Emphysematous Pyelonephritis

Clinicroadiological Classification, Management, Prognosis, and Pathogenesis

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Background: Emphysematous pyelonephritis (EPN) is a rare, severe gas-forming infection of renal parenchyma and its surrounding areas. The radiological classification and adequate therapeutic regimen are controversial and the prognostic factors and pathogenesis remain uncertain.

Objectives: To elucidate the clinical features, radiological classification, and prognostic factors of EPN; to compare the modalities of management (ie, antibiotic treatment alone, percutaneous catheter drainage combined with antibiotic treatment, or nephrectomy) and outcome among the various radiological classes of EPN; and to clarify the gas-forming mechanism and pathogenesis of EPN by gas analysis and pathological findings.

Patients and Methods: Forty-eight EPN cases from our institution were enrolled between August 1, 1989, and November 30, 1997. According to the radiological findings on computed tomographic scan, they were classified into the following classes: (1) class 1: gas in the collecting system only; (2) class 2: gas in the renal parenchyma without extension to extrarenal space; (3) class 3A: extension of gas or abscess to perinephric space; class 3B: extension of gas or abscess to pararenal space; and (4) class 4: bilateral EPN or solitary kidney with EPN. The clinical manifestations, management, and outcome were compared. The gas contents of specimens from 6 patients were analyzed. The pathological findings from 8 patients who received nephrectomy were reviewed. The statistical methods consisted of the Fisher exact test (2 tailed) for categorical variables and Wilcoxon rank sum test for continuous variables to test the predictors of poor prognosis.

Results: Forty-six patients (96%) had diabetes mellitus, and 10 (22%) of the 46 also had urinary tract obstruction in the corresponding renoureteral unit. The other 2 non-diabetic patients (4%) had severe hydronephrosis. Twenty-one (72%) of the 29 patients with diabetes mellitus also had a glycosylated hemoglobin A1c level higher than 0.08. Escherichia coli (69%) and Klebsiella pneumoniae (29%) were the most common pathogens. The mortality rate in patients who received antibiotic treatment alone was 40% (2 of 5 patients). The success rate of management by percutaneous catheter drainage (PCD) combined with antibiotic treatment was 66% (27 of 41 patients). In classes 1 and 2 EPN, all the patients who were treated using a PCD or ureteral catheter combined with antibiotic treatment survived. In extensive EPN (classes 3 and 4), 17 (85%) of the 20 patients with fewer than 2 risk factors (ie, thrombocytopenia, acute renal function impairment, disturbance of consciousness, or shock) were successfully treated using PCD combined with antibiotic treatment; and the patients with 2 or more risk factors had a significantly higher failure rate than those with no or only 1 risk factor (92% vs 15%, P<.001). Eight of the 14 patients who had an unsuccessful treatment using a PCD underwent subsequent nephrectomy, 7 of whom survived. Only 2 patients were managed by direct nephrectomy and survived. The overall success rate of nephrectomy was 90% (9 of 10 patients). The total mortality was 18.8% (9 of 48 patients). Five of the 6 gas samples contained hydrogen (average, 12.8%), and all had carbon dioxide (average, 14.4%). The pathological findings from 8 of 10 who underwent nephrectomy revealed poor perfusion in most cases (ie, infarction, 5 patients; vascular thrombosis, 3 patients; and arteriosclerosis and/or glomerulosclerosis, 4 patients).

Conclusions: Acute renal infection with E coli or K pneumoniae in patients with diabetes mellitus and/or urinary tract obstruction is the cornerstone for the development of EPN. Mixed acid fermentation of glucose by Enterobacteriaceae is the major pathway of gas formation. For localized EPN (classes 1 and 2), PCD combined with antibiotic treatment can provide a good outcome. For extensive EPN (classes 3 and 4) with a more benign manifestation (ie, <2 risks), when saving of the kidney is possible, PCD combined with antibiotic treatment may be attempted due to the high success rate, and may preserve the kidney. However, nephrectomy can provide the best management outcome and should be promptly attempted for extensive EPN with a fulminating course (ie, ≥2 risks).

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PATIENTS AND METHODS

PATIENTS

Among the patients who were admitted to the National Chen Kung University Hospital, Taiwan, Republic of China, between August 1, 1989, and November 30, 1997, 48 consecutive cases were diagnosed as EPN and met all of the following criteria: (1) symptoms and signs of upper UTI, or fever with a positive urine culture or pyuria without other identified infectious foci; (2) radiological evidence by CT scan of gas accumulation in the collecting system, renal parenchyma, or perinephric or pararenal space; (3) no fistula between the urinary tract and bowel; and (4) no recent history of trauma, urinary catheter insertion, or drainage.

METHODS

The baseline characteristics, clinical features, and laboratory data at the initial presentation, management, and outcome were collected by comprehensive review of the medical records. The baseline characteristics included age, sex, history of DM, status of glucose control (fasting glucose level, >11.1 mmol/L [>200 mg/dL] or a glycosylated hemoglobin A1c level >0.08 was defined as a glucose level in poor control), and the presence of diabetic retinopathy and other underlying diseases. The clinical features at the initial presentation included the hemodynamic status, renal function, and the degree of consciousness. The duration from the onset of symptoms and signs to diagnosis of EPN were also checked. Shock was defined as a systolic blood pressure less than 90 mm Hg. Disturbance of consciousness included confusion, delirium, stupor, and coma. Leukocytosis was defined as a blood leukocyte count higher than 12 × 10⁹/L. According to the criteria of disseminated intravascular coagulation, thrombocytopenia was defined as platelet count lower than 120 × 10⁹/L. Acute renal function impairment was defined as further elevation of the serum creatinine level more than 88.4 µmol/L (>1 mg/dL), if the baseline serum creatinine level of the patient was higher than 265.2 µmol/L (>3 mg/dL). It was also defined as further elevation of the serum creatinine level more than 44.2 µmol/L (>0.5 mg/dL) if the baseline serum creatinine level was less than 265.2 µmol/L (<3 mg/dL). Macrohematuria was defined as red blood cells in urinary sediment of more than 100 per high-power field. Severe proteinuria was defined as a urine protein concentration greater than 3 g/L on at least 2 occasions during hospital admission.

Abdominal CT scan and echography were performed for all 48 cases. Severe hydronephrosis was defined as marked dilatation of renal pelvis and thinning of cortex. According to the radiological findings on the CT scan, they were classified into the following classes: (1) class 1: gas in the collecting system only (so-called emphysematous pyelitis); (2) class 2: gas in the renal parenchyma without extension to the extrarenal space; (3) class 3A: extension of gas or abscess to the perinephric space; class 3B: extension of gas or abscess to the pararenal space; and (4) class 4: bilateral EPN or solitary kidney with EPN (Figures 1, 2, 3, and 4). The perinephric space was defined as the area between the fibrous renal capsule and renal fascia. The pararenal space was defined as the space beyond the renal fascia and/or extending to the adjacent tissues such as the psoas muscle. The differences of clinical features, management, and outcome among the 4 classes were compared and analyzed. Insertion of percutaneous catheter into the renal or extrarenal lesion was performed via imaging guidance (ie, renal CT scan or echography). “Unsuccessful” PCD was defined as progressive or persistent lesions on imaging studies with clinical manifestations of unstable hemodynamics or prolonged fever after management. We also divided our cases into “good” and “poor” outcome groups to elucidate the risk factors. The patients who were successfully treated with antibiotics alone or using PCD combined with antibiotics were assigned to the “good” outcome group. The patients who had an unsuccessful PCD followed by nephrectomy or mortality were assigned to the “poor” outcome group. These 2 groups were compared for baseline characteristics, clinical features, and laboratory data at the initial presentation.

Under the guidance of renal echography or CT scan, some gas and pus were aspirated successfully from 6 patients. All the connections of the aspiration system were immersed in distilled water. The puncture needle and aspiration tube were sealed with aseptic jelly. The gas samples were aspirated from rubber-sealed collecting syringes with a gas-tight syringe (for analysis, which used a gas chromatography/thermal conductivity detector and a gas chromatography/mass spectrometer detector, etc.17 The pus was also analyzed for bacterial content and pH value. The pathological findings from 8 patients who underwent nephrectomy were analyzed and compared with their radiological manifestations.

STATISTICAL METHODS

The differences between the survival and mortality groups were quantified using the Fisher exact test (2 tailed) for categorical variables, and the Wilcoxon rank sum test for continuous variables. To test the predictors of poor prognosis, the Fisher exact test (2 tailed) was used for categorical variables, and the Wilcoxon rank sum test for continuous variables. The multiple logistic regression test was used to examine the independent prognostic factors for EPN. The differences between the 4 classes of EPN were tested with the Mantel-Haenszel χ² test for categoric variables, and the Kruskal-Wallis test with χ² approximation for continuous variables. P<.05 was taken as the upper level of statistical significance.

and has been generally regarded as a rare renal infection. However, with the more extensive use of abdominal ultrasound (echography) and computed tomography (CT scan) in the evaluation of patients with symptoms and signs of sepsis or complicated urinary tract infection (UTI), more cases of EPN are being recognized and these cases are being reported in the urology and radiology journals,1-22 and less frequently in internal medicine or nephrology journals.23-31 We believe that EPN is not rare and should be considered an important clinical entity. Nevertheless, no large clinical experience of EPN concerned with management and prognostic factors has
been reported from a single institution. The mechanism of gas formation and pathogenesis of EPN are also unclear.

Ahlering et al,8 Pontin et al,9 and Shokeir et al10 had concluded that vigorous resuscitation and appropriate medical treatment should be attempted, but immediate nephrectomy should not be delayed for successful management of EPN. However, successful treatment of EPN using percutaneous catheter drainage (PCD) and antibiotic treatment has also been reported.3-5,11-15 Therefore, the adequate therapeutic modalities for EPN are still controversial. Emphysematous pyelonephritis has been classified according to the location of gas accumulation because of various outcomes.1,26 Nevertheless, the radiological classification, adequate management, and prognosis have rarely been well studied.

Our objectives in this study included (1) elucidating the clinical features, radiological classification, and prognostic factors of EPN; (2) comparing the modalities of management (ie, antibiotic treatment alone, PCD combined with antibiotic treatment, or nephrectomy) and outcome among the various radiological classes of EPN; and (3) clarifying the gas-forming mechanism and pathogenesis of EPN by gas analysis and pathological findings.

## RESULTS

### BASELINE CHARACTERISTICS AND CLINICAL PRESENTATIONS

The mean age of our patients was 60 years (age range, 37-83 years). Women outnumbered men (41:7). Forty-six patients (96%) had DM. Ten (22%) of them also had urinary tract obstruction; 2 (4%) had underlying polycystic kidney disease; and 2 (4%) had end-stage renal failure. The other 2 patients without DM had severe hydronephrosis in the corresponding renoureteral unit caused by bladder and ureteral transitional cell carcinoma in one case and ureteral stone in the other. Eighteen (69%) of the 26 patients with DM also had diabetic retinopathy; 12 were background; and 6 were proliferative. Twenty-one (72%) of the 29 patients with DM had a glycosylated hemoglobin A1c level higher than 0.08. Clinical features and laboratory data at the initial presentation are given in Table 1.

The involved site was more frequent...
in the left kidney (67%) than in the right one (25%). Urinary tract obstruction also occurred more frequently in the left kidney than the right one (64% vs 36%). Pathogens were identified in 47 (98%) of our 48 cases. Escherichia coli was the most common organism (69%) cultured, and Klebsiella pneumoniae was the second (29%). Two patients had E. coli infection mixed with group B Streptococcus or Proteus. Bacteremia occurred in more than half of our cases (26/48 [54%]), and all of the organisms from blood culture were the same as those found in the urine or pus culture. Anaerobic organisms were not obtained in our study.

**PROGNOSTIC FACTORS OF MORTALITY AND POOR OUTCOME**

The baseline characteristics, clinical features, and laboratory data at the initial presentation in survival and mortality groups are given in Table 2. No significant differences were noted in the patients’ mean age, glycosylated hemoglobin HbA1c, level, diabetic retinopathy, urinary tract obstruction, or mean duration from the onset of symptoms and signs to the diagnosis of EPN between the survival and mortality groups (Table 2). Initial presentations of thrombocytopenia, disturbance of consciousness, and shock were significantly associated with mortality (Table 2).

Thirty cases were classified as having a good outcome. Sixteen cases were classified as having a poor outcome. The patients in the remaining 2 cases were managed by direct nephrectomy and survived. The comparison of baseline characteristics, clinical features, and laboratory data at the initial presentation between the good and poor outcome is given in Table 2. It revealed that thrombocytopenia, disturbance of consciousness, and shock on admission to the hospital were significantly associated with poor outcome; and the initial presentations of severe proteinuria and acute renal function impairment seemed to be a risk factor of poor outcome ($P = .05$). Multiple logistic regression tests showed severe proteinuria ($P = .03$), thrombocytopenia ($P = .05$), and disturbance of consciousness ($P = .04$) on hospital admission as being the independent factors for poor outcome.

**MANAGEMENT, RADIOLOGICAL CLASSIFICATION, AND OUTCOME**

The modalities of management and outcome in our patients are given in Table 3. The mortality rate of treatment with antibiotics alone was 40% (2 of 5 patients). The success rate of management with PCD combined with antibiotics was 66% (27 of 41 patients). Eight (20%) of 41 cases were unsuccessfully treated by PCD and antibiotics, with clinical manifestations of unstable hemodynamics or prolonged fever; and 7 of them were successfully treated by subsequent nephrectomy. The overall successful rate of nephrectomy was 90% (9 of 10 patients). The total mortality rate in our cases was 18.8% (9 of 48 patients).

Five patients were seen with gas confined in the collecting system (class 1, Figure 1), 3 of whom also had severe hydronephrosis at the site of EPN. Eleven patients had gas within the renal parenchyma (class 2, Figure 2). The gas or abscess extended to the perinephric space (class 3A, Figure 3, left) in 7 patients, and further spread to the pararenal space (class 3B, Figure 3, right) in 21 patients. Four patients were grouped into class 4 EPN, 3 of whom had bilateral EPN (Figure 4); the other one had a solitary kidney due to nephrectomy for previous right-sided EPN and suffered from recurrent EPN in the left kidney. Thirty cases were classified as having a good outcome. Sixteen cases were classified as having a poor outcome. The patients in the remaining 2 cases were managed by direct nephrectomy and survived. The comparison of baseline characteristics, clinical features, and laboratory data at the initial presentation between the good and poor outcome is given in Table 2. It revealed that thrombocytopenia, disturbance of consciousness, and shock on admission to the hospital were significantly associated with poor outcome; and the initial presentations of severe proteinuria and acute renal function impairment seemed to be a risk factor of poor outcome ($P = .05$). Multiple logistic regression tests showed severe proteinuria ($P = .03$), thrombocytopenia ($P = .05$), and disturbance of consciousness ($P = .04$) on hospital admission as being the independent factors for poor outcome.

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cessfully treated with PCD combined with antibiotics; 1 was managed by direct nephrectomy and survived; the only 1 treated with antibiotics alone died. In class 3A and class 3B EPN, 61% (17 of 28 patients) were successfully treated with PCD combined with antibiotics, and 11 cases (39%) failed with progressive or persistent lesions on imaging studies and unstable manifestations after management. Seven patients in the 11 cases underwent subsequent nephrectomy, and 6 of them survived after the operation. Class 4 EPN (4 patients) had a higher prevalence of severe manifestations and the poorest prognosis (Table 4). Bilateral PCD was performed for 3 patients with bilateral EPN: 1 was successfully treated, 1 died, and 1 survived after undergoing subsequent nephrectomy. If we take the thrombocytopenia, acute renal function impairment, disturbance of consciousness, and shock at the initial presentation as 4 risk factors of predicting poor response to PCD combined with antibiotic treatment, classes 3 and 4 EPN cases with 2 or more risk factors would have significantly higher failure rate of PCD than those with no or only 1 risk factor (92% vs 15%, P<.001).

### GAS ANALYSIS AND PATHOLOGICAL FINDINGS

The gas samples contained neither oxygen-containing hydrocarbons (eg, alcohol, aldehydes, and organic acids), nor sulfur-containing compounds. Five of the 6 gas samples contained hydrogen (H2, 3.4–28%; average, 12.8%) and all had carbon dioxide (CO2, 4.0–39.5%; average, 14.4%). The only 1 without H2 was obtained because H2 itself was used as a carrier gas for gas analysis, and could not detect the H2. Large amounts of...
Comment

Kelly and MacCallum²³ reported the first case of gas-forming renal infection (pneumaturia) in 1898. Since then, a multiplicity of terms such as “renal emphysema,” “pneumonitis,” and “empysematous pyelonephritis” have been used to describe this gas-forming infectious disease. As suggested by Schultz and Klorfein²² in 1962, emphysematous pyelonephritis is the preferred designation, since it stresses the relation between acute infectious process and gas formation. Some investigators have suggested that the term emphysematous pyelonephritis should be applied only to gas formed within the renal parenchyma or perinephric space.²⁴-²⁶ However, others have advocated that EPN is an infection of the renal parenchyma and perinephric tissue, which results in the presence of gas in the collecting system, renal parenchyma, or perinephric tissue.²⁷-²⁹ The latter definition is favored because it includes all the possible manifestations of gas-forming acute renal infections.

Clinical Features and Diagnosis of EPN

In our series, EPN preponderantly affected females (female-male ratio, 5:9:1). This result is similar to that of other series,²⁰,³⁰ and is supposed to be due to the increased susceptibility to UTI in females.¹⁰ The left kidney was more frequently involved than the right one (67% vs 25%). This also corresponds to the results of other series,¹² The preponderance of left-sided urinary tract obstruction (64% vs 36% in the right side) may be one of the causes. The most common clinical manifestations of EPN (ie, fever, flank pain, and pyuria) were nonspecific and not different from the classic triad of upper UTI other than EPN. However, thrombocytopenia (46%), acute renal function impairment (33%), disturbance of consciousness (19%), and shock (29%) can be the initial presentations, especially in severe cases or in patients not given an early diagnosis and management of EPN. The diagnosis of EPN is classically made by demonstrating gas in renal or perinephric tissue by plain abdominal x-ray film or renal echography. However, gas could be demonstrated only on 33% of plain abdominal radiographs by Michaeli et al in 1984, and it may be difficult to distinguish the necrotic gas-filled area from gas in the bowel by echography. In contrast, CT scan not only can confirm the diagnosis but also show the extent of disease. Therefore, severe manifestations or persistence of fever to resolve after antibiotic treatment in patients with upper UTI should arouse the suspicion that a serious acute renal infection, such as acute bacterial nephritis, renal abscess, or even EPN, is ongoing. The abdominal CT scan is necessary for an early diagnosis and further management of EPN.

Prognostic Factors for EPN

Michaeli et al³¹ attempted to correlate the clinical features of EPN with outcome. They concluded that age, sex, site of infection, serum urea nitrogen level, and blood glucose level were not the prognostic factors, and the best combination of characteristics of EPN with favorable outcome was that of a patient with nonobstructive unilateral disease receiving combined medical and surgical treatment within a short interval of symptom onset. We also showed that age, sex, site of infection, and blood glucose level were not associated with mortality or poor outcome. It has been supposed that high tissue glucose levels may be a risk for EPN to develop and cause a fulminant course in patients with DM, because it can provide gas-forming microbes with a microenvironment more favor-
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RADIOLICAL CLASSIFICATION, MANAGEMENT, AND OUTCOME

In 1970, Langston and Pfister described 3 main radiographic patterns and postulated that they were correlated with the stage of disease. They were diffuse mottling of the renal parenchyma, bubbly renal parenchyma surrounded by a crescent of gas (perinephric space), and extension through Gerota’s fascia (ie, pararenal space). Because the mottled gas and crescent formation were not frequently found, Michaeli et al suggested the following simpler descriptive classification: stage I, gas within the renal parenchyma or the perinephric tissues; stage II, the presence of gas in the kidney and its surroundings; and stage III, extension of gas through Gerota’s fascia or presence of bilateral EPN. However, they did not demonstrate a significant prognostic implication in this staging system. The relations between their staging system and management or outcome were not stated. In our study, we tried to do a more detailed classification according to the extension of gas and abscess, and studied their prognosis and management. The gas limited in the collecting system (ie, emphysematous pyelitis) was designated as class 1 EPN because we found various degrees of renal lesions (such as acute bacterial nephritis) on the CT scan, and it really was a special form of EPN. According to our early observation, the prognosis of gas extending to the perinephric or pararenal space (ie, class 3A or 3B) was different from gas limited to the renal parenchyma (ie, class 2). Although there were no significant differences in the clinical features among the 4 classes, we showed a tendency toward higher mortality rate and failure rate of PCD from class 1 to 4 EPN. The patients with class 1 EPN had the best prognosis, and all of them survived by PCD and/or relief of the urinary tract obstruction (if it existed) combined with antibiotic treatment. The prognosis of class 2 EPN was as good as that of class 1 EPN. In class 2 EPN, all patients treated with PCD combined with an antibiotic regimen were cured. Therefore, PCD and relief of the urinary tract obstruction (if it exists) combined with antibiotic treatment is the choice of modality for limited disease (class 1 or 2). For adequate management of extensive EPN with gas or abscess extension beyond the renal capsule or bilateral EPN (class 3 or 4), our study showed that 17 (85%) of the 20 patients with less than 2 risk factors (ie, thrombocytopenia, acute renal function impairment, disturbance of consciousness, and shock) were successfully treated with PCD combined with antibiotic treatment; and the patients with 2 or more risk factors would have a significantly higher failure rate than those with no or only 1 risk factor (92% vs 15%, P < .001). Nephrectomy can provide the best management outcome (Table 3). But, the advantages of PCD include drainage of pus, relief of gas pressure to local circulation, and provide a high success rate in extensive EPN. Therefore, we suggest that for patients with extensive EPN (class 3 or 4) with the benign manifestation (ie, <2 risk factors), PCD combined with antibiotic treatment may be attempted owing to the high success rate and so preserve their kidney. However, nephrectomy can provide the best management outcome and should be promptly attempted for extensive EPN cases with the fulminating course (ie, ≥2 risk factors). In class 4 EPN, bilateral PCD can be tried first because of the high risk of emergency nephrectomy in these unstable patients, but nephrectomy should be done if PCD fails. The flowchart for management of EPN according to the clinicoradiological classification is shown in Figure 6.

In 1996, Wan et al described 2 distinct radiological classifications of EPN by CT scan: type 1, having a fulminating course and a mortality of 69% (11 of 16 patients), is characterized by parenchymal destruction with
either absence of fluid collection or presence of streaky or motiled gas; and type 2, having a mortality of 18% (4 of 22 patients), is characterized as either renal or perirenal fluid collection with bubbly or located gas or gas in the collecting system (Table 4). According to the pathological findings, Wan et al hypothesized that the clinicopathological differences between types 1 and 2 EPN are probably related to the difference in severity of immunity compromise and vascular insufficiency in the kidneys and immunodeficiency in patients with DM. In our series, we also demonstrated that type 1 (dry) EPN was a significant risk factor of poor outcome \((P<.01)\). Among 14 cases with type 1 EPN, 9 (64%) the extent of disease was to the extrarenal tissue or bilateral kidney. In 8 patients with available pathological results, 5 patients had type 1 EPN, which revealed some degree of vascular thrombosis and wedge infarction (Figure 5). The pathological findings of the other 3 patients with type 2 EPN revealed only inflammation and abscess formation. Although our pathological results support the hypothesis of Wan et al,\(^a\) a definite conclusion cannot be made from such a small number of cases.

**MECHANISM OF EPN**

Although various theories have been postulated for the mechanism of gas formation in EPN,\(^{34,35}\) actual analysis of gas content has rarely been performed.\(^{10,17}\) Most bacteria obtain their energy through the fermentation of glucose via the glycolytic pathway. Among these pathways, only mixed acid fermentation (most Enterobacteriaceae, eg, *E coli*, *K pneumoniae*, and *Proteus*) and butyric fermentation (*Clostridium*) can give rise to \(H_2\) as an end product.\(^{36}\) In our study, 5 of the 6 gas samples contained \(H_2\), and all the gas samples contained \(CO_2\). Moreover, 5 cases of *E coli* and 1 case of *K pneumoniae* were isolated from these patients. Although anaerobic organisms were not obtained in our study, *Clostridium* as the causative pathogen has been previously reported.\(^{37}\) Therefore, mixed acid fermentation of glucose by Enterobacteriaceae and rarely via butyric fermentation of glucose by anaerobes were the pathways by which emphysematous UTI developed. The trace amounts of \(NH_3\) and methane in 1 patient may have arisen from degradation of necrotic tissue and the fermentation of amino acids.\(^{17}\)

The mechanism of gas chamber (ie, large gas bubbles) formation has been hypothesized as a series of increased gas production, impaired transportation of gas by vascular compromise, creation of a gas chamber, equilibrium of gas chamber and tissue gas, and the expansion or collapse of a gas chamber.\(^{19}\) We have postulated 4 factors that may be involved in the pathogenesis of EPN, including gas-forming bacteria, high tissue glucose level, impaired tissue perfusion, and a defective immune response (such as DM).\(^{17}\) Twenty-one (72%) of the 29 patients with DM had a level of glycosylated hemoglobin \(HbA_1c\) higher than 0.08, and they had poor control of their blood glucose levels before getting EPN. We hypothesize that high tissue glucose levels in patients with DM may provide gas-forming microbes with a microenvironment more favorable for their growth and rapid catabolism, which can cause the massive production of gas.\(^{16,18}\)

In 1997, Shokeir et al\(^{10}\) revealed that urinary tract obstruction was evident in all of their patients without DM and in half of their patients with DM. In our series, 10 of the 46 diabetic patients and both of the patients without DM also had obstruction of the corresponding ureteral unit with moderate to severe hydronephrosis. The uninjured urinary tract obstruction and hydronephrosis may increase pelviccalyceal pressure and compromise renal circulation, and result in impaired transportation of gas and subsequent creation of a gas chamber (ie, EPN). Impaired tissue perfusion has been speculated as a risk factor and a poor prognostic factor for EPN.\(^{12,17}\) However, we do not have sufficient evidence to support this speculation owing to limited pathological reports. The pathological findings revealed the evidence of impaired tissue perfusion (ie, infarction or vascular thrombosis) in most patients with class 3 or 4 EPN, but not in the only patient with class 2 EPN. We suppose that extensive infarction resulted in the absence of blood supply, which brought leukocytes and antibiotic treatment into this area. The infection could not be cleared and the affected tissue required excision.

**Escheria coli** or **K pneumoniae** infection in patients with DM and/or urinary tract obstruction is the cornerstone for the development of EPN. In patients with DM, the high level of blood glucose may provide gas-forming microorganisms with a more favorable environment for gas formation via mixed acid fermentation of glucose. For localized EPN (class 1 or 2), PCD and/or relief of the urinary tract obstruction (if it exists) combined with antibiotic treatment can provide a good outcome. For extensive EPN (class 3 or 4) with a more benign manifestation (ie, <2 risk factors), PCD combined with antibiotic treatment may be attempted due to its high success rate for these patients and preservation of as much renal function as possible. However, nephrectomy can provide the best management outcome and should be promptly attempted for extensive EPN with a fulminant course (ie, ≥2 risk factors) or for cases with an unsuc-
successful PCD. The flowchart for management of EPN according to the clinicoradiological classification is shown in Figure 6.

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