Original Article

DOI: 10.7860/JCDR/2016/22830.8720

Retrospective Comparison of Clinical Characteristics and In-Hospital Outcomes among Diabetic and Non-Diabetic Adults with Acute Pyelonephritis

Internal Medicine Section

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ABSTRACT

Introduction: Acute Pyelonephritis (APN) is a common infection in community. Diabetes Mellitus (DM) may have different effect on clinical characteristics and outcomes of APN compared to non-diabetic individuals.

Aim: To compare clinical characteristics and assess outcomes of APN patients with and without DM.

Materials and Methods: A retrospective analysis of 122 patients with DM (n=61) and without DM (n=61) was conducted at a single, private, urban set-up from Gujarat, India. Clinical symptoms, laboratory investigations, antibiotics treatment and outcomes in terms of mortality and prolonged hospitalization (10 days and above) were compared in two groups.

Results: Mean age was significantly higher in diabetics than non-diabetics (55.2±12.5 vs 41.5±17.3, p<0.0001) and females were proportionally higher in both groups (65.6% Vs 62.3%, p=0.706). Fever was most frequent symptom (83.6% Vs 90.2%, p=0.283) followed by nausea/vomiting (50.8% Vs 63.9%, p=0.143), dysuria (66.7% Vs 74.4%, p=0.433) and flank pain (8.2 Vs 13.1, p=0.379). Backache/back pain (47.5% Vs 29.5%, p=0.041) and Chronic Kidney Disease (CKD) (63.9% Vs 45.9%, p=0.045) were significantly higher in diabetics than non-diabetics. Mean hospital stay did not vary significantly in two groups (7.0±3.2 Vs 6.50±2.9, p=0.346) but proportion of patients with longer hospital stay was higher in DM (16.4% Vs 8.2%). Elevated white cell count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine and presence of red cell in urine (> 5/ high power field [hpf]) did not vary significantly in two groups. Cephalosporin-beta-lactamase inhibitor (Cefaperazone-Sulbactam/Cefepime-Tazobactam) was the most prescribed antibiotic in both the groups. No deaths were observed in any group during this evaluation period. Only raised ESR (>30 mm/hr) {Odds Ratio (OR): 1.58, 95% Confidence Interval (CI) 1.36-1.82, p=0.004} and presence of CKD (OR: 1.71, 95% CI 1.30-2.25, p=0.008) were found to be the significant predictors of prolonged hospitalization in overall population.

Conclusion: APN in diabetic and non-diabetic patients has similar clinical characteristics. Impact of diabetes on clinical outcomes of mortality and prolonged hospitalization warrants further investigation in a large, randomized, prospective trial.

Keywords: Chronic kidney disease, Prolonged hospitalization, Risk predictors

INTRODUCTION

Acute Pyelonephritis (APN) forms a part of progressive renal infection wherein mild infection can progress to APN leading to abscess or emphysematous pyelonephritis. Usually the result of ascending infection, APN is associated with acute tubule-interstitial and tubular cell necrosis [1]. Recent community survey identify Urinary Tract Infections (UTIs) as second most common infections after respiratory tract infections in diabetic patients [2]. APN is one of the common infections in community. Estimates suggests incidence rate of 15 to 17 cases per 10,000 population in the United States [3]. Similarly, annual incidence rate reported from South Korea was 35.7 cases per 10,000 populations with 59% females being affected [4]. APN requiring hospitalization is five-times more frequent in females than males [5,6].

Risk factors identified for increased risk of APN include extremes of ages, anatomical or functional abnormalities of kidneys, obstructive uropathies, presence of diabetes mellitus (DM), immunosuppressed conditions, and pregnancy [5]. Diabetes is one of the important risk factors associated with poor outcomes and poses higher risk of complications in APN [7–9]. Given the influence of diabetes on course of APN, the clinical presentation and outcomes of APN in diabetics can be different than non-diabetic population. A prospective study compared APN in diabetic and non-diabetic population but was restricted to female patients [10]. Currently, limited clinical evidence comparing APN in diabetic and non-diabetic patients and involving both sexes exists. Therefore, we planned this retrospective evaluation with objective to compare clinical characteristics of APN patients in diabetic and non-diabetic individuals.

MATERIALS AND METHODS

We retrospectively evaluated APN patients admitted at a private, tertiary care hospital in Gujarat, India. Data of patients from January 2015 to May 2016 who were diagnosed with APN and admitted to our centre were screened for inclusion into the study. Adults above 18 years of either gender with culture-proven APN were included in analysis. We did not restrict to the type of diabetes and both type 1 and type 2 DM were considered for inclusion along with those without DM. Pregnant and lactating females, major co-morbid illness and patients on cancer chemotherapy regimens were excluded. APN was diagnosed based on clinical presentations and laboratory investigations.

Clinical characteristics and demographic data were analysed and compared in diabetic and non-diabetic individuals. 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.

As per protocol, these patients were treated with standard antibiotic regimens given either by intravenous (IV) or oral routes.

Antibiotic selection was based on culture and sensitivity report in all cases. Total number of antibiotics prescribed in each patient were assessed and compared in two groups.

Laboratory evaluations were performed in all patients. Complete haemogram which included Total Leucocyte Counts (TLC) was performed in all patients. Urinary analysis included urinary excretion of pus cells, red blood cells (RBCs), epithelial cells. Haematuria was defined as presence of RBCs of 5 or more per high power field. Renal function assessment was performed with blood urea nitrogen assessment and serum creatinine determination. Chronic Kidney Disease (CKD) stage was evaluated based on estimated glomerular filtration rate (eGFR – mL/min/1.73m^2) assessed by the Modification of Diet in Renal Disease (MDRD) formula. Patients were graded in five stages of CKD as stage I (eGFR ≥ 90), II (60 - 89), III (30 - 59), IV (15 - 29) and V (< 15). However, for evaluation purpose grading was done as mild CKD (eGFR: 60 - 89), moderate CKD (eGFR: 30 - 59), severe CKD (eGFR: 15 - 29) and end-stage renal disease (eGFR: < 15). Data on inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were assessed in all patients as a standard protocol followed at the hospital.

We also collected data on hospital stay expressed in terms of days of stay in the hospital. In-hospital mortality data was also looked for, in each patient. Factors associated with prolonged hospitalization or mortality were assessed in both the groups and compared. For overall population, we assessed factors predicting the outcome of prolonged hospitalization and mortality.

STATISTICAL ANALYSIS

Data assimilation and organization was performed with use of Microsoft Excel 2007. Data was presented as means and standard deviations for continuous variables. Frequency and proportions were used to represent categorical variables. Means of two groups were compared by independent sample t-test or Mann-Whitney U test where necessary. Fisher's exact-test or Chi-square comparisons were used for categorical variables comparison. Odds Ratio (OR) were estimated with 95% confidence interval limits which were used to describe factors predicting outcomes of prolonged hospitalization and mortality in overall study population. Factors included in OR assessment were age above 65 years, gender, residence, diabetic status, clinical symptoms such as fever, dysuria, nausea and vomiting, and backache, haemoglobin below 10 gm/dL, TLC > 15000 cells/mm^3, ESR > 30 mm/hr, CRP > 20 mg/dL, serum creatinine ≥ 1.5 gm/dL and any CKD level. p-value less than < 0.05 was considered significant for all the comparisons.

Sample size was not predetermined in this study. Being a retrospective, we analysed patients in a confined time period of nearly one-and-half year duration.

RESULTS

Overall, 122 patients were identified and data was analysed. There were equal proportions of patients in diabetic (n=61) and non-diabetic (n=61) groups [Table/Fig-1]. Mean age of patients in diabetic group was higher than non-diabetic population (p<0.0001). Females (63.9%) were more frequently affected than males (36.1%) but the difference in proportions did not reach statistical significance (p=0.706) in two groups.

Clinical characteristics of the patients are summarized in [Table/Fig-2]. Fever (86.9%) was most common presentation of APN with no significant difference between two groups (p=0.283). Dysuria (70.6%), nausea with or without vomiting (57.4%) and general aches and pains (46.7%) were other symptoms. Only backache/back pain was found in significantly higher (p=0.041) proportion of patients in diabetic (47.5%) than non-diabetic (29.5%) group.

Characteristics	Total (n=122)	Diabetic (n=61)	Non-Diabetic (n=61)	p-value
Age (Mean±SD)	48.3±16.5	55.2±12.5	41.5±17.3	<0.0001*
Age ≥ 65 years	19 (15.6)	12 (19.7)	7 (11.5)	0.212**
Gender				
Male (%)	44 (36.1)	21 (34.4)	23 (37.7)	0.706**
Female (%)	78 (63.9)	40 (65.6)	38 (62.3)	
Residence				
Urban	94 (77.0)	50 (82.0)	44 (72.1)	0.196**
Rural	28 (23.0)	11 (18.0)	17 (27.9)	

[Table/Fig-1]: Baseline characteristics in study population and study groups. Data presented as frequency (%) and mean(±SD).
*Two sample t-test; **Chi Square test, p<0.05 significant

Characteristics	Total (n=122)	Diabetic (n=61)	Non-Diabetic (n=61)	p-value#
Clinical Features				
Fever	106 (86.9)	51 (83.6)	55 (90.2)	0.283
Dysuria	60 (70.6)	28 (66.7)	32 (74.4)	0.433
Nausea ± Vomiting	70 (57.4)	31 (50.8)	39 (63.9)	0.143
General Aches and Pains	57 (46.7)	32 (52.5)	25 (41.0)	0.204
Backache/Back pain	47 (38.5)	29 (47.5)	18 (29.5)	0.041
Abdominal Pain*	24 (19.7)	12 (19.7)	12 (19.7)	1.000
Flank Pain	13 (10.7)	5 (8.2)	8 (13.1)	0.379
Headache	25 (20.5)	13 (21.3)	12 (19.7)	0.823
Increased Urinary Frequency	18 (14.8)	11 (18.0)	7 (11.5)	0.307
Chills and Rigors	13 (12.4)	4 (7.8)	9 (16.7)	0.238
Respiratory symptoms**	11 (9.0)	4 (6.6)	7 (11.5)	0.529
Lower Limb Pain	4 (3.3)	1 (1.6)	3 (4.9)	0.619
Reduced Appetite	4 (3.3)	2 (3.3)	2 (3.3)	1.000
CKD	67 (54.9)	39 (63.9)	28 (45.9)	0.045
Mild (eGFR: 60-89.99)	34 (50.7)	20 (51.3)	14 (50.0)	
Moderate (eGFR:30-59.99)	22 (32.8)	12 (30.8)	10 (35.7)	
Severe (eGFR:15-29.99)	10 (14.9)	6 (15.4)	4 (14.3)	
End-stage (eGFR:<15)	1 (1.5)	1 (2.6)	0	
Duration of Antibiotic	6.7±3.1	7.0±3.2	6.5±2.9	0.346
Hospital Stay (days)				
Mean (SD)	6.74±3.1	7.0±3.2	6.50±2.9	0.346
Range	1 to 23	2 to 23	1 to 20	
< 10	107 (87.7)	51 (83.6)	56 (91.8)	0.168
≥ 10	15 (12.3)	10 (16.4)	5 (8.2)	
Laboratory				
Hb<10 gm/dL	35 (28.7)	19 (31.1)	16 (26.2)	0.548
White cell count>15000 cell/mm^3	22 (18.0)	8 (13.1)	14 (23.0)	0.158
ESR>30 mm/h	82 (67.8)	43 (71.7)	39 (63.9)	0.363
CRP>20 mg/dL	94 (77.0)	47 (77.0)	47 (77.0)	1.000
Haematuria (RBC ≥ 5/hpf)	41 (33.6)	23 (37.7)	18 (29.5)	0.338
Creatinine ≥ 1.5 mg/dL	24 (19.7)	11 (18.0)	13 (21.3)	0.649

[Table/Fig-2]: Clinical characteristics in two study groups. Data presented as frequency (%) and mean(±SD).
*Abdominal pain includes any abdominal pain except flank pain – hypogastric pain, hypochondriac pain, epigastric pain, lower abdominal pain, lumbar pain, umbilical pain, etc. **Respiratory symptoms include cough, breathlessness, orthopnoea, etc.
#p-values derived by two-sample t-test and Chi-Square or Fischer-exact-test, p<0.05 significant
CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate (mL/min/1.73m^2), Hb: haemoglobin, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

Overall, CKD was observed in 54.9% of cases and seen in significantly higher proportion in diabetic than non-diabetic patients (63.9% Vs 45.9%, p=0.045). Severe CKD (14.9%) was seen in 15.4% in diabetic and 14.3% in non-diabetic patients.

Prolonged hospitalization (10 days and above) was seen in 12.3% cases with numerically higher number of cases from diabetic

(16.4%) than non-diabetic (8.2%) group (p=0.168). Mean duration of antibiotics did not differ in two groups (7.0±3.2 in diabetic and 6.5±2.9 in non-diabetic patients, p=0.346).

Anaemia (haemoglobin below 10 gm/dL) was found in 28.7% cases and only 18% patients had elevated total leukocyte counts (above 15000 cells/mm^3). Among inflammatory markers, ESR above 30 mm/hour and CRP above 20mg/dl were observed in 67.8% and 77% cases respectively. Greater number of diabetic cases (71.7%) had raised ESR than non-diabetic (63.9%) population but no difference was seen in CRP elevation. Haematuria (33.6%) was relatively more in diabetic cases (37.7%) than non-diabetic (29.5%) cases.

Majority of cases required two antibiotics (58.2%) with higher proportion in diabetic group (63.9%) [Table/Fig-3]. Cefaperazone-sulbactam combination (92.6%) was most common prescribed antibiotic overall as well as in two groups followed by amikacin in 50% of cases. Other antibiotics prescribed are summarized in [Table/Fig-3].

There were no deaths in patients analysed during the stay in hospital. We assessed predictors for prolonged hospitalization (hospital stay 10 days and above). Overall, 15 patients had prolonged hospital stay. Only raised ESR (Odds Ratio (OR) 1.58, 95% confidence interval (CI), 1.36 – 1.82; p=0.004) and presence of CKD (OR 1.71, 95% CI, 1.30 – 2.25; p=0.008) had significant association with prolonged hospitalization [Table/Fig-4]. There were no co-morbidities other than diabetes in any patient and no patient developed any complications resulting from APN.

Antibiotic	Total (n=122)	Diabetic (n=61)	Non-Diabetic (n=61)
Total Antibiotics			
1	40 (32.8)	17 (27.8)	23 (37.7)
2	71 (58.2)	39 (63.9)	32 (52.4)
3	11 (9.0)	5 (8.2)	6 (9.8)
Cefaperazone-Sulbactam	113 (92.6)	59 (96.7)	54 (88.5)
Amikacin	61 (50.0)	28 (45.9)	33 (54.0)
Meropenem	12 (9.8)	6 (9.8)	6 (9.8)
Metronidazole	7 (5.7)	5 (8.2)	2 (3.3)
Ceftriaxone	4 (3.3)	3 (4.9)	1 (1.6)
Cefepime-Tazobactam	3 (2.5)	2 (3.3)	1 (1.6)
Colistin	1 (1.9)	1 (1.6)	0
Ertapenem	1 (1.9)	1 (1.6)	0
Imipenem	1 (1.9)	0	1 (1.6)
Levofloxacin	1 (1.9)	1 (1.6)	0
Clarithromycin	1 (1.9)	0	1 (1.6)
Linezolid	1 (1.9)	0	1 (1.6)

[Table/Fig-3]: Antibiotic prescribed in study population.
Data presented as frequency (%).

Characteristic	Prolonged Hospitalization (n=15)	OR (95% CI)	p-value
Age ≥ 65 years	2 (13.3)	0.83 (0.21-3.27)	0.798
Female gender	10 (66.7)	1.05 (0.71-1.54)	0.814
Urban Residence	12 (80.0)	1.04 (0.79-1.37)	0.772
Diabetes	10 (66.7)	1.39 (0.93-2.11)	0.168
Fever	14 (93.3)	1.09 (0.93-1.27)	0.430
Dysuria	8 (66.7)	0.93 (0.61-1.43)	0.748
Nausea/vomiting	9 (60.0)	1.05 (0.67-1.64)	0.826
Backache	4 (26.7)	0.67 (0.27-1.58)	0.314
Hb ≤ 10 gm%	4 (26.7)	0.92 (0.37-2.42)	0.853
WBC > 15000 cells/mm3	4 (26.7)	1.58 (0.62-4.05)	0.353
ESR > 30 mm/hr	15 (100.0)	1.58 (1.36-1.82)	0.004
CRP > 20 mg/dL	13 (86.7)	1.14 (0.91-1.43)	0.344
Creatinine ≥ 1.5 mg/dL	5 (33.3)	1.87 (0.82-4.27)	0.155
CKD	13 (86.7)	1.71 (1.30-2.25)	0.008

[Table/Fig-4]: Clinical predictors of prolonged hospitalization (≥10 days) in overall population.
OR: Odds Ratio, CI: Confidence interval, Hb: haemoglobin, WBC: White blood cell count, ESR: Erythrocyte Sedimentation rate, CRP: C-reactive protein, CKD: Chronic kidney disease

DISCUSSION

This study provides an Indian experience of APN in both genders with comparison of clinical characteristics in diabetic and non-diabetic individuals. Diabetes is a well-known risk factors for APN development and progression [8]. But studies comparing the clinical characteristics and outcomes in diabetics and non-diabetic population in Indian subset are lacking. Our retrospective analysis is one of the large series of APN from India. Observation of higher age at presentation of APN in diabetics probably suggests a delayed presentation in diabetics. Similar findings have been reported in previous studies. Kim et al., comparing community acquired pyelonephritis (CA-APN) in diabetic and non-diabetic women found significant difference in median age (69.0 Vs 53 years respectively p<0.001) [10]. Also, in an Indian study, mean age of diabetic population with emphysematous and non-emphysematous pyelonephritis was 56.62 years and 58.18 years respectively [11]. Elderly population is also at risk for APN. It did not differ in diabetic population as compared to those without diabetes (p=0.212). Females are also at a greater risk of APN as suggested by previous reports. Muneishi et al., compared gender specific risk factors in Japanese population who reported higher frequency of APN in females (n=106) than males (n=66). Diabetic status was not associated with increased risk of APN in their gender specific analysis [12]. We also observed higher proportion of females in both the groups. These findings point that diabetes may not affect two gender differentially and occurrence of APN in females should not solely be attributed to diabetes. Nevertheless, diabetic females should always be screened for APN when present with features suggestive of UTI.

Clinical presentation of patients did not vary in diabetic and non-diabetic population significantly except for backache or back pain (p=0.041). Though not specifically referred to as pain at costo-vertebral site, this back pain can be due to APN manifesting at costo-vertebral angle. In a study involving females with CA-APN, similar findings were reported with no significant differences in clinical symptoms in diabetic vs non-diabetic population. Interestingly, frequency of lower UTI symptoms was significantly higher in non-diabetic patients (p=0.001) [10]. Thus the presentation of patients with APN may not vary depending on diabetic status of the individual. However, watchfulness towards progression of renal dysfunction is necessary. Diabetes being a risk for renal dysfunction, significantly higher proportion of patients with diabetes had CKD.

Among laboratory parameters also, no significant differences were observed. Similar findings were reported by Horcajad et al., in a community acquired febrile UTI cases. There were with no significant differences in serum creatinine, total leucocyte counts, and CRP [8]. But in contrast to this, some reports suggest significant elevation of CRP in diabetic individuals with APN as compared to non-diabetic population [10]. However, only females were studied in this particular study whereas we included both genders. Another study reported a higher CRP level in males (median-15.2 mg/dL) than females (median-11.6) (p=0.0293) in patients with APN [12]. Thus, a gender specific influence on CRP in diabetic and non-diabetic patients with APN requires further evaluation to credit it as a useful marker in APN.

In majority of the cases, gram-negative organisms especially *Escherichia coli* is the causative pathogen for APN [12,13]. Treating such infections involve antibiotics directed to gram-

negative organisms. Inappropriate antibiotic therapy can lead to worse outcomes. Cefaperazone-sulbactam followed by amikacin was frequent antibiotics in our study. Usually intravenous antibiotic protocol is advised during in-hospital management but some reports suggested as short IV course followed by oral antibiotic for 7 days may also demonstrate significant clinical improvement [14]. Combination of cephalosporin with beta-lactamase inhibitor can also serve as useful alternative to carbapenems as identified in a larger RCT [15]. The treatment of APN in our study reflected adherence to guidelines recommended therapy [16]. As all the treatments were based on culture sensitivity reports, overall clinical outcome of the patients was good. There were no cases of in-hospital mortality and clinical improvement occurred in all cases. This prompted to evaluate factors associated with prolonged hospitalization. Amongst various factors assessed, only raised ESR (OR: 1.58) and presence of CKD (OR: 1.71) had significant association with prolonged hospital stay. Though duration of hospitalization was similar in diabetic and non-diabetic populations, some studies reported higher hospital stay in diabetics with APN [10,17]. Age above 65 years, nausea/vomiting, bacteraemia, azotemia, dementia are also predictors of prolonged hospitalization in APN [10,12]. Our finding of association of raised ESR with prolonged hospitalization is probably an incidental one and demands further evaluation. Though we found no mortality, previous reports suggest that age above 65 years, septic shock, bed ridden status, recurrent APN, diabetes, nephrolithiasis, and resistant infection are associated with higher mortality risk along with prolonged hospitalization [7,12,18].

STRENGTHS AND LIMITATIONS

Comparative evaluation of clinical characteristics of APN in patients with and without diabetes is the strength of our study. Study adds useful insights on this subject having limited evidence in an Indian setting. Also, we included both genders as against inclusion of only women by many of the previous reports. Though no mortality outcomes occurred, we assessed predictors of prolonged hospitalization. Our study was limited in by retrospective design. A limited data on prior antibiotic usage and microbiological details also limits clear assessments. Inclusion of only hospitalized cases may not give overall picture of APN as mild cases treated on outpatients' basis were not included in this analysis. Also, assessment by severity of diabetes was not performed which may have different impact on clinical presentation.

CONCLUSION

Clinical presentation of APN did not vary significantly in patients with and without diabetes. CKD appeared to be frequent in patients with diabetes. Prescribing guidelines directed antibiotics probably resulted in improved clinical outcomes in both diabetic and non-diabetics as no mortality was noted in any patient from two groups. We found no difference in total hospital stay duration in diabetics compared to non-diabetics. Presence of CKD but not age above 65 or CRP predicted prolonged hospitalization in overall population. Significant association of ESR with prolonged hospitalization is an incidental finding and requires further evaluation in the prospective studies.

ACKNOWLEDGMENTS

We are thankful to the hospital staff and technical experts who helped in clinical data collection, assimilation and editing in computer.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 17, 2016**
Date of Peer Review: **Sep 01, 2016**
Date of Acceptance: **Sep 06, 2016**
Date of Publishing: **Oct 01, 2016**