Emphysematous Pyelonephritis: Multicenter Clinical and Therapeutic Experience in Mexico

Daniel Olvera-Posada, Ghislaine Armengod-Fischer, Luis G. Vázquez-Lavista, Miguel Maldonado-Ávila, Emmanuel Rosas-Nava, Hugo Manzanilla-García, Ricardo A. Castillejos-Molina, Carlos E. Méndez-Probst, Mariano Sotomayor, Guillermo Feria-Bernal, and Francisco Rodríguez-Covarrubias

OBJECTIVE To analyze the outcomes of emphysematous pyelonephritis (EPN), the impact of different treatment modalities, and to determine risk factors associated with mortality.

METHODS We retrospectively reviewed cases of EPN from 3 tertiary care institutions in Mexico. The diagnosis was confirmed with computed tomographic scan. Treatment was classified as follows: medical management (MM), minimally invasive, and surgical. Demographic, clinical, biochemical, and radiological characteristics were assessed and compared between survivors and nonsurvivors. Comparison was assessed using 1-way analysis of variance and chi-square. Univariate and multivariate logistic regression analyses were performed to determine prognostic factors. Main end point was mortality.

RESULTS A total of 62 patients were included (49 women and 13 men), with a mean age of 53.9 years. The most common comorbidities were diabetes (69.3%) and hypertension (40.3%). *Escherichia coli* was the most common isolated microorganism (62.7%). MM was provided to 24.2%, minimally invasive treatment to 51.6%, open drainage to 19.3%, and emergency nephrectomy to 4.8%. Overall mortality was 14.5% and was similar among different treatment modalities ($P = .06$). Survivors were younger ($P = .004$), had lower creatinine ($P = .002$), and better estimated glomerular filtration rate ($P = .007$). In univariate analysis, age ($P = .009$), creatinine ($P = .009$), and need for nephrectomy ($P = .03$) were associated with mortality. In multivariate logistic regression analysis, creatinine (odds ratio 1.56, 95% confidence interval 1.03-2.35, $P = .03$) and nephrectomy (odds ratio 9.7, 95% confidence interval 1.007-93.51, $P = .049$) remained significant predictors of mortality.

CONCLUSION EPN needs an aggressive MM and stepwise approach; nephrectomy should be the last resort of treatment. Creatinine level and need for nephrectomy are the strongest predictors of mortality according our analysis. UROLOGY 83: 1280–1284, 2014. © 2014 Elsevier Inc.

Emphysematous pyelonephritis (EPN) is a life-threatening infectious disease characterized by the presence of gas in renal parenchyma, collecting systems, and/or adjacent tissues.[1-4] This condition was first described by Kelly and McCallum in 1898, but it was until 1962 when Schultz and Klorfein applied the currently used term. Historically, it has been associated with immunocompromised patients, such as those under chronic steroids prescription or diabetes.[5] Some authors have suggested the existence of 2 different clinical scenarios: emphysematous pyelitis, a condition with good prognosis and, conversely, EPN, a severe necrotizing life-threatening infection.[4,6] In our study, we used the radiological classification proposed 13 years ago by Huang and Tseng based on the largest series published to date, which specifies the localization of gas or abscess pattern.[2] Since then, medical management (MM) has become the mainstay of treatment, and some experts have warned that surgical treatment could be associated with worse outcomes.[7]

The objective of this study was to analyze the outcomes of patients with EPN from 3 large tertiary care centers in Mexico. We compared the impact of different treatment modalities on mortality. We looked for predisposing

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Department of Urology, Salvador Zubirán National Institute of Medical Sciences and Nutrition (INNSZ), Mexico City, México; the Department of Urology, General Hospital of Mexico (HGM), Mexico City, México; and the Department of Urology, Social Security Institute of Mexican State and Municipalities (ISSEMyM), Estado de México, México

The original abstract of this article was presented at the 92nd South Central Section Meeting of the American Urological Association in Chicago, IL, held in September 2013.

Reprint requests: Francisco Rodríguez-Covarrubias, M.D., Department of Urology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Col. Sección XVI, Tlalpan 14000, Mexico City, México. E-mail: frodriguez.covarrubias@gmail.com

Submitted: January 13, 2014, accepted (with revisions): February 7, 2014

0090-4295/14/$36.00
http://dx.doi.org/10.1016/j.urology.2014.02.010

Table 1. Clinical, biochemical, radiological, and management features according to institutions

Variable	INNSZ	ISSEMYM	HGM	Total	*P* Value
Patients	20	13	29	62	
Gender (F/M)	19/1	11/2	20/9	50/12	
Age	51.45	59.76	53.03	53.93	.11
Huang classification					
1	8	4	7	19	.5
2	7	5	5	17	.24
3a	2	1	3	6	.96
3b	2	2	9	13	.18
4	1	1	5	7	.37
Lithiasis	11	7	13	31	.74
Glycaemia (mg/dL)	291	279	200	246	.26
Leukocyte number (K)	14.17	20.39	14.6	15.69	**.026**
Platelet count (K)	248	213	246	240	.28
Thrombocytopenia	5	5	6	16	.48
Mean creatinine (mg/dL)	2.36	2.4	3	2.67	.49
Mean eGFR (mL/min/1.73 m^2)	51.9	32.5	35.8	40.34	.15
Medical management	10 (50%)	3 (23%)	2 (7%)	15	**.003**
Minimal invasive	10	6	16	32	.9
Open drainage	0	1	13*	14	**<.001**
Nephrectomy	1	5	1	7*	**.003**
Mortality	2/20 (10%)	3/13 (23%)	4/29 (14%)	9/62	.58

eGFR, estimated glomerular filtration rate; HGM, Hospital General de México Eduardo Liceaga; INNSZ, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán; ISSEMYM, Instituto de Seguridad Social del Estado de México y Municipios.

Values in bold are statistically significant.

* Two patients required open drainage after unsuccessful minimally invasive management; 4 nephrectomies were a second-line treatment option.

factors and characteristics associated with poor prognosis. We also proposed a management algorithm for patients presenting with radiological diagnosis of EPN.

MATERIALS AND METHODS

We reviewed the medical records of those patients admitted to the emergency room for the diagnosis of EPN at 3 tertiary care institutions in Mexico from 2005 to 2012. All patients had signs and symptoms of upper urinary tract infection and systemic inflammatory response. After initial workup consisting of physical examination and a biochemical profile, patients underwent hemodynamic and metabolic stabilization and empirical intravenous antibiotics. Once the urine or blood culture results were obtained, the antibiotic therapy was adjusted accordingly. Abdominal noncontrast computed tomographic scan was performed in all patients, and the radiological classification of Huang was assigned according radiologists criteria. Other findings such as lithiasis and hydronephrosis were investigated.[2]

Demographic characteristics including age, sex, comorbidities, and history of recurrent urinary tract infection were reviewed. Clinical, biochemical, and radiological features were analyzed to determine risk factors associated with poor outcome. Mortality was defined as death secondary to the EPN. Laboratory parameters included complete blood count, urinalysis, serum electrolytes, blood chemistry, and microbiological cultures. Leukocytosis was defined as more than 10.5×10^9/L leukocytes. Thrombocytopenia was defined as platelet count lower than 150,000/L. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to estimate the glomerular filtration rate according creatinine levels on admission.[8]

Data from clinical follow-up, culture results, and type of management were analyzed. Definitive treatment was selected according to physician discretion and classified as follows: MM consisting of hemodynamic stabilization, metabolic control, and antibiotic therapy; minimally invasive (MI) approach with either percutaneous drainage (PCD) or ureteral stent placement based on radiologic findings and the treating urologist preference; and surgical therapy such as open drainage or nephrectomy. Nephrectomy was performed when MM and MI were insufficient to control the infectious process.

Patient's characteristics were compared among the 3 different institutions using 1-way analysis of variance for continuous variables and chi-square for categorical variables. Patients were grouped as diabetics and nondiabetics to search for an association between this comorbidity and mortality. Predisposing factors for nephrectomy were studied. We also compared features between survivors and nonsurvivors using Student's *t* and Kruskal-Wallis tests. We performed univariate and multivariate logistic regression analyses to determine prognostic factors associated with mortality. SPSS v.20 was used for the statistical analysis, and a *P* value of $<.05$ was consider to indicate statistical significance.

RESULTS

A total of 62 patients were included in the analysis. Table 1 shows the characteristics according to each of the 3 institutions. Fifty patients (80.6%) were female. Mean age was 53.9 years (23-78 years). Left and right side were affected in 56.5% and 37%, respectively, whereas bilateral affection was noted in 6.5%. All patients presented to emergency room with systemic inflammatory response, with 70.9% having leukocytosis and 25.8% thrombocytopenia. Mean biochemical findings are shown in Table 2.

The most common radiological category was Huang 1 in 19 cases (30.6%), followed by Huang 2 in 17 (27.4%), 3a in 6 (9.7%), 3b in 13 (20.9%), and type 4 in 7 patients (11.3%). Other computed tomographic findings consisted

Table 2. Mean biochemical findings

Parameter	Mean	SD
Glycemia (mg/dL)	246.4	208.02
WBC (K)	15.93	7.23
Platelet (K)	240.3	139.54
Creatinine (mg/dL)	2.61	1.94
eGFR (mL/min/1.73 m^2)	40.34	33.07

SD, standard deviation; WBC, white blood cells; other abbreviation as in Table 1.

of lithiasis in 50%. Microbiological cultures showed *Escherichia coli* as the most common pathogen (62.7%).

The management strategy and outcomes are described in Supplementary Figure 1. MM was provided to 24.2%; MI treatment to 51.6% (ureteral stent in 23, PCD in 8, and one requiring both); open drainage to 19.3%; and emergency nephrectomy to 4.8%. In addition, 5 patients required subsequent interventions, including 1 open drainage, 3 emergency nephrectomies, and 1 open drainage and nephrectomy.

Of 62 patients, 43 had diabetes, and 19 were nondiabetic. At admission, diabetics had higher serum glycemia (307 vs 108 mg/dL; $P = .0001$) and lower estimated glomerular filtration rate (34 vs 53 mL/min/1.73 m^2; $P = .03$). Huang 2 category was also most common among diabetic patients (59% vs 5%; $P = .01$). On the other hand, the frequency of lithiasis was higher in nondiabetics (79% vs 37%; $P = .005$). Mortality was similar between both groups.

We grouped patients according radiological classification (Huang type 1 vs Huang type 2, 3a, 3b, and 4) to determine if emphysematous pyelitis has a better prognosis. No statistically significant differences were found in mortality (2 of 19 vs 7 of 43, $P = .55$) between patients with emphysematous pyelitis and those with other types of EPN.

After comparing all features among institutions (Table 1), the only significant differences were leukocyte count and proportion of MM and surgical treatment. MM was more frequently performed at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, nephrectomy was more used at Instituto de Seguridad Social del Estado de México y Municipios, and open drainage at Hospital General de México Eduardo Liceaga. Nevertheless, there were no statistical differences in mortality rates among institutions ($P = .58$). Overall mortality was 14.5%. Mortality rates among definitive management strategies were similar comparing MM, MI, and surgical therapy ($P = .06$) and also between those who underwent nephrectomy compared with other types of treatment ($P = .056$).

Table 3 shows clinical, radiological, biochemical, and treatment differences between survivors and nonsurvivors. Nonsurvivors tend to be older (63.8 vs 52.2, $P = .004$) with higher creatinine levels (4.5 vs 2.3, $P = .002$) at initial evaluation. Also, nephrectomy was most commonly performed among this group (33.3% vs 7.5%, $P = .024$). No other analyzed variable was significantly associated with the need for nephrectomy. Interestingly, there was no difference in mortality rates when comparing Huang categories ($P = .55$).

In univariate analysis, we found that age (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.02-1.21, $P = .009$), creatinine (OR 1.53, 95% CI 1.11-2.1, $P = .009$), and the need for nephrectomy (OR 6.12, 95% CI 1.09-34.21, $P = .03$) were associated with mortality. Multivariate logistic regression analysis demonstrated that creatinine and nephrectomy remained as significant risk factors for mortality (Table 4).

COMMENT

To our knowledge, this is the largest published series of EPN. One of the main strengths is the inclusion of patients from 3 care centers with different strategies for EPN management. The overall mortality was similar to that recently reported,[7,9,10] and demographic characteristics are in line with previous reports. In a meta-analysis by Falagas et al, most patients were women (85.4%).[5] The frequency of type 2 diabetes is high, ranging from 69% to 85%.[2,7,11,5] Despite comorbidities that may compromise survival because of pre-existing renal failure and impairment of metabolic response to septic process, our results showed that diabetes did not impact mortality.

Others and we have previously investigated the risk factors associated with poor outcome. Wan et al[1] evaluated radiological characteristics and their role in prognosis. Later, Huang and Tseng[2] analyzed a single-center series of 48 patients with EPN and found that thrombocytopenia, acute kidney injury, disturbance of consciousness, and shock were associated with mortality. They also noted that mortality was higher as long as EPN radiological category increased. Furthermore, Falagas et al[5] concluded that conservative management, bilateral disease, EPN type I category (according Wan radiological classification[1]), and thrombocytopenia were associated with increased mortality. In a previous report from one of our institutions, we found that altered consciousness, multiple organ failure, hyperglycemia, and elevated leukocyte count were more frequent in nonsurvivors.[9] This multicentric study showed in multivariate analysis that higher creatinine levels and nephrectomy were significantly associated with mortality.

Excluding the association between nonsurvivors and nephrectomy, we did not find any correlation between clinical, radiological, and biochemical features and the need for nephrectomy. No clinical and biochemical differences were found between those who underwent emergency nephrectomy and patients who required it after unsuccessful MM and MI treatment. This could reflect the subjective decision to perform a nephrectomy, and it shows the absence of standardization in the definitive management among the 3 institutions. However, nephrectomy should be avoided because it is associated with poor outcome.

Table 3. Analysis comparing survivors vs nonsurvivors

Variable	Survivors	%	Nonsurvivors	%	*P* Value
Patients	53	85.5	9	14.5	
Gender (F/M)	43/10		7/2		.81
Age (y)	52.2		63.8		.004
Huang-Tseng classification	17	32.07	2	22.22	.55
	16	30.18	1	11.11	.23
	4	7.54	2	22.22	.17
	10	18.86	3	33.33	.32
	6	11.32	1	11.11	.98
Lithiasis	29	54.70	2	22.22	.74
Glycaemia (mg/dL)	234		318		.49
Leukocyte number (K)	15.2		18		.16
Platelet count (K)	250		179		.97
Thrombocytopenia	12	22.64	4	44.44	.17
Mean creatinine (mg/dL)	2.3		4.5		.002
Mean eGFR (mL/min/1.73 m^2)	44.9		13.4		.007
Medical management alone	14	26.41	1	11.1	.32
Minimal invasive management	28	52.83	4	44.4	.27
Open drainage	10	18.86	4	44.4	.09
Nephrectomy	4	7.54	3	33.3	.024

Abbreviation as in Table 1.

Table 4. Multivariate analysis of factors associated with mortality

Risk Factor	Odds Ratio	95% CI	*P* Value
Age	1.11	0.993-1.248	.065
Creatinine level	1.56	1.034-2.35	.034
Nephrectomy	9.70	1.007-93.513	.049
Thrombocytopenia	0.54	0.06-4.95	.58
Huang classification	0.89	0.46-1.72	.74

CI, confidence interval.

It can be postulated that increased serum creatinine is associated with extensive parenchymal damage. Nevertheless, it could be because of subjacent chronic renal impairment commonly found in long-term diabetic patients or those critically ill experiencing multiple organ failure. Recently, other authors have suggested that MI treatment has better results[12] and that nephrectomy could be associated with worst outcome.[7,13] However, this finding could be the result of a selection bias, reflecting that patients undergoing surgery have more advanced EPN and do not necessarily imply that nephrectomy is deleterious.

Unfortunately, the recommended EPN management strategies are derived from retrospective series using different definitions, severity scales, and variables rendering difficult the standardization of criteria.[14-17] Thus, we believe that treatment should be individualized and MM should be aggressive according recent guidelines for management of sepsis.[18] On the basis of our experience, we propose the following management algorithm (Supplementary Fig. 2). All patients should undergo hemodynamic stabilization and broad-spectrum antibiotics such as third-generation cephalosporins or carbapenems. The need for ureteral stent placement or PCD should be considered based on radiological findings and the patient's clinical status to control the source of infection. Open drainage could be used in selected cases, in which large and pararenal collections are found. It could be an option in institutions in which percutaneous facilities are lacking. In the absence of hydronephrosis of fluid collections MM could be a safe and successful strategy. Clinical monitoring should always be taken into consideration, and reassessment of any MI intervention must be ruled out. Intravenous antibiotics should be prescribed for at least 14 days. Emergency nephrectomy should always be the last resort of treatment. We recommend combining different MI strategies before emergency nephrectomy. After the acute EPN episode, all patients must be re-evaluated to determine kidney function and provide definitive treatment of the predisposing cause.

Interestingly, the highest mortality rate was seen in Instituto de Seguridad Social del Estado de México y Municipios (23% vs 10%-14%), although it was not statistically significant, it draws the attention because 5 of 7 nephrectomies of the entire series were performed at this institution. This suggests the negative impact of surgery to resolve the infectious process or a more aggressive disease reflected by the highest leukocyte count.

The principal limitation of the present study is the retrospective nature and the small number of patients included in every health care center, albeit it is difficult to include a large number of patients in prospective series of this rare entity. The heterogeneity of nephrectomized patients could be a limitation of the statistical analysis. Although performed in patients who did not resolve infectious process, no specific surgical indication was followed. The multicentric nature of this investigation precluded us to obtain full data to make an analysis regarding "Surviving Sepsis guidelines".[9,18]

CONCLUSION

Prognosis of patients with EPN has changed over the last years. Mortality has declined with aggressive MM and MI strategies. Mortality rates were similar among the 3 health care centers despite the different proportion of treatment strategies used. Nonsurvivors tend to be older with higher creatinine values at initial evaluation. Also, compared with survivors they were more commonly managed with emergency nephrectomy.

Creatinine level at initial workup and the need for nephrectomy are the strongest predictors of mortality. The radiological classification of Huang did not have impact in overall mortality. Emphysematous pyelitis should also be considered a life-threatening condition. We suggest that emergency nephrectomy should be performed only if aggressive MM and MI strategies are insufficient to control the infectious process.

References

1. Wan YL, Lee TU, Bullard MJ, et al. Acute gas producing bacterial renal infection: correlation between imaging findings and clinical outcome. *Radiology*. 1996;198:433-438.
2. Huang JJ, Tseng CC. Emphysematous pyelonephritis: clinicoradiological classification, management, prognosis, and pathogenesis. *Arch Intern Med*. 2000;160:797-805.
3. Schultz EH Jr, Klorfein EH. Emphysematous pyelonephritis. *J Urol*. 1962;87:762-766.
4. Pontin AR, Barnes RD. Current management of emphysematous pyelonephritis. *Nat Rev Urol*. 2009;6:272-279.
5. Falagas ME, Alexiou VG, Giannopoulou KP, et al. Risk factors for mortality in patients with emphysematous pyelonephritis: a meta-analysis. *J Urol*. 2007;178:880-885.
6. Ubee SS, McGlynn L, Fordham M. Emphysematous pyelonephritis. *BJU Int*. 2011;107:1474-1478.
7. Kapoor R, Muruganandham K, Gulia AK, et al. Predictive factors for mortality and need for nephrectomy in patients with emphysematous pyelonephritis. *BJU Int*. 2010;105:986-989.
8. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.
9. Olvera-Posada D, Garcia-Mora A, Culebro-García C, et al. Prognostic factors in emphysematous pyelonephritis. *Actas Urol Esp*. 2013;37:228-232.
10. Fatima R, Jha R, Muthukrishnan J, et al. Emphysematous pyelonephritis: a single center study. *Indian J Nephrol*. 2013;23:119-124.
11. Aswathaman K, Gopalakrishnan G, Gnanaraj L, et al. Emphysematous pyelonephritis: outcome of conservative management. *Urology*. 2008;71:1007-1009.
12. Somani BK, Nabi G, Thorpe P, et al. Is percutaneous drainage the new gold standard in the management of emphysematous pyelonephritis? Evidence from a systematic review. *J Urol*. 2008;179:1844-1849.
13. Dhabalia JV, Nelivigi GG, Kumar V, et al. Emphysematous pyelonephritis: tertiary care center experience in management and review of the literature. *Urol Int*. 2010;85:304-308.
14. Chen MT, Huang CN, Chou YH, et al. Percutaneous drainage in the treatment of emphysematous pyelonephritis, 10 year experience. *J Urol*. 1997;157:1569-1573.
15. Chan PH, Kho VK, Lai SK, et al. Treatment of emphysematous pyelonephritis with broad spectrum antibiotics and percutaneous drainage. An analysis of 10 patients. *J Chin Med Assoc*. 2005;68:29-32.
16. Tsu JH, Chan CK, Chu RW, et al. Emphysematous pyelonephritis: an 8-year retrospective review across four acute hospitals. *Asian J Surg*. 2013;36:121-125.
17. Kuzgunbay B, Turunc T, Tokmak N, et al. Tailored treatment approach for emphysematous pyelonephritis. *Urol Int*. 2011;86:444-447.
18. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. 2012. *Crit Care Med*. 2013;41:580-637.

APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2014.02.010.