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Original Article

Clinical features and prognostic factors of emphysematous urinary tract infection

Cheng-Yu Kuo[1], Chun-Yu Lin[1,2], Tun-Chieh Chen[1,2], Wei-Ru Lin[1], Po-Liang Lu[1,2], Jih-Jin Tsai[1], Ko Chang[3], Hsiao-Cheng Hsieh[3], Yen-Hsu Chen[1,2]

[1]Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital; [2]Graduate Institute of Medicine, College of Medicine; and [3]Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

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Background and purpose: Emphysematous urinary tract infection (EUTI) is a rare and potentially life-threatening condition that requires prompt evaluation and management. This study was conducted to ascertain the clinical features and prognostic factors of EUTI.

Methods: Patients diagnosed with EUTI radiologically and treated at the Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, from March 2001 to February 2007 were evaluated. The patients' demographic and clinical characteristics, laboratory data, treatment, and outcomes were analyzed retrospectively.

Results: Of 31 patients enrolled, 16 had emphysematous pyelonephritis (EP) and 15 had emphysematous cystitis (EC) classified according to the imaging findings. The symptoms and signs of fever, chills, flank pain, and percussion tenderness at the costovertebral angle were significantly greater among patients in the EP group than in the EC group ($p = 0.029$, $p = 0.009$, $p < 0.001$, and $p < 0.001$, respectively). There were no statistically significant differences in the initial laboratory data except for C-reactive protein between the 2 groups (220.4 μg/mL vs 91.4 μg/mL; $p = 0.001$). *Escherichia coli* was the most commonly isolated organism. The overall mortality rate was similar in both groups. Significant differences in renal function and hematuria were seen between the patients who died and the survivors in the EP group ($p = 0.004$ and $p = 0.027$, respectively), but these were not noted in the EC group.

Conclusions: There was no significant clinical feature suggesting the presence of EC. The clinical features of EP were similar to uncomplicated pyelonephritis. Impaired renal function and hematuria were poor prognostic factors for patients with EP, but not for patients with EC.

Key words: Cystitis; Prognosis; Pyelonephritis; Urinary tract infections

Introduction

Gas-producing infections may occur in almost all organs. These infections are potentially life threatening and require prompt evaluation and management. Gas-forming infections of the urinary tract are rare and any part of this system may be involved [1]. Emphysematous urinary tract infection (EUTI) is a necrotizing infection of the renal parenchyma and its surrounding areas, resulting in gas collection in the renal parenchyma, collecting system, perinephric tissue, and urinary bladder [2]. Gas within the urinary tract was initially described in 1671, in a patient presenting with pneumaturia [3]. A variety of etiologies may result in gas within the urinary tract, including gas-forming infections, tissue infarction with necrosis, a fistula between the urinary tract and a hollow organ, urinary catheter insertion, or as a result of surgery [4]. EUTI is typically diagnosed radiologically, and the incidence of reported cases is increasing due to the wider use of abdominal imaging and a greater awareness of this disorder.

Emphysematous pyelonephritis (EP) usually occurs in patients with diabetes, but it is occasionally

Corresponding author: Dr. Wei-Ru Lin, 100 Tzyou 1st Rd., Kaohsiung 807, Taiwan.
E-mail: lwru@mail2000.com.tw

seen in non-diabetic patients with obstructive uropathy, polycystic kidney disease, end-stage renal disease, or those who are immunosuppressed [5]. Clinical symptoms and signs of EP are similar to those of uncomplicated pyelonephritis but the morbidity and mortality rates are higher for EP. The risk factors for emphysematous cystitis (EC) include diabetes mellitus, chronic urinary tract infection, indwelling urethral catheter, and urinary tract outlet obstruction [6]. Clinical manifestations of EC vary and do not correlate with the severity of inflammation, despite the high morbidity and mortality rates [7]. Thus, a high index of suspicion is necessary for the early diagnosis of EUTI. Although the features of EP or EC have been described in several reports [8-11], few articles focus on the differences between EP and EC and the clinical prognostic factors among patients with EUTI [7,11]. This study was performed to compare the clinical presentations, morbidities, laboratory and microbiological findings, treatments, and outcomes between EP and EC, and to ascertain the prognostic factors.

Methods

From March 2001 to February 2007, patients who were diagnosed with EUTI radiologically at the Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, were enrolled in the study. All patients met the inclusion criteria of imaging findings of a gas-producing lesion in the renal parenchyma, its surrounding areas, or urinary bladder without a fistula to a hollow viscus or possible iatrogenic causes that could have led to the gas collection in the urinary tract. The patients presenting with EP were categorized into 2 subgroups: type I EP was characterized by renal necrosis with either total absence of fluid content on computed tomography (CT) or the presence of a streaky/mottled gas pattern on radiograph or CT with lung window display; and type II EP was marked by either the presence of renal/perirenal fluid in association with a bubbly/lobulated gas pattern, or the presence of gas in the collection system [12].

The patients' medical records were retrospectively reviewed, including age, sex, body mass index (BMI), underlying disease, clinical presentation, laboratory data at admission, culture results (blood, urine, and abscess), treatment modality, and clinical outcomes. Obesity was defined as a BMI of ≥24 kg/m^2. Hematuria and proteinuria were defined as a red blood cell count of ≥10 cells/high-power field and a protein amount of ≥30 mg/dL in a random uncentrifuged urine sample, respectively. Creatinine clearance (CCr) was calculated by using the Modification of Diet in Renal Disease Study Group Simplify Equation [13].

Statistical analysis

Owing to the skewed nature of the data, robust non-parametric statistical procedures were used. The differences between EP and EC were tested using the Wilcoxon rank sum and Mann-Whitney *U* tests for continuous variables and Fisher's exact test for categorical variables. A p value of <0.05 was considered statistically significant.

Results

Clinical findings

Thirty one patients with EUTI were enrolled in this study. The incidence rate of EUTI was 5/1000 inpatient years. There were 16 and 15 patients in the EP and EC groups, respectively. The demographic characteristics, underlying diseases, clinical features, laboratory data, treatments, and clinical outcomes for the EP and EC groups are summarized in Table 1. In the EP group, there were 13 women and 3 men, and the median age at presentation was 59 years (range, 40-87 years). There were 12 women and 3 men in the EC group, and the median age at presentation was 72 years (range, 49-83 years). No statistically significant differences between the 2 groups were present for age, sex, BMI, indwelling urethral catheter before admission, diabetes mellitus, obstructive uropathy, recurrent urinary tract infection, and malignancy. However, the incidence of obesity was higher in the EP group than in the EC group (56% vs 21%; $p = 0.072$). Malignancy was less associated with EP than with EC (16.7% vs 33.3%; $p = 0.083$).

Fever, chills, flank pain, and percussion tenderness at the costovertebral angle were significantly more common in the EP group ($p = 0.029$, $p = 0.009$, $p < 0.001$, and $p < 0.001$, respectively). Symptoms and signs of dysuria, gross hematuria, shock, oliguria, and altered mental status were similar between the 2 groups. The median duration from the onset of symptoms and signs to the diagnosis of EUTI was shorter in the EP group than in the EC group, but there was no significant difference (5 vs 10 days; $p = 0.197$).

Radiological findings

Radiograph of the abdomen was obtained for 30 patients with EUTI but was diagnostic for only 3 patients (10%).

Table 1. Clinical features, laboratory parameters, treatment modality, and clinical outcomes of 31 patients with emphysematous urinary tract infection.

Variable	Emphysematous pyelonephritis (n = 16) No. (%)	Emphysematous cystitis (n = 15) No. (%)	p^a
Age (years; mean ± SD)	61.2 ± 11.5	68.1 ± 11.3	0.118
Female sex	13 (81.3)	12 (80.0)	1.000
Obesity[b]	9 (56.3)	3 (21.4)	0.072
Days to diagnosis (mean ± SD)	7.3 ± 5.9	17.3 ± 20.5	0.197
Coexisting condition			
Diabetes mellitus	13 (81.3)	10 (66.7)	0.433
Obstructive uropathy	7 (43.8)	5 (33.3)	0.716
Malignancy	1 (16.7)	5 (33.3)	0.083
Signs and symptoms			
Fever	13 (81.3)	6 (40.0)	0.029
Chills	10 (62.5)	2 (13.3)	0.009
Dysuria	7 (43.8)	6 (40.0)	1.000
Suprapubic pain	0	6 (40.0)	0.007
Flank pain	12 (75.0)	1 (6.7)	<0.001
Costovertebral angle percussion pain	14 (87.5)	3 (20.0)	<0.001
Laboratory parameters			
Leukocytes (× 10^3/μL; mean ± SD)	15.68 ± 9.03	13.36 ± 6.92	0.566
Platelets (× 10^3/μL; mean ± SD)	195 ± 186	234 ± 144	0.179
C-reactive protein (μg/mL; mean ± SD)	220.4 ± 96.3	91.4 ± 83.2	0.001
Creatinine clearance[c] (mL/min/1.73 m^2; mean ± SD)	32.2 ± 23.5	45.1 ± 35.6	0.323
Hemoglobin A_{1C} (%; mean ± SD)	10.2 ± 4.1	7.9 ± 2.3	0.189
Blood glucose (mg/dL; mean ± SD)	327 ± 232	206 ± 128	0.136
Treatment modality			
Medical treatment alone	1 (6.3)	12 (80.0)	<0.001
Medical treatment and percutaneous drainage	15 (93.8)	3 (20.0)	<0.001
Overall mortality	4 (25.0)	3 (20.0)	1.000
Hospital stay (days; mean ± SD)	24.4 ± 16.7	29 ± 25.9	0.984

[a]Mann-Whitney *U* test for continuous variables or Fisher's exact test for categorical variables.

[b]Obesity was defined as body mass index ≥24 kg/m^2.

[c]Creatinine clearance was calculated by the Modification of Diet in Renal Disease Study Group Simplify Equation.

Abbreviation: SD = standard deviation.

Among the EP group, 15 patients had a radiograph of the abdomen, which was diagnostic for only 1 patient (7%). In the EC group, all patients had a radiograph of the abdomen, which was diagnostic for only 2 patients (13%). Abdominal ultrasonography was performed for 10 patients in the EP group and confirmed the presence of EP for 5 patients (50%); only 5 patients in the EC group had abdominal ultrasonography and the presence of EC was confirmed in 1 patient (20%). All patients received abdominal and/or pelvic CT and all images were diagnostic of the emphysematous lesion in the urinary tract.

EP involved the left kidney more frequently (9/16; 56%) than the right (6/16; 38%); only 1 patient (8%) had bilateral kidney involvement. Among the EP group, 6 patients (37%) were classified as having type I EP and 10 patients (63%) had type II EP. In 1 patient, abdominal CT demonstrated a separate gas formation within the kidney and peritoneum. Air accumulation within the vertebral body was seen in the abdominal CT image of 1 patient.

Laboratory and microbiologic findings

Table 1 shows that initial C-reactive protein was significantly higher in the EP group than in the EC group (220.4 vs 91.4 μg/mL; $p = 0.001$). There were no statistically significant differences between the 2 groups in initial white blood cell counts, platelet counts, albumin levels, CCr, hemoglobin A_{1C} (HbA_{1C}), blood glucose levels at admission, proteinuria, and hematuria.

Blood and urine cultures were obtained from all patients and aspirated pus cultures were collected

from 15 patients in the EP group and 3 patients in the EC group. The positive blood culture rate was significantly higher in the EP group than in the EC group (56.3% vs 13.3%; $p = 0.023$). The isolation rate of organisms from urine was lower in the EP group than in the EC group (18.8% vs 53.3%; $p = 0.066$). *Escherichia coli* was the most frequently isolated organism in the EP group (38%, 6%, and 40% in blood, urine, and abscess culture, respectively), followed by *Klebsiella pneumoniae* (19%, 3%, and 20%, respectively). The most commonly isolated organisms in the EC group were also *E. coli* and *K. pneumoniae*. Polymicrobial infection only occurred in 1 patient with EP. Urine culture yielded *Morganella morganii*, and mixed organisms with *Bacteroides thetaiotaomicron* and *Proteus mirabilis* were isolated from the culture of aspirated pus. Another patient presenting with EC, diagnosed 18 days after admission, had *Candida albicans* isolated from the urine, possibly due to colonization from long-term urethral catheter use. Four patients in the EP group and 6 patients in the EC group had no organisms isolated from the specimens. Only 1 *K. pneumoniae* isolate produced extended-spectrum β-lactamase, which was isolated from both urine and blood of a patient with EC diagnosed 2 weeks after admission.

Treatment and outcomes

All patients received appropriate antibiotics and prompt blood sugar control as well as adequate fluid resuscitation. The rate for medical treatment combined with percutaneous nephrostomy drainage (PCD) was significantly higher for the EP group ($p < 0.001$). The rate for medical therapy alone was significantly higher for the EC group ($p < 0.001$). Among the EP group, only 1 patient was treated with only medical therapy and survived; the remainder received medical treatment combined with PCD, among whom 4 died of septic complications. Three patients (50%) with type I EP and 1 patient (10%) with type II EP died. Among the EC group, only 3 patients received medical treatment combined with PCD, 2 of whom died; the remainder were treated only with medical therapy, 1 of whom died. None of the patients presenting with EP or EC was treated by surgical nephrectomy. There was no statistically significant difference in overall mortality rate between the 2 groups (25% vs 20%; $p = 1.000$). There was no significant difference in median duration of hospital stay between the 2 groups (19.5 vs 16 days; $p = 0.984$).

Prognostic factors for mortality

The demographic characteristics, clinical features, and laboratory parameters at initial presentation among the patients who died are summarized in Table 2. There were no statistically significant differences in age, BMI, underlying diseases, white blood cell counts, platelet counts, blood glucose levels at admission, creatinine clearance, proteinuria, and hematuria between patients who survived and those who died. No statistically significant difference was seen between patients who survived and those who died in the EC group. In the EP group, worse renal function and hematuria were significantly more frequent among patients who died than among those who lived ($p = 0.004$ and $p = 0.027$, respectively).

Discussion

EUTI is a necrotizing infection of the renal parenchyma and its surrounding areas, resulting in gas collection in the renal parenchyma, collecting system, perinephric tissue, and urinary bladder. The infection is uncommon, often rapidly progressive, and occasionally fatal [2]. This study found that there was no significant clinical feature suggesting the presence of EC. The clinical manifestations of EP were specific, but similar to uncomplicated pyelonephritis. Although the overall mortality rate for both groups was similar, impaired renal function and hematuria were predictors of poor outcome in patients with EP but not in patients with EC.

In this study, both EP and EC had a predilection for women (81% and 83%, respectively), as has been reported in other studies [8,14]. This characteristic is believed to be due to the increased susceptibility of women to urinary tract infection. Patients with diabetes mellitus, neurogenic bladder, obstructive uropathy, or recurrent urinary tract infection are at increased risk for this disease [15]. The most common underlying disease in patients with EP or EC was diabetes mellitus in this study. EUTI usually occurs in patients with established diabetes, but it could also be an initial presenting feature for diabetes. Tang et al reported that the incidence of malignancy associated with EP was 14% [9], and Grupper et al found that the incidence of malignancy associated with EC was 8% [10]. However, in this study, malignancy was less associated with EP than with EC (16.7% vs 33.3%; $p = 0.083$). Patients in the EP group were more obese than in the EC group. The relationship of obesity and EP necessitates further study.

Table 2. Demographic data and laboratory parameters of patients who died.

Variable	Death due to EUTI (n = 7) No. (%)	p^a	Death due to EP (n = 4) No. (%)	p^a	Death due to EC (n = 3) No. (%)	p^a
Age (years; median [range])	60 (49-87)	0.850	67 (58-87)	0.100	50 (49-82)	0.246
Female sex	4 (57.1)	0.110	2 (50.0)	0.136	2 (66.7)	0.516
Body mass index[b] (kg/m^2; mean ± SD)	24.37 ± 6.05	0.959	23.99 ± 6.85	0.544	25.15 ± 6.36	0.465
Days to diagnosis (median [range])	7 (3-24)	0.813	8.5 (4-24)	0.180	7 (3-10)	0.426
Coexisting condition						
Diabetes mellitus	3 (42.9)	0.053	2 (50.0)	0.136	1 (33.3)	0.242
Chronic kidney disease	4 (57.1)	0.210	3 (75.0)	0.063	1 (33.3)	1.000
Obstructive uropathy	3 (42.9)	1.000	3 (75.0)	0.262	0	
Malignancy	2 (28.6)	0.596	1 (25.0)	0.250	1 (33.3)	1.000
Laboratory parameters						
Leukocytes (× 10^3/μL; mean ± SD)	15.93 ± 8.82	0.508	15.45 ± 10.16	1.000	16.56 ± 8.80	0.312
Platelets (× 10^3/μL; mean ± SD)	226 ± 148	0.524	209 ± 44	0.129	248 ± 247	0.563
C-reactive protein (μg/mL; mean ± SD)	116.40 ± 92.40	0.292	168.00 ± 88.00	0.182	48.20 ± 42.70	0.586
Creatinine clearance[c] (mL/min/1.73 m^2; mean ± SD)	29.88 ± 36.06	0.119	6.35 ± 1.16	0.004	61.20 ± 36.30	0.248
Blood glucose (mg/dL; mean ± SD)	175 ± 84	0.114	175 ± 70	0.146	176 ± 118	0.735
Proteinuria[d]	5 (19.2)	0.562	4 (100)	1.000	1 (33.3)	0.154
Hematuria[e]	4 (36.4)	0.210	3 (75.0)	0.027	1 (33.3)	1.000

[a]Mann-Whitney *U* test for continuous variables or Fisher's exact test for categorical variables.
[b]Body mass index was defined as the individual's body weight divided by the square of their height.
[c]Creatinine clearance was calculated by the Modification of Diet in Renal Disease Study Group Simplify Equation.
[d]Proteinuria was defined as a protein amount of ≥30 mg/dL in a random uncentrifuged urine specimen.
[e]Hematuria was defined as a red blood cell count of ≥10 cells/high-power field in a random uncentrifuged urine specimen.
Abbreviations: EUTI = emphysematous urinary tract infection; EP = emphysematous pyelonephritis; EC = emphysematous cystitis; SD = standard deviation.

The clinical manifestations of EP in this study were similar to those in another report [11], and included fever, chills, flank pain, and dysuria. The clinical presentation of EC may be varied and non-specific, and does not correlate with the severity of the inflammation. Bobba et al reported that 7% of patients with EC were asymptomatic and were diagnosed incidentally by abdominal imaging for other concurrent illnesses [16]. In this study, fever, chills, flank pain, and percussion tenderness at the costovertebral angle were significantly more frequent in the EP group than the EC group.

EUTIs are defined and diagnosed by means of imaging, and the incidence is increasing with the increased use of abdominal imaging and a greater awareness of such diseases. As abdominal imaging is not routinely used for patients with urinary tract infection, the number of EUTIs might be underestimated. Abdominal X-ray has been shown to have a very low specificity and sensitivity (33%) [17], because the finding on plain X-ray may be confused with bowel gas, emphysematous cholecystitis, and pneumatosis intestinalis. In this study, X-ray was a poor diagnostic tool. Ultrasonography was mainly used to exclude urinary tract obstruction, but overlying bowel gas may obscure intraparenchymal air. Abdominal and/or pelvic CT is the most valuable imaging modality for diagnosis of EUTI. CT is capable of differentiating soft tissue from gas, fluid, calcification, or contrast medium, and can more accurately define the extent and severity of such diseases. The median duration from the onset of symptoms and signs to the diagnosis of EUTI was 5 days for the EP group and 10 days for the EC group. When patients had any risk for complicated urinary tract infection and persistent clinical symptoms after 5 to 10 days of appropriate antimicrobial therapy, patients underwent CT scan to evaluate for obstruction, abscess, gas formation, or other complications. Intravenous pyelography was not frequently performed because most patients had impaired renal function. Thus, pyelography was only used if CT was not available. There is no specific information regarding the use of magnetic resonance imaging (MRI) for the diagnosis of EUTI. As gas-forming infections can cause signal

voids, which are difficult to interpret on MRI, the value of MRI seems limited for this condition [18].

Some investigators have found that the left kidney is more frequently involved than the right kidney in the EP group [19,20], and this study had the same result. It is thought that EP is more common in the left kidney because urinary tract obstruction occurs more frequently on the left side. Most of the patients in the EP group presented with unilateral kidney involvement, and the presence of bilateral kidney involvement was found in only 1 patient who died after receiving medical treatment combined with PCD. The clinical manifestations of bilateral EP were similar to those for unilateral EP [21]. The presence of bilateral EP was associated with a poor prognosis, and more aggressive PCD or even surgical intervention was indicated. The only patient with bilateral EP in this study died after receiving medical treatment combined with PCD. Some authors have reported that type I EP was associated with a more fulminant clinical course, more extensive parenchymal necrosis, and a worse prognosis than type II EP [22]. Grossly, type I EP is characterized by necrosis, hemorrhagic infarction, and a fragile and spongy kidney with honeycomb-like gas-containing spaces; microscopy pathology reveals vasculitis, microscopic abscess, and infarction. These findings may be indicative of disseminated intravascular coagulation leading to renal thrombosis. The pathological findings of type II EP include diffuse infiltration of acute and chronic inflammatory cells, exudate, abscess formation, and necrosis. The streaky/mottle gas pattern and absence of exudative response in patients with type I EP may result from a defective immune reaction in the host, whereas the presence of exudate in patients with type II EP suggests better host immunity and a more favorable prognosis [23]. This study resulted in a higher mortality rate for patients with type I EP.

There are several theories about the pathogenesis of these rare gas-forming infections, including the presence of a glucose-fermenting pathogen, high tissue glucose concentration, impaired vascular supply with decreased tissue perfusion, impaired host immunity, and urinary tract obstruction in non-diabetic patients [24]. Various bacterial and fungal organisms have been isolated, with *E. coli* being the most prevalent isolate, which was confirmed again in this study. The renal medulla is normally hypoxemic, which may be further exacerbated by renal ischemia in a diabetic kidney. Then, low oxygen tension within the renal medulla forms and induces an anaerobic condition. Facultative anaerobic organisms such as *E. coli*, *P. mirabilis*, and *K. pneumoniae* are able to ferment glucose to lactate and carbon dioxide. However, anaerobic pathogens have a propensity for gas formation, but have little or no role in the pathogenesis of EUTI. There are extremely rare reports of EUTI with anaerobic isolates, such as *Clostridium* spp. [10]. In this study, 1 patient presenting with EP had mixed organisms (*B. thetaiotaomicron* and *P. mirabilis*) in the aspirated pus culture.

EUTI is usually considered to be life threatening and requires prompt evaluation and management. The treatment generally includes broad-spectrum antibiotics, and optimal blood glucose control with correction of any underlying comorbid disorders. The mortality rate for patients with EP treated only medically approaches 75%, and survival is improved if early surgical intervention is performed [25]. Before the development of invasive radiologic intervention, nephrectomy was the gold standard for treating EP. In 1997, Chen et al reported that medical therapy combined with CT-guided PCD was an acceptable alternative to medical therapy combined with nephrectomy [26]. The management of EC generally needs only bladder drainage by the indwelling urethral catheter. Patients with EC not responding to medical therapy or those with severe necrotizing infections might require partial cystectomy, cystectomy, or surgical debridement. In this study, medical therapy combined with early CT-guided PCD was undertaken among the patients with EP, except for 1 patient who was treated medically; most patients with EC received medical therapy except for 3 patients for whom antibiotics combined with CT-guided PCD was performed. EP is known to have a higher mortality rate then EC. The overall mortality rate for EP was approximately 20%, but less than 10% of the overall mortality rate for EC was observed [8]. EC has the potential to ascend to the upper urinary tract, which could increase the associated morbidity and mortality of this infectious condition. However, the overall mortality rate for EC was similar to that for EP in this study. This result could be attributed to factors of insufficient sample size, older age among the EC group, and higher incidence of malignancy associated with EC.

Previous investigators have attempted to correlate the clinical features and laboratory parameters to predict outcomes [11,22]. EUTI is usually seen in middle-aged to elderly women, but this study did not

find that advanced age and sex were associated with a poor prognosis. Although this condition is more frequently seen in diabetic patients, there was no association between diabetes and mortality. This study also showed that white blood cell counts, platelet counts, initial blood glucose levels, CCr, and hematuria are not prognostic factors for EUTI. Similarly, no significant predictors of poor outcome were seen in the patients with EC. However, impaired renal function and hematuria could predict an increased mortality rate among patients with EP in this study, which is concordant with previous reports [22,27]. The severity of impaired renal function and hematuria in patients with EP may partly reflect the degree of destruction or necrosis of the kidney due to the infectious process and presence of renal vascular thrombosis.

In conclusion, patients presenting with EUTI are usually diabetic women. The most common causative pathogens are *E. coli*, followed by *K. pneumoniae*. The clinical features of EP are more specific, but are similar to uncomplicated pyelonephritis. The diagnosis of EUTI is often delayed, probably because of the lack of clinical suspicion and the rarity of this condition. An imaging diagnosis is essential for EUTI and CT, which may define the extent and severity of this disorder, is recommended. The overall mortality rate for EC is similar to EP. Impaired renal function and hematuria are predictors of poor outcome for patients with EP but not for patients with EC. Appropriate antibiotics, optimal blood glucose control, and adequate drainage are essential for the treatment of EUTI due to its high mortality rate.

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