Original Research Paper

Volume : 5 | Issue : 10 | October 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Gender Based Comparison of Clinical, Laboratory and Renal Function Parameters in Diabetic Patients with Acute Pyelonephritis

Medical Science

KEYWORDS : Diabetes, Acute pyelonephritis, Male, Female, Treatment response

Dr. Shailesh C. Trivedi Consultant Physician, Anand Hospital, Nizampura, Vadodara, Gujarat, India

Dr. Vijay M. Katekhaye Physician, Dev Clinic, Ayachit Mandir Road, Mahal, Nagpur, Maharashtra. India

ABSTRACT

Introduction

Diabetes mellitus (DM) is important risk factor for poor outcomes in acute pyelonephritis (APN). Gender based differentiation of APN in terms of clinical manifestations and treatment outcomes defined by laboratory and renal function changes remains to be explored.

***Objective**: To compare clinical manifestations and assess treatment efficacy by laboratory and renal function parameters in diabetic males and females with APN*

***Materials and Methods**: In a retrospective analysis, data of diabetic patients with APN was analysed. Clinical manifestations were compared in two genders. Treatment efficacy was compared in two genders as assessed by changes in laboratory parameters like pyuria, haematuria, total leucocyte count, C-reactive protein, and renal function with changes in serum creatinine and estimated glomerular filtration rate.*

***Results**: In 39 patients, 23 (58.9%) were females and 16 (41.1%) were males. No differences in two genders for clinical presentation were seen except for flank pain being significant in females than males (34.8% Vs 6.3%, p=0.038). Hospital stay (p=0.062) and duration of intravenous antibiotics (p=0.170) did not differ in two genders. Cefaperazone-sulbactam was the most used antibiotic in males (93.8%) and females (100.0%). After a mean follow-up of 15.5±4.63 days, treatment was associated with significant improvement in haematuria (p<0.0001), leucocyte counts (p<0.0001), CRP (p<0.0001), serum creatinine (p=0.002) and eGFR (p=0.035) only in females but not in males. Rise of serum creatinine from baseline was seen in 10 (25.6%) cases (7 males and 3 females) with 4 males having 30% or more rise of creatinine levels.*

***Conclusion**: Despite similar clinical presentation, improvements were significant in females than males. Renal function changes in APN may be frequent in males. This gender-based difference in treatment outcome and impact of renal function to treatment response require detailed evaluation in a prospective, long-term, clinical trial.*

INTRODUCTION

Acute pyelonephritis (APN) is the renal infection which is characterised by the acute interstitial inflammation and tubular necrosis. It can range from mild infection to abscess and emphysematous form.(1) In outpatient and in-patients setting, reported annual incidence rates of APN were 12-13 and 3-4 per 10,000 population in females respectively and 2-3 and 1-2 per 10,000 population in males respectively.(2) Only few reports describe APN exclusively in males. (3) Diabetes mellitus (DM) is one of the most important risk factor for APN. It is associated with increased risk of hospitalization and poorer outcomes. (4–6) Further, diabetes adds substantially to the development of complications. (7) Recent evaluation of APN in females reported that diabetes was associated with more severe disease and prolonged hospital stay though the clinical failure rate and mortality did not differ significantly from non-diabetic females.(8)Treating APN is usually based on antimicrobial therapy guided by local sensitivity and resistance pattern. Initial treatment with intravenous administration regime is recommended especially in females. (9)

Acute renal failure in the setting of APN have been reported previously.(10,11) But the presence of renal dysfunction in APN patients with DM may be due to renal injury from DM. Renal function derangements are not uncommon and chronic kidney disease (CKD) may be coexisting in many cases of APN. Significant association of CKD and azotemia have been reported in diabetic females with APN. (8) Though improvements in clinical, laboratory parameters and renal function are expected with treatment, gender-specific treatment outcomes and renal function changes in APN remain to be explored. We aimed to compare the clinical presentation, treatment outcomes and renal function changes in males and females with diabetes after treatment of APN.

MATERIALS AND METHODS

A retrospective, observational, comparative study was conducted at a private, tertiary referral care centre for diabetes from Gujarat, India. Patient population catering to this centre is from rural as well as urban parts of the Gujarat state. Patients included in the study were adults above 18 years with type 2 diabetes who had developed APN. All patients were hospitalized at the diagnosis of APN. Patients with follow-up after initial hospitalization and renal function assessment data being available were included in final analysis.

Baseline clinical assessment of patients were done at initial hospitalization. Demographic data included age, gender, residence (urban/rural), etc., presenting symptoms of APN like fever, lower urinary symptoms such as dysuria, burning micturition, etc., flank pain, back pain, generalised weakness, nausea with or without vomiting etc. were recorded. Laboratory evaluations were performed as a part of clinical assessment of APN. Complete blood hemogram including total and differential leucocyte counts, and routine as well as microscopic urinary examination were performed. Pyuria was defined as presence of more than 10 leucocytes per high power field (hpf) by microscopy. Haematuria was defined as more than 5 red blood cells per hpf. Renal function assessment was done by serum creatinine and estimated glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease (MDRD) equation. Based on eGFR, CKD was staged as mild CKD (eGFR: 60 - 89), moderate CKD (eGFR: 30 - 59), severe CKD (eGFR: 15 - 29) and end-stage renal disease (eGFR: < 15). We also assessed change of serum creatinine from baseline to follow-up. Proportion of patients who had no change and either increase or decrease of serum creatinine were assessed. Inflammatory markers assessed in patients were erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Data of these parameters available from database was taken in final analysis.

APN patients were treated according to the guideline-directed therapy. The choice antibiotics was done as per local culture-sensitivity and resistance reports. Total number of antibiotics and type of antibiotic in each patient was assessed and analyzed. Effectiveness of prescribed treatment was assessed in terms of improvements in objective parameters like pyuria, haematuria, total leucocyte counts, ESR, and CRP. Further, change of kidney function after treatment was assessed by serum creatinine and eGFR. A gender specific comparison was performed to look for differences in clinical and laboratory abnormalities as well as treatment response in APN among two genders.

Statistical Analysis

Data was compiled in Microsoft Excel 2007. Continuous variables were presented as means and standard deviations (SD) or median with inter-quartile range (IQR) of 25% to 75% where appropriate. Frequency and percentages were used to represent categorical variables. Means were compared by independent sample t test or Mann-Whitney U test where necessary. Fishers exact test or Chi-square comparisons were used for categorical variables. Wilcoxon signed rank sum test was used to assess difference in continuous variables whereas McNemar test was used to compare differences in dichotomous variables at baseline and follow-up. P-value less than < 0.05 was considered significant for all the comparisons. Analyses were performed using R-software.

RESULT

In 39 patients, mean age of the population was 55.23 years and 59% were females with majority (82.1%) from urban region. Fever (82.1%) was most common symptom followed by aches and pain (64.1%), dysuria (53.8%) among others as summarized in table 1. There were no differences in symptoms in males and females except for flank pain which was higher in females than males (34.8% Vs 6.3% respectively, p=0.038). Duration of intravenous antibiotics administration (7.13 days) was almost similar to the mean duration of hospital stay (7.38 days) with no difference among two genders. However, females frequently necessitated treatment with two or more antibiotics as compared to males and the difference in proportions was significant (p=0.022) (table 2). Cefaperazone-sulbactam (97.4%) was most frequent antibiotic in overall population and two genders. Most antibiotics used were against gram-negative organisms and included amikacin (41.0%), meropenem (10.3%), ceftriaxone (5.1%) with ertapenem, and colistin in one case each.

Mean follow up duration in was 15.5±4.63 days. Treatment efficacy assessed in terms of corrections of laboratory abnormalities and renal function is summarized in table 3. Haematuria (p<0.0001), total leucocyte count (p<0.0001), CRP (p<0.0001), serum creatinine (p=0.002) and eGFR (p=0.005) significantly improved as compared to baseline. Significant improvements in renal function occurred. Proportion of patients with mild CKD improved from 61.5% at baseline to 74.4% at follow up and severe CKD reduced to none from baseline proportion of 12.8%. Compared to baseline, no change in serum creatinine was observed in 17.9% patients at follow up whereas reduction of 10 to 20%, 20 to 30% and >30% was seen in 25.6%, 15.4% and 15.4% patients respectively at follow-up evaluation. A rise of serum creatinine was seen in 25.6% cases. Such rise of 30% from baseline was seen in 10.3% cases at follow-up (mean levels 0.89±0.36 and 1.27±0.45 mg/dL respectively). From among 10 cases of rise in creatinine levels, 7 were males and of these 3 had increase of 30% and above from baseline (data not shown in table).

Treatment efficacy stratified by gender is shown in table 4. In males, though the improvements were seen, statistical significance was not reached for any of the assessment parameter. Pyuria, haematuria, leucocyte counts non-significantly reduced from baseline to follow-up. Kidney function improved slightly as suggested by slight reduction in serum creatinine and non-significant improvement in eGFR improved. Contrast to males, females had significant reduction in haematuria, leucocyte count, CRP (all p<0.0001) with exception of pyuria (p=0.180). Renal function also improved with significant reduction in serum creatinine level (p=0.002) and increase in eGFR (p=0.035). There were no complications in any patient and no deaths occurred during follow-up period.

DISCUSSION

Diabetes mellitus is known risk for APN and is associated with increased morbidity and mortality in APN. Higher incidence of APN in females than males can lead to complications and poor outcomes in diabetic women. Gender specific differentiation of APN thus becomes essential the factors contributing to disease progression and increased hospital stay are different.(12) Although the risk factors and factors associated with mortality have been evaluated in previous studies, gender specific treatment outcomes are not studied. In our study, females outnumbered males with as reported previously.(13,14) We found no difference in clinical symptoms of males and females except for flank pain being significantly higher in women (34.8%) than men (6.3%). Also, hospital stay did no differ in two genders. In a similar gender specific comparative study, Muneishi et al. reported frequent lower abdominal pain (p=0.035) and vomiting/diarrhoea (0.020) in females than males and the duration of hospital stay was similar in two genders (8 days in females and 9 days in males, p=0.071). However, this study involved both diabetic and non-diabetic population.(12) Though clinical manifestations were similar, treating females (78.3%) necessitated two or more antibiotics more frequently than males (56.9%). Initial antibiotics as selected by bacterial sensitivity are recommended by IV route.(9) Beta-lactam were frequent although non-beta lactam antibiotics were also identified be sensitive. Gram-negative bacteria especially *Escherichia coli* are common isolates from APN cases. A study reported equal clinical effectiveness of non-carbapenem antibiotics like aminoglycosides, fluoroquinolones, etc. as that of carbapenems in *E. coli* producing extended spectrum beta-lactamase isolated from APN patients. (15) Lu et al also reported most frequent use of third-generation cephalosporins (40.9%) as initial antibiotic in cases of emphysematous APN.(16) Treatment of APN in our study was associated with significant improvements in haematuria (p<0.0001), total leucocyte count (p<0.0001), CRP (p<0.0001), and serum creatinine (p=0.002). This dictates selection of antibiotics guided by local sensitivity patterns. Inappropriate antibiotic therapy was reported as one of the factor leading to poorer outcomes.(16)

Gender stratified treatment efficacy analysis suggested a better response in females than males. Except for pyuria, improvements in haematuria, leucocyte count, CRP levels, serum creatinine and eGFR were significant in females but not in males for any of these parameters. This could be due to two reasons. Firstly, number of males were lesser so as to identify a difference in these parameters at follow up. Secondly, males may behave differently to the treatment than females and have poorer outcomes. This is supported by the finding that male sex has been reported to be a risk factor for increased mortality (odds ratio 11.75, 95% confidence interval 1.22 to 113.0, p=0.033) in a multivariate analysis of APN. (17)This finding need to be explored further in

Volume : 5 | Issue : 10 | October 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

large, prospective study.

APN may differentially impact renal function. Chung et al. reported deranged renal function to be independent predictor of mortality in APN (p=0.045). (17) But other reports suggest no association of renal dysfunction in predicting good or poor outcome.(13) Treatment in our study was associated with significant improvement in renal function (p=0.012) as measured by eGFR. However, renal dysfunction in APN may persist, improve or progress.(14) We observed rise of serum creatinine in 10 cases which was majorly seen in males than females. Whether this association exposes males to a greater risk of poorer outcomes need to be studied further. Also, the impact of diabetes on renal function need to be considered while associating this finding in males. Use of aminoglycosides were frequent in our study which might also contribute to the change in renal function.

STRENGTHS AND LIMITATIONS

Our study is first of its kind comparing clinical manifestations and renal function outcomes in diabetic males and females with APN. The study sheds light on important aspects as studies comparing outcomes of APN in males with diabetes are lacking. Further, importance of treatment based on culture and sensitivity is essentially noted as there were no mortality outcomes. Also, our study provides new hypothesis for prospective studies as to assessing impact of renal function on outcomes and to assess gender stratified outcomes in diabetics with APN. Our study had few limitations like retrospective design, limited sample size, insufficient data for some parameters. We did not assess effect of confounders like diabetes, drugs, body weight, and comorbidities on renal function in both genders. A short follow-up may not have provided a complete outcome assessment in terms of mortality and renal function which can be ascertained in long term follow-up.

CONCLUSION

Diabetes being an established risk factor for poorer outcomes in APN, a gender-wise differentiation in diabetic APN suggested better treatment outcomes in females than males. Improvements in haematuria, leucocytosis, CRP, serum creatinine and eGFR were significant in females than males despite no differences in clinical manifestations, duration of antibiotics and hospital stay in two genders. A rise in creatinine from baseline was more frequent in males than females. These findings need detailed evaluation in a large, prospective, randomized trial with long term follow-up of diabetic patients with APN.

Source of Support: Nil

Conflict of Interest: None

Table 1: Baseline characteristics of study population

Characteristics	Total (n=39)	Males (n=16)	Females (n=23)	P value
Age (mean/SD)	55.23±12.75	59.06±11.25	52.57±13.28	0.119
Urban residence (%)	32 (82.1)	12 (75.0)	20 (87.0)	0.339
Clinical Symptoms				
Fever	32 (82.1)	14 (87.5)	18 (78.3)	0.460
Aches and Pains	25 (64.1)	11 (68.8)	14 (60.9)	0.614
Dysuria	21 (53.8)	9 (56.3)	12 (52.2)	0.802
Vomiting	19 (48.7)	8 (50.0)	11 (47.8)	0.894
Backache	16 (41.0)	7 (43.8)	9 (39.1)	0.773
Headache	10 (25.6)	2 (12.5)	8 (34.8)	0.117
Flank Pain	9 (23.1)	1 (6.3)	8 (34.8)	0.038*
Frequent micturition	6 (15.4)	4 (25.0)	2 (8.7)	0.165
Insulin treatment	34 (87.2)	13 (81.3)	21 (91.3)	0.356
Hospital stay (days)	7.38±3.64	8.69±4.66	6.48±2.46	0.062
Prolonged stay (≥ 10 days)	7 (17.9)	5 (31.3)	2 (8.7)	0.101
Duration of IV antibiotics (days)	7.13±3.52	8.06±4.56	6.48±2.46	0.170

IV: Intravenous, Data presented as mean±SD or Frequency and percentages. *p<0.05

Table 2: Antibiotic prescribed in study population

Antibiotics	Total (n=39)	Males (n=16)	Females (n=23)	P value
Total				
1	12 (30.8)	7 (43.8)	5 (21.7)	0.022
2	22 (56.4)	5 (31.3)	17 (73.9)	
3	5 (12.8)	4 (25.0)	1 (4.3)	
Individual Antibiotic				
Cefaperazone-Sulbactam	38 (97.4)	15 (93.8)	23 (100.0)	-
Amikacin	16 (41.0)	4 (25.0)	12 (52.2)	-
Metronidazole	5 (12.8)	1 (6.3)	4 (17.4)	-
Meropenem	4 (10.3)	2 (12.5)	2 (8.7)	-
Ceftriaxone	2 (5.1)	1 (6.3)	1 (4.3)	-
Ertapenem	1 (2.6)	1 (6.3)	-	-
Colistin	1 (2.6)	1 (6.3)	-	-
Levofloxacin	1 (2.6)	1 (6.3)	-	-

Data presented as frequency and percentages

Table 3: Changes in laboratory parameters after treatment in study population

Characteristics	N*	Baseline	At Follow-up	P value
Follow-up duration (days)		-	15.5±4.63	-
Pyuria	39/32	27 (69.20)	18 (56.25)	0.180
Haematuria	39/39	27 (69.20)	3 (7.7)	<0.0001
Haemoglobin (gm%)	39/30	10.8 [9.8 – 12.1]	11.05 [9.8 – 12.3]	0.608
Leucocyte count (cells/cmm)	39/30	9200 [7100 - 11400]	6750 [5375 - 8850]	<0.0001
ESR (mm/hr)	39/30	46 [22 - 70]	41.5 [25 - 54]	0.156
CRP (mg/dL)	39/35	65 [40 - 104]	5 [1 - 23]	<0.0001
Serum creatinine (mg/dL)	39/39	0.98 [0.69-1.52]	0.81 [0.60 – 1.2]	0.002
eGFR (mL/min/1.73 m^2)	39/39	73.3 [47.3 – 106.9]	91.3 [59.8 – 116.1]	0.005
CKD Stage	39/39			
Mild (eGFR: 60-89.99)		24 (61.5)	29 (74.4)	0.012
Moderate (eGFR:30-59.99)		9 (23.1)	9 (23.1)	
Severe (eGFR:15-29.99)		5 (12.8)	-	
End-stage (eGFR:<15)		1 (2.6)	1 (2.6)	

Serum Creatinine				
No change		-	7 (17.9)	
% Reduction			22 (56.4)	
10% to 20%		-	10 (25.6)	
20% to 30%		-	6 (15.4)	
>30%		-	6 (15.4)	
% Increase			10 (25.6)	
<10%		-	4 (10.3)	
10% to 20%		-	0	
20% to 30%		-	2 (5.1)	
>30%		-	4 (10.3)	

Data presented as frequency and percentages (circular brackets) or median with interquartile range (IQR) 25-75% [Square brackets]. ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, CKD: Chronic kidney disease.

Table 4: Changes in laboratory parameters with treatment in two genders

Characteristics	Males				Females			
	N*	Baseline	At Follow-up	P value	N*	Baseline	At Follow-up	P value
Pyuria	16/11	8 (50.0)	5 (45.5)	1.000	23/21	19 (82.6)	13 (61.9)	0.180
Haematuria	16/16	8 (50.0)	2 (12.5)	0.070	23/23	19 (82.6)	1 (4.3)	<0.0001
Leucocyte count (cells/cmm)	16/10	9150 [7100 - 13650]	7050 [5525 - 9150]	0.086	23/20	9300 [7300 - 10800]	6700 [5175 - 8925]	<0.0001
CRP (mg/dL)	16/14	53.5 [6 – 95.75]	12.5 [4.75 – 66.25]	0.162	23/21	72 [61 - 178]	2.0 [1.0 - 7.0]	<0.0001
Serum creatinine (mg/dL)	16/16	1.26 [0.93-1.57]	1.17 [0.90 – 1.39]	0.330	23/23	0.80 [0.60 -1.50]	0.57 [0.63 - 0.90]	0.002
eGFR (mL/min/1.73 m^2)	16/16	64.9 [49.6 – 97.5]	67.9 [55.8 – 98.1]	0.778	23/23	81.3 [39.0 - 107.0]	103.2 [70.7 -120.4]	0.035

Data presented as frequency and percentages (circular brackets) or median with interquartile range (IQR) 25-75% [Square brackets]. ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, CKD: Chronic kidney disease

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