary retention (Figure 2), a febrile urinary tract infection and an incidental asymptomatic 10 mm ureteric stone without hydronephrosis. They were

Figure 2 Sagittal CT projection demonstrating emphysematous cystitis secondary to chronic urinary retention.

managed with a ureteric stent and bladder catheterization and following discharge underwent elective ureteroscopic laser fragmentation and removal of the ureteric stone followed by a staged transurethral resection of prostate.

Discussion

At least anecdotally, EUTI is a rarely encountered pathology in major metropolitan hospitals in our country, and indeed contemporary publication patterns suggest a higher burden of this disease in low- and middle-income countries. We hypothesize that geographical factors are largely responsible for the uncharacteristically high incidence of EUTI encountered at our institution, with approximately 55% of patients transferred from rural or remote facilities. There is a well-established link between rurality and adverse health outcomes in Australia.[28] Higher burdens of chronic disease, delayed presentations, and reduced access to healthcare services are likely key factors that contribute to the higher incidence of EUTI in this setting, and clinicians working in regional centers should be wary of this disease.

Gas-forming renal infections were first described by Kelly and MacCallum in 1898,[29] and the term emphysematous pyelonephritis was coined by Schultz and Klorfein in 1962 to highlight the link between infection and gas formation.[30] The first attempt to classify patterns of gas formation was made by Wan et al (1996) who divided 38 patients into either Type 1 (dry type with mottled or streaky gas) or Type 2 (wet type with fluid collections and bubbly or loculated gas), and found a higher mortality in Type 1 patterns (68%) compared to Type 2 (18%).[20] However, a subsequent study of 25 patients by Chen at al (1997) showed no correlation between this gas pattern classification and response to treatment.[25]

Further work by Huang and Tseng in 2000 resulted in the development of the Huang-Tseng classification system, as their 48-patient study demonstrated a direct correlation between class and mortality.[1]

More recent multi-center studies and meta-analysis have confirmed a strong correlation between Type III EPN (especially Type IIIb – gas extension beyond Gerota's fascia) and mortality, but not so with Type IV.[6,11] It is postulated that, as Type III EPN indicates extension of gas beyond the kidney, this reflects a severe infection involving a large proportion of the renal parenchyma as well as surrounding tissue; whereas Type IV EPN indicates only the presence bilateral gas or gas within a single kidney, but does not necessarily correspond to volume of gas or extent of tissue infection.[6] For this reason, we chose to classify cases of bilateral emphysematous pyelitis (ie Type I EPN) as EP rather than assign them a Type IV EPN classification, as this is a more anatomically consistent classification of gas extension, and avoids exaggerating the severity of the disease.

In our study, only one of five total ICU admissions in EP patients was due to bilateral disease, supporting the notion that the presence of bilateral gas does not necessarily correspond to more severe disease.

The work of multiple investigators over the last few decades has led to a shift away from emergency nephrectomy towards a nephron-sparing approach in EPN management, demonstrating improved outcomes.[7,11,12,21,23,26] Most notably, Aboumarzouk et al conducted a meta-analysis of 628 EPN patients in 2013, finding that medical management and PCD had superior survival compared to both open drainage and emergency nephrectomy.[11] The authors recommended that aggressive management of shock should be the cornerstone of treatment, as well as relief of urinary obstruction if present. They proposed an escalating treatment algorithm based on the patient's response to treatment, consisting of medical management and relief of obstruction initially, followed by PCD, then open drainage, and lastly consideration of emergency nephrectomy. Importantly, the investigators recommended that whilst the radiological pattern of gas formation may aid in identifying high-risk patients, treatment should primarily be guided by their clinical condition. The findings from our study provide further support for this approach. By utilizing a nephron-sparing management strategy, all patients were spared from PCD or nephrectomy, and only a single mortality was encountered.

The presence of gas forming bacteria is requisite for development of EUTI.[1,3,4,9] Accordingly, all isolated strains of pathogens in this study were facultative anaerobes, predominantly *E. coli* and *K. pneumoniae*. This pattern reflects trends observed in other studies.[1,9–14] In three patients, no specific pathogen could be isolated, with culture results showing growth of mixed enteric species, of which one was presumably the causative organism. Given that the microbiological pattern of EUTI closely resembles those of non-gas forming UTI,[31] it can be concluded that the presence of facultative anaerobic pathogens is not the sole factor in the etiology of EUTI.

Consequently, diabetes mellitus is another key criteria in the pathogenesis of EUTI.[11,26,32] Diabetes mellitus (DM) has been implicated in up to 90% of cases of EUTI.[7,11,20,33,34] We found a similarly high rate of DM in our cohort of 76%.

DM facilitates gas formation via fermentation of excess glucose within the urine and soft tissue into hydrogen and carbon dioxide by action of facultative anaerobes.[4,7] In non-diabetic patients, albumin is thought to be an alternative fermentation substrate.[34] The average percentage hemoglobin A1c of diabetic patients in this series was 9.8%, considerably higher than the recommended target of <7%,[35] implying an association between chronically elevated glucose levels within renal tissue and EUTI pathogenesis. In support of this, Trujillo-Santamaría et al found a 2.5-fold increased EPN mortality rate in patients with serum glucose levels >200mg/dL.[6] Due to the low mortality rate in our cohort, we were unable to demonstrate the same link between serum glucose and mortality risk. Nonetheless, control of glucose should be initiated immediately in patients presenting with EUTI.[6,11]

Urinary tract obstruction provides favorable conditions for anaerobic fermentation and subsequent gas formation due to impaired tissue perfusion secondary to obstructive uropathy and is reported to be present in about one-third of EUTI cases.[11,36] We encountered a comparatively high rate of obstruction in this series, with 70% of EP and 50% of EPN cases requiring insertion of ureteric stent, and all cases of EC had a history of impaired bladder emptying which was subsequently managed with indwelling catheter insertion. In our cohort, severe illness was associated with the presence of obstructive uropathy – all six patients admitted to the ICU also required ureteric stent insertion. The comparatively high rate of urinary obstruction observed in our study may be explained by two factors. Firstly, geographical isolation, as discussed above, could result in delayed management of urinary obstruction, leading to interval development of EUTI within the obstructed system. Secondly, non-obstructed EUTI cases encountered at peripheral medical facilities may not have been referred to our center, resulting in a selection bias towards obstructed EUTI in our cohort.

Interestingly, however, other authors have demonstrated that obstructive uropathy appears to be a positive prognostic factor in EPN, presumably because these patients are urgently referred for urological intervention, resulting in rapid dissipation of the septic source and subsequent improvement following the relief of obstruction.[11,26] Our data further supports this finding, with a low mortality rate despite high rates of urinary obstruction and highlights the merits of the nephron-sparing management approach utilized in our cohort.

There was a high rate of antibiotic resistance (81.6%) identified in the isolated organisms. Nine isolates (23.6%) were multiple-drug resistant (defined as resistant to at least three different classes of antimicrobials[27]), and, concerningly, four cases of ESBL-producing *E. coli* were detected. No extensively-drug resistant strains were identified. The rate of resistant and multi-resistant strains in this series is significantly higher than that encountered in non-gas-forming UTI. The 2012 Australian Community-onset Gram-negative Surveillance Program annual report found the rate of microbial resistant in gram-negative urinary pathogens in the broader community to be only 49.8% in *E. coli* and 40.4% in *klebsiella* species, with multi-drug resistance only identified in 7.6% of *E. coli* and 5.1% of *klebsiella* isolates.[37] The increased rate of antibiotic resistance observed in EUTI may be a result of several factors. Firstly, these patients often suffer from recurrent UTI, resulting in frequent antimicrobial exposure. There was also a high burden of chronic disease in this cohort, which may correlate to frequent exposure to healthcare facilities and antimicrobials. Lastly, many EUTI patients live in rural and remote communities, which are increasingly understood to harbor resistant pathogens.[38] EUTI-specific antimicrobial resistance patterns are sparsely reported in the existing literature, and variations in reporting mean that direct comparison is not possible. However, we did encounter a significantly lower rate of ESBL-producing *E. coli* compared to Trujillo-Santamaría et al (2022) – this discrepancy may also be explained by geographical variations in resistance patterns.

Complications following EUTI were uncommon in this series. Four patients developed recurrent EUTI, all of whom were diabetic, again implicating the role of hyperglycemia in EUTI pathogenesis. One patient with a history of pelvic radiotherapy developed osteomyelitis of the pubic bone secondary to EC, presumably due to extra-cystic extension of the infection. A single patient developed significant functional decline resulting in placement in an aged care facility.

There was only one mortality in our cohort, resulting in an upper tract EUTI mortality rate of 3.5%, in line with a recent prospective study from Kone et al (2022) who instituted a nephron-sparing management protocol at their institution and reported only a 4% mortality across 25 EPN patients.[26] It should be noted that in our series, we only encountered EC, EP (Huang-Tseng EPN Type 1) and Huang-Tseng EPN Type II patterns of gas formation, which are generally considered to be lower-risk pathologies,[1] and this most certainly contributed to our low observed mortality. Nonetheless, our findings further support the effectiveness of nephron-sparing management of EUTI. Additionally, the

lack of mortality in patients with bilateral EP, which would be typically classified as Huang-Tseng Type IV EPN, supports the notion that this classification may over-represent the severity of disease in these cases.

This study has limitations innate to any retrospective case series performed at a single center. Firstly, the data is subject to availability bias as it can only be retroactively retrieved from medical records. Secondly, there was no standardized treatment protocol employed. Furthermore, the single center nature of this cohort limits the generalizability of the findings. Additionally, there were only a limited number of patients captured, and importantly there were no cases of high-risk (Huang-Tseng Type III) radiological gas patterns encountered. Furthermore, the very low mortality rate means no meaningful conclusions can be drawn regarding prognostic factors. Several investigators have recently developed and validated prognostication algorithms that utilize clinicopathological information on initial presentation to determine mortality risk in patients with EPN.[6,10,13] We acknowledge that such information, including initial observations, examination findings, and laboratory results, would improve our case series. However, as many patients were initially managed at peripheral facilities prior to transfer to our center, the presentational clinicopathological information was too limited or inconsistently reported to meaningfully interpret and thus excluded.

Regardless, this series has for the first time demonstrated an association between EUTI and regional and remote settings, as well as with Aboriginal and Torres Strait Islander populations. We present the first published Australian data regarding this rare disease and have further highlighted the link between facultative anaerobes, diabetes mellitus and urinary obstruction in the etiology of EUTI. Additionally, our low observed mortality rate demonstrates the success of nephron-sparing management, albeit within the limitations of a single-center retrospective study.

Conclusion

EUTI remains a rare clinical entity but appears to have a relatively high incidence in regional and remote areas of Australia. We have again demonstrated that female gender, gas-forming pathogens, diabetes mellitus and urinary obstruction are significant risk factors for EUTI, which have high antimicrobial resistance rates. Our experience supports the modern consensus that nephron-sparing management approaches have reduced both mortality rates and the need for emergency nephrectomy.

Abbreviations

CT, computed tomography; DM, diabetes mellitus; EC, emphysematous cystitis; EP, emphysematous pyelitis; EPN, emphysematous pyelonephritis; ESBL, extended spectrum beta-lactamase-producing; EUTI, emphysematous urinary tract infection; UTI, urinary tract infection.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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